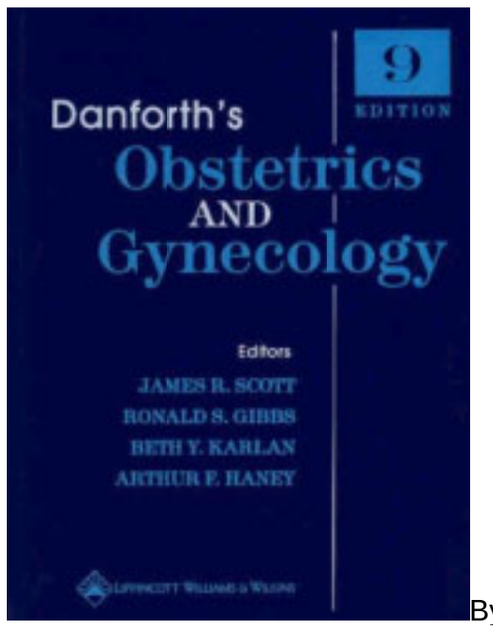
Danforth's Obstetrics and Gynecology, 9th Ed: James R., Md. Scott, Ronald S., Md. Gibbs, Beth Y., Md. Karlan, Arthur F., Md. Haney, David N. Danforth By Lippincott Williams & Wilkins Publishers; 9th edition (August 2003)



By OkDoKeY

Danforth's Obstetrics and Gynecology

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Preface

Now in its ninth edition, **Danforth's Obstetrics and Gynecology** has been widely recognized as a standard textbook for practicing physicians, residents, medical students, and nurses. It is gratifying that previous editions have been translated into several languages and have enjoyed worldwide acceptance. For many practitioners, this text has been the basis of learning and an essential reference in our beloved specialty.

The ninth edition has a new look. Three of the four editors of the eighth edition (Drs. DiSaia, Hammond, and Spellacy) have now turned over the reins to new editors. We are delighted that Jim Scott has continued to serve as an editor for the ninth edition to bring perspective, experience, and continuity. In planning this edition, we carefully reviewed the topic of each chapter and its contents. Consisting of 59 chapters, the ninth edition is now focused to provide a practical, clinically-useful text that covers all of obstetrics and gynecology in one volume. In previous editions, basic science chapters were free standing. In the ninth edition, the basic science concepts have been incorporated into pertinent, more clinically oriented chapters. We have strived to incorporate evidence-based medicine in each of the chapters and have strengthened each of the component chapters. We are also pleased to welcome new contributing authors who are all experts in their field and we thank, also, the contributing authors who have updated and revised their previous chapters.

For ready learning, each chapter contains summary points, conveniently placed at the end of the chapter. In addition, rather than using a heavily referenced format, each author has included a concise list of up-to-date suggested readings at the end of each chapter.

The editors are most grateful for the contributions of the administrative staff at our respective universities: Jane Cook and Barb Carpenter at the University of Colorado; Sheryl Martin at the University of Utah; and Phyllis Lopez at Cedars Sinai Medical Center. We also wish to thank Lisa McAllister, Sonya Seigafuse, and Jenny Kim at Lippincott Williams & Wilkins for their great editorial assistance, support, encouragement—and patience during the gestation of this work.

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Beth Y. Karlan, MD

Arthur F. Haney, MD

Farewell

With this ninth edition, I end my editorship of Danforth's Obstetrics and Gynecology. When Dr. Danforth first asked me almost 20 years ago to serve as co-editor for the fifth edition, it was only after careful thought and preparation that I was willing to take on such a monumental task. We also added three co-editors I considered to be the leading authorities in each subspecialty: Drs. Philip DiSaia (Gynecologic Oncology), Charles Hammond (Reproductive Endocrinology), and William Spellacy (Maternal-Fetal Medicine). It was a privilege and pleasure to work with them as we edited the sixth, seventh and eighth editions. Now it is time for a transition. As Sparky Anderson once said as he stepped down as manager of the Detroit Tigers after 17 seasons, “It's just time.” Dr. Ronald Gibbs has served as the lead editor for this edition, and Drs. Beth Karlan and Arthur Haney are the other new editors. Each was carefully chosen as a highly respected and nationally recognized expert in his/her subspecialty. They have done a superb job, and I am confident that the book is in good hands for future editions. Dr. Danforth would have agreed.

James R. Scott, MD

Chapter 1

Vern L. Katz

Prenatal Care

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This chapter reviews the principles and specifics of prenatal care. The time period from the periconceptual visit through labor and delivery is, for most women, the single greatest psychological transition that a woman undergoes. During these months, the obstetrician, family physician, or midwife serves a much larger role than just as health care provider. Our role is not only to assess the health of the mother and fetus, prescribe interventions, and try to influence behaviors, but also to advise and help our patients as they undergo this challenging psychological passage.

Over the three trimesters of pregnancy a woman must develop new aspects of identity. Her self-image develops an additional sense of femininity beyond what was developed at puberty, and a maternal self-concept must develop as well. Reba Rubin, in her works on the maternal experience, describes a new mother's psychological tasks as the woman grows into her new role. These tasks include:

- accepting a new body image, which is often in conflict with accepted societal views of attractiveness
- accepting the child that is growing inside her
- reordering her identity with her mother, her friends, and the father of the pregnancy
- symbolically finding acceptance and safety for her child (i.e., making a new home).

For many women with good social support these tasks are anticipated and desired roles, which bring a sense of fulfillment. For other women, some or all of these tasks are unanticipated and difficult. The obstetrician, in multiple ways, helps the mother through these transitions, while at the same time ensures the physical health of both patients (mother and fetus). Many aspects of prenatal care have grown from their original role of health promotion to ritualized traditions that have acquired symbolic value in helping women and their families adapt to these psychological transitions. For example, studies have found that for women of average weight, the practice of weighing a woman during each visit has minimal medical value. Yet, if the nurse forgets to weigh a patient, that woman usually remarks quite quickly about having her weight taken. Another example is the routine ultrasound. This is now a demand ritual. At this visit, a mother will usually bring several female family members or friends, to see the sonogram. The new mother not only uses the sonogram to bond with her child, but also shows the baby to the other women around her for their acceptance. Throughout the world, cultures and subcultures view prenatal care differently, but most all hold it with respect. A woman might miss her annual Pap smear, but she rarely misses her prenatal visit.

Many authors have commented on the special relationship of obstetrician and mother, and the window of opportunity to affect healthy behaviors, such as smoking cessation or nutrition. Compared to other physician–patient relationships, the time period of pregnancy allows much greater involvement of the physician in the patient's life. It is with this developmental background that prenatal care has evolved in the last century.

In the United States, the first organized prenatal care programs began in 1901 with home nurse visits. The first prenatal clinic was established in 1911. It is not surprising that this focus on maternal and infant health occurred as a direct outgrowth of the women's suffrage movement. The emergence of the physician-obstetrician as the primary caregiver for women of reproductive age also took place during the last century. This role has become one of partnership with allied health care providers, including nurses, nurse midwives, nurse practitioners, nutritionists, and social workers. This team not only may provide advice and medical treatment, but also serves as the patient's advocate.

Our current emphasis on prenatal care stems from historic pronouncements and retrospective analyses that concluded that women who receive prenatal care have less fetal, infant, and maternal morbidity and mortality. However, a conclusive scientific foundation is lacking for the content of prenatal care and the relationship of its components to good outcomes. As technology flourishes and resources dwindle, it has become increasingly important to obtain scientifically based evidence demonstrating which components of prenatal care are clinically appropriate, cost-effective, and deserving of preferential funding. At this time, the optimal content and delivery of prenatal care remain the subject of discussion and debate. Given the increasing number of tools of prenatal assessment, the current consensus is that the best prenatal care is individualized for the specific needs of the mother.

PRIMARY AND PRECONCEPTION CARE

Philosophy

Care of the woman of reproductive age for both preconception and pregnancy is integrated and accessible, focuses on the majority of personal health care needs, represents a sustained partnership between patient and provider, and occurs within the context of family and community. For many women, pregnancy care occurs as a part of the continuum in a long-term relationship with the health care provider.

The first visit may be a preconception visit or may occur after the woman is pregnant. The content of the visits is similar. If a woman is seen for a preconceptual visit, many issues need not be readdressed when she becomes pregnant. This next section focuses on the preconception visit.

Content of the Preconception Visit

The preconception visit is a focused visit for the woman who is planning to or is considering becoming pregnant in the near future. The content of this interval visit includes a history, physical examination, risk assessment and intervention, selected laboratory testing based on the patient's age and the results of the foregoing evaluation, ongoing management of medical conditions, and a plan of care. A purposeful discussion of contraception, sexually transmitted disease prevention, and timing of conception is appropriate. Timely administration of routine immunizations, educational counseling, and advice complete the visit.

Risk Assessment

A goal specific to the preconception interval visit is the systematic identification of potential risks to pregnancy and the implementation of early intervention as necessary. These risks fall into several categories, described in the following sections.

Unalterable Factors These are preexisting factors and cannot at present be altered in any medical way by clinical intervention. These include the patient's height, age, reproductive history, ethnicity, educational level, socioeconomic status, and genetic composition.
Factors Benefiting from Early Intervention Conditions that should or could be modified before pregnancy is attempted include poor nutrition, an underweight or obese body mass index (BMI), and poorly controlled medical diseases such as diabetes mellitus, asthma, epilepsy, phenylketonuria, hypertension, and thyroid disease. Some prescription medications that are known teratogens should be discontinued and appropriate substitutions made. These include medications such as isotretinoin (Accutane), warfarin sodium (Coumadin), certain anticonvulsants, and angiotensin-converting enzyme inhibitors. Many medications are safe and patients may be assured of medications for asthma, most antihistamines, and antidepressants. Determining the status of a patient's immunity to rubella, varicella, and hepatitis is appropriate during the preconception visit. In high-risk populations or endemic geographic areas, patients should be assessed for active tuberculosis with skin testing and chest x-ray.
Social Risk Factors Inquiry should be made regarding occupational hazards involving exposure to toxins such as lead, mercury and other atom heavy metals, and organic solvents (both liquid and vapors). Hazards in the home, such as exposure to toxoplasmosis or toxic chemicals (asbestos, pesticides), are important to identify. If a woman uses well water, it may be assessed for acidity, lead, and copper. Family violence is a particularly important household hazard. Nonjudgmental, open-ended evaluation should be applied. Judith MacFarland has recommended questions such as “Are you in a relationship in which you are being hit, kicked, slapped, or threatened?” “Do you feel threatened?” “Have you been forced to do things against your will?” These questions should be asked again at the first prenatal visit. Some studies have suggested that a written questionnaire, in addition to oral questions, will allow for greater identification of domestic abuse.
Risky Health Habits The use of illicit drugs or abuse of alcohol represents a significant health hazard to pregnancy. Alcohol is a known teratogen. There is no consensus on the correlation between the quantity of alcohol consumed and the manifestation of adverse fetal effects. Therefore, the best advice to women who wish to become pregnant is to stop drinking. The T-A-C-E screen for alcohol abuse has been well studied. The letters stand for four questions asked in a nonjudgmental manner:

1. T—“How much you drink to feel drunk?” (*tolerance*)
2. A—“Does your drinking *annoy* anyone?”
3. C—“Has anyone told you to *cut* down?”
4. E—“Do you drink in the morning to feel better?” (*eye-opener*).

Smoking cigarettes is associated with adverse pregnancy outcomes including low birth weight, premature birth, and perinatal death. Smoking by both the pregnant woman and members of the household should be avoided during pregnancy and, preferably, not resumed postpartum. The relative risk of intrauterine growth restriction (IUGR) among pregnant smokers has been calculated at 2.2 to 4.2. Because of the morbidity associated with smoking, various methods to assist women to quit smoking should be encouraged prior to pregnancy. Numerous interventions are available (Table 1.1). Use of the transdermal nicotine patch in pregnancy is thought to be preferable to smoking. One benefit of using a nicotine patch is the elimination of exposure to other toxins such as carbon monoxide inhaled in cigarette smoke. Its theoretical risk is that it creates a constant blood level of nicotine, as opposed to the vacillations that occur with smoking. Similarly, all illicit drugs have the potential of harming the pregnancy.

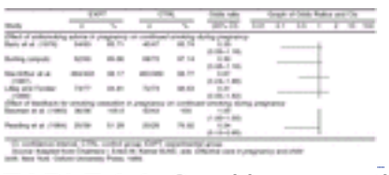

TABLE 1.1. *Smoking cessation in pregnancy*

Other behaviors that should be avoided are those that promote exposure to sexually transmitted and other infectious diseases. These include unprotected sexual intercourse in a nonmonogamous relationship and the sharing of needles between addicts.

Interventions

The final phase of the preconception visit involves specific interventions derived from the information obtained during the history, physical examination, and risk assessment phases. The specific interventions may include immunization against rubella, varicella, or hepatitis, changes in prescribed medications, behavior modification, genetic screening for such conditions as Tay–Sachs disease, cystic fibrosis and sickle cell anemia, and nutritional and physical activity recommendations.

During the physical examination, evaluation of thyroid and breast examinations is important. If a woman is 35 years of age or older, a screening mammogram should be ordered, since as much as two and a half years may pass before she will be able to have one (mammograms have significantly decreased sensitivity during pregnancy and for up to six months after lactation). If a woman has a family history of premenopausal breast cancer, a mammogram may be considered at younger ages. If a Pap smear has not been done within a year, this test should be repeated at this time. Additionally, it is valuable at this visit to examine the patient's skin. The incidence of melanoma is increasing faster than any other malignancy in the United States. The obstetrician has the unique opportunity to assess and teach at this visit regarding this cancer.

Folic acid as a supplement can reduce the occurrence and recurrence of neural tube defects, and may reduce the risk of other birth defects as well. Women who have had a previous pregnancy affected by neural tube defects should take 4 mg of folic acid per day, starting 4 weeks prior to conception through the first trimester. For all other women of reproductive age who have the potential to become pregnant, 1 mg of folic acid should be prescribed.

Approximately 20% of all pregnant women are battered during their pregnancy. About one half of women who are physically abused prior to pregnancy continue to be battered during pregnancy. For some women, the violence begins with pregnancy. All such patients require information regarding their immediate safety and referrals for counseling and support.

Some patients purposely initiate a preconception visit to determine whether or not a preexisting medical condition is an absolute contraindication to pregnancy. Pulmonary hypertension, for example, although rare, is associated with up to a 50% maternal mortality and a greater than 40% fetal mortality. It is possible to obtain epidemiologic studies that provide statistics on the morbidity and mortality for mother and fetus for most disease states. These cannot, however, provide specific data for any one patient with her own unique set of medical, demographic, and social variables. Many patients who make these inquiries will benefit by reading the relevant medical materials themselves and by obtaining more than one opinion. Consultation with other medical specialists may be necessary. For example, women with orthopedic problems often inquire about vaginal delivery. Another common concern is advanced maternal age. Specific risks of increased rates of aneuploidy and

miscarriage should be discussed. Women over 40 have been found to have higher rates of low birth weight, preterm birth, and operative delivery.

It is also important to discuss how and when to discontinue contraceptive measures. Patients using medroxy-progesterone acetate (Depo-Provera) injections may experience a delay of several months in the return of regular ovulatory menstrual cycles. An intrauterine device (IUD) may be removed at any time in the cycle. It should be removed as soon as conception is considered, since removal during pregnancy (although much better than leaving in place) is associated with a higher rate of pregnancy loss. Likewise, birth control pills may be discontinued at any time prior to attempting conception. Many physicians believe that discontinuing the use of oral contraceptives for one cycle allows better growth of the endometrium. Although definitive evidence is lacking, the thought is that there may be better implantation.

The patient should be advised to seek early prenatal care by making an appointment after missed menses or on confirmation of pregnancy by a home pregnancy test. Unfortunately, in the United States, only 75% of pregnant women receive prenatal care beginning in the first trimester. Ongoing barriers to prenatal care access include lack of money or insurance to pay for care, system under-capacity for appointments, and inadequate transportation (Table 1.2).

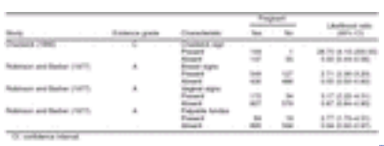

TABLE 1.2. *Probability of pregnancy based on presumptive signs*

INITIAL PRENATAL VISIT

This visit represents the first detailed assessment of the pregnant patient. The optimal timing of this visit may vary. For women who have not undergone the comprehensive preconception visit, prenatal visits should begin as soon as pregnancy is recognized. For these women, much of the content of the preconception visit will need to be addressed at this time—for example, screening for domestic abuse and alcohol use. All other women should be seen by about 8 menstrual weeks (6 weeks after conception) of gestation. For all patients, the appropriate content of prenatal care and the first prenatal visit is contained in the antepartum record published by the American College of Obstetrics and Gynecology (ACOG) (see Appendix I). Identifying data, a menstrual history, and a pregnancy history are obtained. Past medical, surgical, and social history are recorded, along with symptoms of pregnancy. A focused genetic screen, infection history, and risk status evaluation are performed.

Diagnosis of Pregnancy

Evaluation of the signs and symptoms associated with the presumptive diagnosis of pregnancy (see Table 1.2), while a useful adjunct, has been largely superseded by the widely available urine pregnancy test. The detection of greater than 35 mIU of human chorionic gonadotropin (hCG) in the first morning void has a very high specificity for pregnancy. Other tests for confirming the presence of pregnancy include a positive serum ß-hCG and demonstration of the fetal heart by either auscultation or ultrasound. Using a transvaginal probe, fetal cardiac activity should be seen by postconception week 3. Ultrasound imaging is not routinely indicated to diagnose pregnancy but may be used in the evaluation of a patient who is at increased risk for ectopic pregnancy or threatened abortion. In conjunction with early quantitative serum ß-hCG assessments, these conditions can be clearly differentiated from a normal intrauterine pregnancy and timely therapy initiated.

Gestational Age

The Nägele rule is commonly applied in calculating an estimated date of confinement (EDC). Using the date of the patient's last menstrual period minus 3 months, plus 1 week and 1 year, it is based on the assumptions that a normal gestation is 280 days and that all patients have 28-day menstrual cycles. Although several studies have found the average length of gestation for primiparous women to be 282 to 283 days, for convention 280 days is the currently accepted average gestation. After adjustment for a patient's actual cycle length, natality statistics indicate that the majority of pregnancies deliver within 2 weeks before or after this estimated date. During prenatal care, the week of gestation can be obtained based on the calculated EDC. When the last menstrual period is unknown or the cycle is irregular, ultrasound measurements between the 14th and 20th week of gestation provide an accurate determination of gestational age (see Chapter 8).

Physical Examination

A targeted physical examination during the first prenatal visit includes special attention to the patient's BMI, blood pressure, thyroid, skin, breasts, and pelvis. On pelvic examination, the cervix is inspected for anomalies and for the presence of condylomata, neoplasia, or infection. A Pap smear is performed, and cultures for gonorrhea and chlamydia are taken, if indicated. A small amount of bright red bleeding may occur after these manipulations and the patient can be assured that this is normal. On bimanual examination, the cervix is palpated to assess consistency and length, and to detect the presence of cervical motion tenderness. Size, position, and contour of the uterus are noted. The adnexa are palpated to assess for masses. The pelvic examination may include evaluation of the bony pelvis, specifically, the diagonal conjugate, the ischial spines, the sacral hollow, and the arch of the symphysis pubis. This evaluation need only be performed once during the pregnancy.

Laboratory Evaluation

Several laboratory tests are routinely done at the first prenatal visit.

Blood Tests Hematologic testing includes a white blood cell count, hemoglobin, hematocrit, platelet count for women of Asian descent, a serologic test for syphilis (rapid plasma reagin or VDRL), a rubella titer, a hepatitis B surface antigen, a blood group (ABO), and Rh type and antibody screen. Human immunodeficiency virus (HIV) testing should be offered to all pregnant patients and refusal documented in the chart. Routine assessment for toxoplasmosis, cytomegalovirus, and varicella immunity is not necessary, but may be obtained if indicated. The National Institutes of Health and ACOG recommend offering all Caucasian women testing for cystic fibrosis status. Women with histories suggestive of thrombophilia, or a personal or family history for blood clots, should be screened at this time. Women with a history suggestive of thyroid disease should also be evaluated. Appropriate screening for genetic carrier status, if not performed at the preconception visit, includes, but is not limited to, Tay–Sachs disease, Canavan disease in women of Jewish ancestry, a- and ß-thalassemia in women of Asian and Mediterranean descent, and sickle cell disease in women of African descent.
Urine Tests All women should have a clean-catch urine sent for culture. Asymptotic bacteriuria occurs in 5% to 8% of pregnant women. Urinary stasis is present during pregnancy secondary to physiologic changes in the urinary system, including decreased ureteral peristalsis and mechanical uterine compression of the ureter at the pelvic brim as pregnancy progresses. Bacteriuria combined with urinary stasis predisposes the patient to pyelonephritis, the most common nonobstetric cause for hospitalization during pregnancy. Asymptomatic bacteriuria is identified using microscopic urine analysis, urine culture (>100,000 colonies per mL), or a leukocyte esterase–nitrite dipstick on a clean-catch voided urine.
Cultures and Infections The use of routine genital tract cultures in pregnancy is controversial. While it is clear that chlamydiosis, gonorrhea, group B streptococcal disease, herpes infection, and potentially bacterial vaginosis can be detrimental to the ultimate health of the fetus or newborn, the indications for, and timing of, cultures for these infections are not clear. The ACOG recommends assessment for chlamydiosis and gonorrhea at the first prenatal visit for high-risk patients. The high-risk patient is defined as less than 25 years of age with a past history or current evidence of any sexually transmitted disease, a new sexual partner within the preceding 3 months, or multiple sexual partners. Any abnormal discharge should be assessed with a wet prep or Gram stain. Symptomatic patients should be treated. Tuberculosis skin testing in high-risk populations or in certain geographic areas should be done if the patient has not been vaccinated with BCG vaccine. BCG vaccinations are not given in the United States.

Discussion with the Patient

The first prenatal visit is a time for the caregiver and patient to exchange expectations, to answer questions, and to set the stage for what will occur throughout the rest of normal prenatal care. The timing and content of future visits, and the timing and rationale behind further laboratory testing should be explained. The patient should be given authoritative educational resources and materials that are written at the appropriate reading level. She and her partner are encouraged to ask questions about what they will read and to share the concerns they have about the pregnancy. It is important to reinforce that there is no such thing as a meaningless, “dumb”, or trivial question. Emergency and routine phone numbers should be given to the patient in writing. Social services and community resources, such as Women, Infants, and Children (WIC) programs, may be identified for the patient on an as-needed basis. Discussion regarding sexual activities, physical activities, and nutrition are usually initiated at this time. Instructions on safe and unsafe over-the-counter medications (i.e., acetaminophen vs. ibuprofen) are also initiated. Instruction on the use of seat belts and domestic abuse is also recommended here.

Finally, the patient should be made aware of the warning signs and symptoms of infection (fevers, chills, dysuria/hematuria) or threatened pregnancy loss (bleeding,

cramping, passage of tissue). Should any of these occur, the patient should seek immediate medical attention. At the completion of the first visit, the next prenatal appointment is made.

ROUTINE ANTEPARTUM SURVEILLANCE

Rationale for Routine Prenatal Care

Prenatal care involves the following goals for pregnant women:

- to provide continuing, ongoing primary preventive health care
- to maintain or increase maternal health and the capability for self-care and to improve self-image before, during, and after pregnancy
- to reduce the risk of maternal mortality and morbidity, as well as unnecessary pregnancy intervention
- to reduce the risks to health before subsequent pregnancies and beyond the childbearing years
- to promote the development of parenting skills.

The goals of prenatal care for the fetus are as follows:

- to reduce the risk of preterm birth, IUGR, retardation, and congenital anomalies
- to enhance fetal health and reduce the need for extended hospitalization after birth
- to promote healthy growth and development, immunization, and health supervision of the infant
- to reduce the risk of neurologic, developmental, and other morbidities
- to reduce the risk of child abuse and neglect, injuries, and preventable acute and chronic illness.

The goals of prenatal care for the family during pregnancy and the first year of an infant's life are the following:

- to promote family development and positive parent–infant interaction
- to reduce the number of unintended pregnancies
- to identify and treat behavioral disorders that can lead to child neglect and family violence.

Timing and Frequency of Visits

The traditional timing and number of prenatal visits is summarized as follows:

Preconception:	Up to 1 year before conception
First prenatal:	6 to 8 weeks after missed menses
Monthly:	Up to 28 weeks
Bimonthly:	Up to 36 weeks
Weekly:	Until delivery

For the past decade prenatal care has been modified for the number and timing of visits in low-risk patients. Visits may be based on necessary assessments and interventions. A U.S. Public Health Service report delineated the interventions and tests deemed minimally necessary in a normal pregnancy and the suggested the timing for each (Table 1.3). Randomized, controlled prospective trials have evaluated and confirmed the safety of fewer prenatal visits that are modeled around specific times of intervention, such as 16- and 28-week visits. Studies have looked at 6 to 7 visits instead of the usual 13 to 14 and have found similar outcomes. Interestingly, many women reported that they felt dissatisfied with fewer visits.

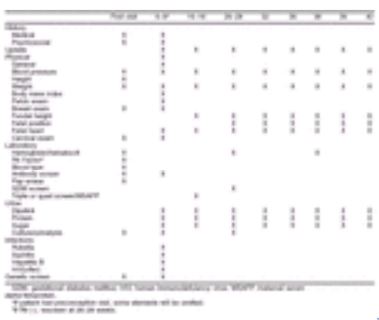

TABLE 1.3. *Timing (in weeks) of prenatal care based on specific interventions*

Content of Subsequent Prenatal Visits

The components of each prenatal visit are the taking of an interval history, assessment of fetal growth and maternal health, risk assessment and identification, intervention as necessary, collection and recording of an ongoing database (see Appendix I), and education, advice and support of the patient and her family.

Interval History Each prenatal visit begins with information gathering. Patients should be asked questions about their general health (see “ Concerns and Questions Particular to Pregnancy” later in the chapter), their diet, sleeping patterns, and fetal movement. Questions regarding warning signs such as bleeding, contractions, leaking of fluid, headache, or visual disturbances are also appropriate. Patients should be given the opportunity to raise their own questions and concerns at each visit, with open-ended inquiries.
Physical Examination The patient is weighed, and total weight gain and trends are evaluated (see “ Nutrition” later in the chapter). The blood pressure is taken and trends are assessed for possible pregnancy-induced hypertension. As blood pressure tends to decrease during the second trimester, increases of 30 mm Hg systolic or 15 mm Hg diastolic over first trimester pressures are considered abnormal. The fundal height is measured with a tape from the top of the symphysis pubis, over the uterine curve, to the top of the fundus (Fig. 1.1 and Fig. 1.2). This technique places an emphasis on change in growth patterns rather than the absolute measurement in centimeters, which can vary between patients. In women who are obese, periodic ultrasound assessments of fetal growth may be necessary. Gestational age is approximately equal to fundal height in centimeters from 16 to 36 weeks gestation. Measurements that are more than 2 cm smaller than expected for week of gestation are suspicious for oligohydramnios, IUGR, fetal anomaly, abnormal fetal lie, or premature fetal descent into the pelvis. Conversely, larger than expected measurements may indicate multiple gestation, polyhydramnios, fetal macrosomia, or leiomyomata. These concerns can be resolved with ultrasound examination.

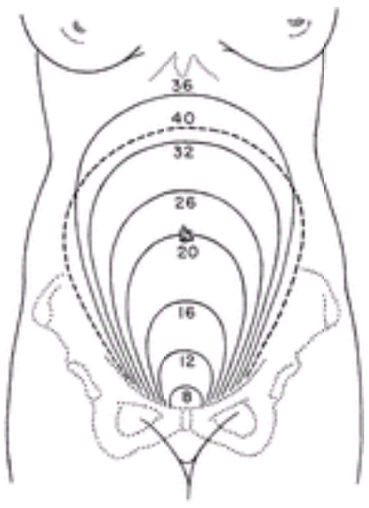

FIG. 1.1. The height of the fundus at comparable gestational dates varies among patients. Those shown are the most common. A convenient rule of thumb is that at 20 weeks gestation, the fundus is at or slightly above the umbilicus.

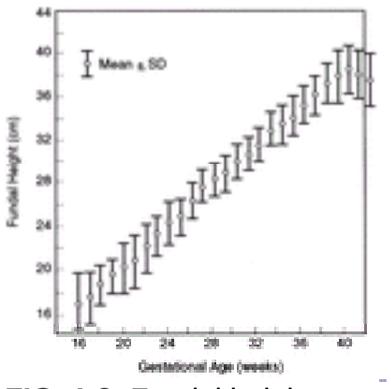

FIG. 1.2. Fundal heights versus gestational age.

Fetal heart rate is auscultated, with care taken to differentiate fetal from maternal rates. The normal fetal heart rate throughout pregnancy is between 120 and 160 beats per minute. Fetal position has been traditionally evaluated with the use of Leopold maneuvers. These are initiated at midpregnancy, when fetal body parts are more clearly identified. The maneuvers consist of four parts; the first three are performed with the examiner standing to one side of the patient and facing her head and the last with the examiner facing the patient's feet.

- The *first maneuver* answers the question, “What fetal part occupies the fundus?” (Fig. 1.3). The examiner palpates the fundal area and differentiates between the irregular, firm breech and the round, hard head.

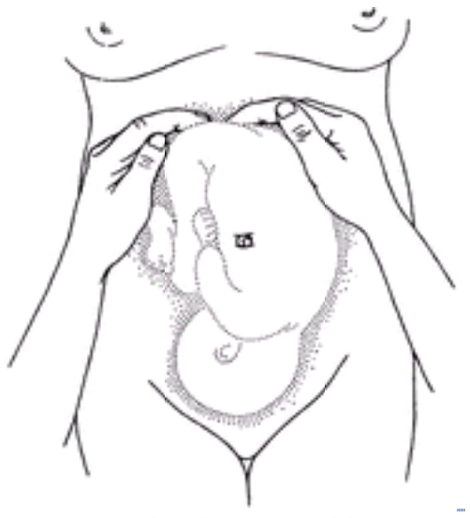

FIG. 1.3. The first Leopold maneuver reveals what fetal part occupies the fundus.

- The *second maneuver* answers the question, “On which side is the fetal back?” (Fig. 1.4). The palms of the hands are placed on either side of the abdomen. On one side, the linear continuous ridge of the back is felt, while on the other side compressible areas and nodular parts are found.

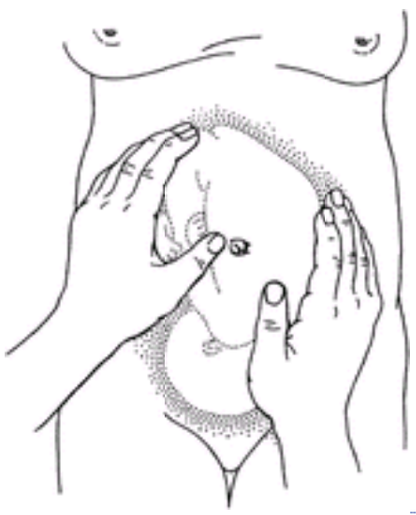

FIG. 1.4. The second Leopold maneuver reveals the position of the fetal back.

- The *third maneuver* answers the question, “What fetal part lies over the pelvic inlet?” (Fig. 1.5). A single examining hand is placed just above the symphysis. The fetal part that overrides the symphysis is grasped between the thumb and third finger. If the head is unengaged, it is readily recognized as a round, hard object that frequently can be displaced upward. After engagement, the back of the head or a shoulder is felt as a relatively fixed, knoblike part. In breech presentations, the irregular, nodular breech is felt in direct continuity with the fetal back.

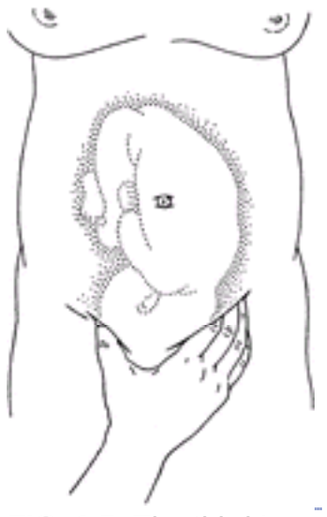

FIG. 1.5. The third Leopold maneuver reveals what fetal part lies over the pelvic inlet.

- The *fourth maneuver* answers the question, “On which side is the cephalic prominence?” (Fig. 1.6 and Fig. 1.7). This maneuver can be performed only when the head is engaged; if the head is floating, the maneuver is inapplicable. The examiner faces the patient's feet and places a hand on either side of the uterus, just above the pelvic inlet. When pressure is exerted in the direction of the inlet, one hand can descend farther than the other. The part of the fetus that prevents the deep descent of one hand is called the cephalic prominence.

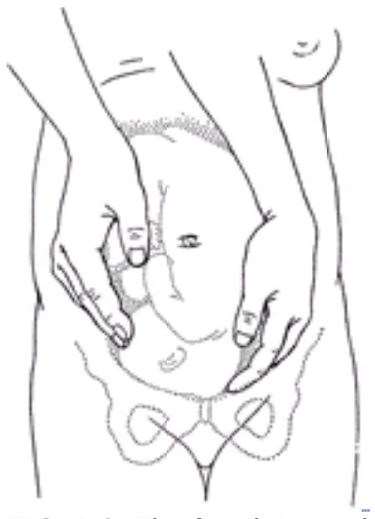

FIG. 1.6. The fourth Leopold maneuver reveals the position of the cephalic prominence. In a flexion attitude, the cephalic prominence is on the same side as the small parts.

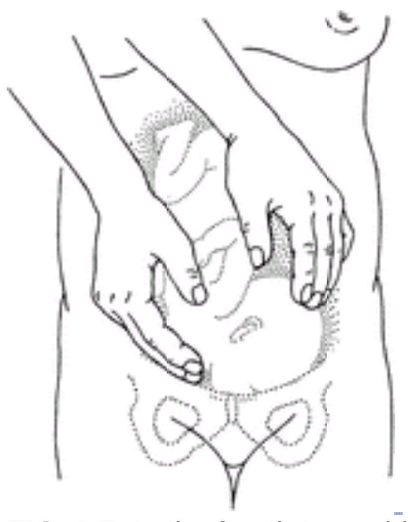

FIG. 1.7. In the fourth Leopold maneuver, in an extension attitude, the cephalic prominence is on the same side as the back.

The routine examination is completed by evaluating the patient for edema. A finding of new-onset edema of the face and hands in association with proteinuria and elevated blood pressure is consistent with preeclampsia. Dependent pitting edema of the ankles and legs in the absence of other findings is normal in late pregnancy. It responds well to resting, with the legs elevated, and therefore is usually absent on rising in the morning. Sudden weight gain in the third trimester to a large extent reflects an increase in edema. The amount of weight gain that is pathologic is not known. However, more than 5 lbs in a week is generally considered problematic. Routine examination of the cervix is not necessary unless the patient is at risk for cervical incompetence or is being evaluated for preterm labor.

Laboratory Evaluation Several laboratory evaluations are offered to all patients. These include screening for neural tube defects and aneuploidy, with alpha-fetoprotein and other serum values (triple or quad screen), screening for gestational diabetes with a glucose challenge, as well as screening for maternal antibodies to fetal blood type.

Maternal Serum Screening Test Screening with maternal serum alpha-fetoprotein (MSAFP) is performed to detect fetal neural tube defects and fetal ventral wall defects. During pregnancy, AFP is produced in sequence by the fetal yolk sac, the fetal gastrointestinal tract, and finally, the fetal liver. Its peak concentration in fetal serum occurs at the end of the first trimester. Excretion of AFP in fetal urine results in high levels of AFP in the amniotic fluid. Transfer of AFP to the maternal serum occurs via the placenta and transamniotically. MSAFP levels continue to rise until approximately 30 weeks gestation (Fig. 1.8). The interpretation of the MSAFP screening test is dependent on gestational age and should be performed at the 15th to 20th menstrual weeks of pregnancy.

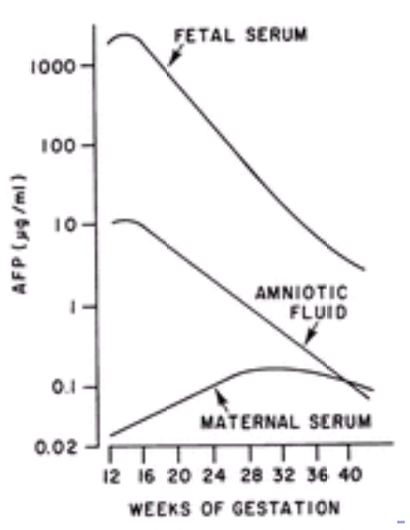

FIG. 1.8. Alpha-fetoprotein concentrations in fetal serum, amniotic fluid, and maternal serum throughout gestation. (From Seppala M, ed. *Amniotic fluid*, second ed. New York: Excerpta Medica, 1978; with permission.)

MSAFP levels are reported as multiples of the median from the database of the individual laboratory. Elevated maternal serum and amniotic fluid levels of AFP detect 85% of open neural tube defects (open spina bifida and anencephaly). Other causes for elevated MSAFP levels include omphalocele, gastroschisis, multiple gestation, fetal demise, incorrect dates, and adverse pregnancy outcomes. Patients with abnormal MSAFP levels require evaluation with targeted fetal ultrasonography (Fig. 1.9)

(see Chapter 6, Chapter 8).

FIG. 1.9. Screening for Down syndrome during pregnancy by measuring markers in maternal serum. (Adapted from Haddow JE, Palomaki GE, Knight, GJ, et al. Prenatal screening for fetal Down syndrome with the use of measurement of maternal serum markers. *N Engl J Med* 1992;327:588.)

The risk of fetal trisomy 21 is related to gestational age/normalized concentrations of MSAFP, total ß-hCG, unconjugated estriol, and inhibin. Thus, these biochemical markers may be used in conjunction with the maternal age-related risk of fetal trisomy 21 to derive a more precise risk of fetal trisomy 21 in a given pregnancy. Called the triple screen or quad screen, this scheme assumes that computed risks for fetal trisomy 21 greater than 1 in 270 (, the mid-trimester risk of fetal trisomy 21 in a 35-year-old woman) should prompt consideration of genetic counseling, targeted ultrasound, and possibly amniocentesis. Using such a scheme, prospective studies show that approximately 60% to 70% of fetal trisomy 21 will be detected, with a false-positive rate of 5%. In women older than age 34 at delivery, the triple marker will detect 80% to 85% of trisomy 21. These women should be offered genetic counseling, as some will opt for amniocentesis or chorionic villus sampling. It is important to counsel a patient about the differences between a screening test and a diagnostic test. The possibility of false-positive and false-negative test results should also be explained. Approximately 60% of trisomy 18 may be detected with biochemical means (triple or quad screen). Many women will opt for first trimester screening, including nuchal thickening and biochemical markers. Early studies hold promise for this type of screening, though precise predictive values are still being estimated.
Screening for Gestational Diabetes The 1-hour, 50-g oral glucose screen is used to detect glucose intolerance in pregnancy. Following an abnormal screen, a 3-hour glucose tolerance test, commencing with a fasting blood sugar, followed by a 100-g Glucola, is currently recommended. Two or more abnormal values on this test are considered diagnostic of gestational diabetes mellitus (GDM). Universal screening is controversial, though most clinicians have opted for a universal approach. Risk factors for GDM include:

- maternal age greater than 30 years
- previous macrosomic, malformed, or stillborn infant
- GDM in a previous pregnancy
- family history of diabetes
- maternal obesity
- persistent glucosuria
- chronic use of certain drugs such as ß-sympathomimetics or corticosteroids.

Proponents of universal screening argue that screening only those patients with risk factors will detect no more than half of patients with glucose intolerance. Opponents argue that the inconvenience and expense of testing are not necessary in patients without these risk factors, because the incidence of frank GDM in this population is so low. Routine screening, if used, is performed on all patients between 26 and 28 weeks gestation. Selective screening based on risks may be performed earlier and repeated as needed, if negative at earlier gestations. A patient may be tested in the fasting or nonfasting state. One hour after administration of a 50-g glucose load, the patient's blood is drawn. A patient with a glucose value greater than 140 mg per dL of serum is a candidate for a 3-hour, 100-g glucose tolerance test. The significance of GDM lies not in an increased risk of fetal loss but in the risk of excessive fetal growth with its attendant birth-related morbidities. In addition, women with GDM have a 60% likelihood of developing overt diabetes mellitus within 16 years.
Rescreening for Rh Antibodies All Rh-negative women who are unsensitized at the beginning of pregnancy should be retested at approximately 26 to 28 weeks gestation. If the antibody screen remains negative, the mother should receive Rh $_0$(D) immune globulin 300 mcg at 28 weeks, to prevent isoimmunization in the third trimester. Approximately 1% of Rh-negative women will become sensitized if not given Rh immune globulins.
Screening for Bacterial Vaginosis Bacterial vaginosis (BV) is a condition in which the normal flora of the vagina (specifically lactobacilli) are reduced in number and replaced by an overgrowth of anaerobic organisms. Studies have linked BV with an increased incidence of preterm labor, endometritis, and premature rupture of the membranes. A simple and effective screen, performed late in the second trimester, consists of a pelvic examination and wet mount to detect BV. A Gram stain is an alternative diagnostic tool. The treatment for women who are positive for BV includes either metronidazole or clindamycin (Cleocin). Because BV is often asymptomatic, a test of cure may be appropriate. Routine screening is not recommended, as studies have not shown that screening and treatment decreases preterm labor and delivery. However, symptomatic women, women with cerclage, or women with preterm dilated cervices should be screened and treated.
Testing for Group B Streptococci Group B streptococci (GBS) are part of the normal vaginal, genitourinary, and gastrointestinal tract flora in up to 30% of healthy women. GBS have been implicated in amnionitis, endometritis, and wound infection in the mother. Vertical transmission during pregnancy, labor, and delivery may result in generalized sepsis in the newborn and related long-term morbidity or neonatal death. Prevention strategies have focused on detection of the bacteria in the mother and early onset of GBS disease in the newborn. The recommended strategy involves routine anogenital cultures of all pregnant women at 35 to 37 weeks gestation. Cultures are obtained from the lower third of the vagina and perianal area. Cervical cultures are not reliable and a speculum is not necessary to obtain an adequate culture sample. Culture-positive women are treated during labor with antibiotic prophylaxis to prevent fetal–neonatal GBS infection. Women with a positive urine culture for GBS should be given antibiotic prophylaxis in labor. These women do not need to be recultured.
Testing Based on Symptoms or Clinical Risk Assessment A part of prenatal care of the normal patient consists of ongoing risk assessment and intervention or referral if a risk is identified. Several clinical signs or symptoms warrant further evaluation. Symptoms suggestive of urinary tract infections should prompt examination of a clean-catch urine specimen and cultures when appropriate. High-risk behaviors, identified during the course of a pregnancy, should prompt a test (or retest) for HIV infection and sexually transmitted diseases (STDs) or performance of a urinary drug screen. Repeated testing of hemoglobin should be done if the patient is symptomatic or at nutritional risk for anemia. Other testing, performed on an as-needed basis, includes ultrasound to detect abnormal fetal growth, antepartum fetal monitoring to assess fetal oxygenation status, or comprehensive targeted ultrasound examinations. A more thorough discussion of antepartum fetal monitoring can be found in Chapter 9.
Discussion with Patients and Families: Answering Questions Patients need the opportunity to engage in dialogue with their health care provider and to feel confident that their concerns are heard. Patients and families will often interact with a nurse or triage person in a physician's office. These individuals need to be trained in careful assessment and evaluation. The value of information ancillary personnel can provide cannot be overemphasized. The prenatal visits are a time to stress the involvement of the entire family in the pregnancy process, including the role of the father and siblings. Therefore, an important part of the prenatal visit is discussion with the patient, her partner, or her family, both to exchange questions and answers, and to provide reassurance and education. The exact content of these discussions will vary from visit to visit. Reaffirming the importance of appropriate social behaviors, such as smoking cessation, is beneficial, as are periodic evaluations of the social support systems and help in the home, both now and after the birth of the infant. Ongoing risk assessment requires that the patient be educated about the signs and symptoms of preterm labor and preeclampsia. The list of warning signs for which an emergent telephone call is warranted includes the following:

- vaginal bleeding
- leaking of fluid from the vagina
- rhythmic cramping pains of more than six per hour
- abdominal pain of a prolonged or increasing nature
- fever or chills
- burning with urination
- prolonged vomiting with inability to hold down liquids or solids for more than 24 hours
- severe continuous headache, visual changes, or generalized edema
- a pronounced decrease in the frequency or intensity of fetal movements.

CONCERNS AND QUESTIONS PARTICULAR TO PREGNANCY

Psychological

Pregnancy is a time of change, expectation, and anticipation. It may also be a time of heightened anxiety, emotionality, concern, and uncertainty. Many symptoms that the nonpregnant patient might view as minor may indicate a cause for alarm during pregnancy. The provision of direct, concise, and accurate information in a

compassionate and reassuring manner will assuage many of these worries and provide direction for day-to-day activities.

Nutrition

The objectives of nutritional assessment and counseling are to develop, in concert with the patient, an analysis of maternal nutritional risk, a goal for total weight gain, and a diet plan that will fit the patient's lifestyle and is ethnically sensitive.

The principle of good nutrition is that there is a positive linear relationship between maternal weight gain and newborn weight *and* that prepregnant maternal BMI can affect fetal weight independently of the amount gained by the mother during pregnancy. Together, initial weight and weight gain have an impact on IUGR and low birth weight. However, for a woman of normal weight and normal nutrition, the relationship between poor weight gain and fetal growth restriction may be an association not a cause and effect.

The BMI is a calculation that relates the patient's weight to her height, thereby providing a more accurate indirect estimate of the patient's body fat distribution than can be obtained by weight alone. The BMI is calculated by dividing weight in kilograms by height in meters squared. If pounds and inches are used, the quotient is multiplied by 700. The BMI of a patient is categorized as underweight, normal weight, overweight, or obese (see Appendix II).

Maternal Weight Gain The ideal weight gain for an individual patient during pregnancy depends on several factors. The most important of these are the prepregnant BMI and the type of gestation (single vs. multiple). It is important to note that weight gain for a normal BMI is 25 to 35 lbs (11 to 16 kg), but the optimal weight gain for an underweight teenager carrying a singleton pregnancy approaches 40 lbs (18.2 kg), or 5 lbs every 4 weeks in the second half of pregnancy (Fig. 1.10). An obese woman, on the other hand, may need to gain no more than 15 lbs (6.8 kg). Figure 1.11 illustrates the components of weight gain in a normal pregnancy. During the first and second trimesters, most of the weight gained reflects maternal changes, primarily an increase in total body water, while fetal growth is most rapid in the last trimester, with the fetus more than tripling its weight. The optimal weight gain for women with twins is usually greater than 40 lbs. Poor weight gain is often a reflection of patients not expanding their intravascular volume. This is associated with low birth weight and greater complications in pregnancy. Having patients “eat more” does not usually help. In contrast, weight gain greater than 30 lbs will often remain as extra weight after delivery. Women should be instructed not to diet during pregnancy. Many women will not gain significant weight until the middle of the second trimester. Patients may be reassured that this is a normal pattern.

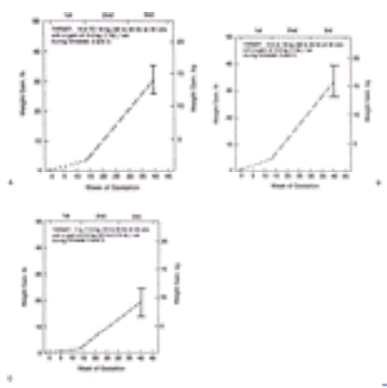

FIG. 1.10. Target weight gains for normal-weight women with body mass index (BMI) of 19.8 to 26, underweight women with a BMI of less than 19.8, and overweight women with a BMI of more than 26 to 29. **A:** A 1.6 kg (3.5 lb) gain in the first trimester and the remaining gain at a rate of 0.44 kg (0.97 lb) per week are assumed. **B:** A 2.3 kg (5 lb) gain in the first trimester and the remaining gain at a rate of 0.49 kg (1.1 lb) per week are assumed. **C:** A 0.9 kg (2 lb) gain in the first trimester and the remaining gain at a rate of 0.3 kg (0.67 lb) per week are assumed.

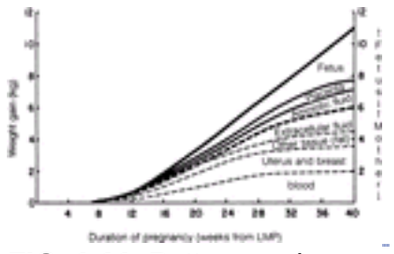

FIG. 1.11. Pattern and components of weight gain during pregnancy (LMP, last menstrual period). (From Pitkin RM. Nutritional support in obstetrics and gynecology. *Clin Obstet Gynecol* 1976;19:489, with permission.)

Maternal Diet While weight gain is an important gauge of caloric intake, the quality of the diet and the frequency of meals may also affect patient and fetal well-being. A diet should be balanced by containing foods from all of the basic food groups. Specifics of a diet will vary considerably according to patient preference, family eating patterns, and cultural and ethnic background. Increased nutritional requirements during pregnancy reflect the needs of the fetus for growth, as well as maternal physiologic needs. To meet the overall increasing energy needs, the average woman must consume an additional 300 kcal per day beyond her baseline needs. The appropriate daily caloric content of a diet required to supply energy needs and achieve appropriate weight gain can be estimated by multiplying the patient's optimal body weight in kilograms by 35 kcal and adding 300 kcal to the total (Table 1.4).

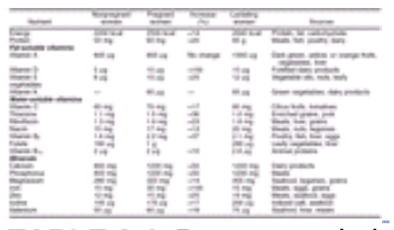

TABLE 1.4. *Recommended dietary allowances for women of reproductive age and for pregnant and lactating women*

Vitamin and Mineral Supplementation Multivitamin supplements are not routinely necessary in a woman eating a well-balanced diet. However, 800 µg of supplemental folic acid daily is necessary because the requirement cannot be met with food alone. Additional folate may be necessary for women with a hemoglobinopathy or MTHFR mutation, for women on antiseizure medications, or for women with a history of neural tube defects. Vitamin D supplementation is not generally required, unless there is inadequate exposure to sunlight. Mineral supplementation is also not needed in healthy women. The exception is iron. The iron requirements of pregnancy total about 1 g. Due to the monthly menses, most women have less than optimal iron stores during their reproductive years. Therefore, supplementation with 30 mg of elemental iron is recommended in the second and third trimesters to prevent anemia and to meet this requirement. One tablet of iron salts per day, ingested between meals or at bedtime, is sufficient to meet this requirement. Women with iron deficiency anemia require 60 to 120 mg of elemental ferrous iron per day. Additional zinc (15 mg) and copper (2 mg) are then needed, as iron inhibits the absorption of these ions. Calcium supplementation is not necessary in women with a diet that includes adequate dairy foods. Absent this, calcium supplementation may be used on an as-needed basis to meet the recommended dietary allowance (RDA) of 1200 to 1500 mg per day during pregnancy and 2000 mg per day with lactation. Zinc is a trace mineral. A zinc deficiency may be teratogenic in humans, although this has not yet been conclusively demonstrated. Zinc levels in amniotic fluid correlate with antimicrobial activity, suggesting that zinc plays a role in protecting against intrauterine infection. Low dietary intake of zinc has been associated with IUGR, although it does not cause IUGR. The RDA for zinc during pregnancy is increased from 15 to 20 mg per day.

Other Dietary Considerations

Vegetarianism Lacto-ovo vegetarians should have no particular nutritional deficiency, with the possible exceptions of iron and zinc, which may be supplemented. The strict vegan, however, must design a diet of sufficient vegetable proteins to provide all of the essential amino acids normally found in animal protein. Due to the decreased protein density of most vegetables, this may cause an unusually high weight gain. Supplementation of zinc, vitamin B_{12}, and iron is necessary.

Food Restriction Dieting and fasting on a chronic basis in an otherwise healthy woman can result in suboptimal fetal growth. Eating disorders such as bulimia and anorexia nervosa reflect extreme forms of food restriction and malnutrition. There are limited data about these disorders in pregnancy, but anorexics in particular place their fetus at risk. Bulimic women may suffer from electrolyte imbalance and a deficit of trace minerals. Many pregnant women in the United States are not eating an optimal diet due to poverty and inadequate resources to purchase food. It is appropriate to inquire about resources in impoverished women and to refer these patients to groups such as WIC and to appropriate agencies providing food stamps.

Pica Pica is the compulsive ingestion of nonfood substances with little or no nutrient value. The practice most commonly involves ice, clay (geophagia), or starch (amylophagia). Although pica is most commonly recognized during pregnancy, it is not specific to the gravid state. Neither the cause nor the medical implications of pica are well understood. It is unusual for pica to cause significant harm if the diet is otherwise nutritionally adequate.

Phenylketonuria Women with phenylketonuria who are not on a phenylalanine-controlled diet are at increased risk of bearing fetuses with microcephaly, growth retardation, and mental retardation. The goal of dietary management is to minimize these adverse fetal outcomes by reducing the maternal serum phenylalanine levels to less than 20 mg per dL before and during the pregnancy. At the first prenatal visit, every pregnant woman should be asked if she was on a special diet as a child.
Megadose Vitamins The misuse of megadose nutrients can be categorized as a fad type of dietary manipulation. Water-soluble vitamins such as vitamin C cannot be consumed in harmful quantities because they are readily excreted in the urine. However, a problem occurs with fat-soluble vitamin A. There is an association between high doses of supplemental vitamin A and birth defects similar to those seen with isotretinoin. Although the minimum teratogenic dose in humans has not been identified, it may be a little as 10,000 IU per day. Beta-carotene is a provitamin of vitamin A, but it does not produce similar toxicity. Most prenatal vitamins contain less than 5000 IU of vitamin A and, until further data are available, this should be considered the maximum safe supplemental dose.
Caffeine Caffeine is contained in numerous foodstuffs such as coffee, tea, chocolate, and cola beverages. A naturally occurring substance, it is the most widely used psychoactive drug in the United States. It is a central nervous system stimulant and is physically and psychologically addictive. Withdrawal symptoms include nausea, lethargy, malaise, and headache. The only evidence for teratogenic effects of caffeine comes from animal studies using doses not compatible with human consumption. Several large human studies have failed to show that caffeine has deleterious effects on the fetus, when ingested in low amounts. However, it is associated with an increased risk of miscarriage when taken in greater than the equivalent of three cups of coffee. Caffeine intake of the equivalent of two to three cups is thus discouraged. Adverse maternal effects of caffeine include insomnia, acid indigestion, reflux, and urinary frequency. As these problems are already exaggerated in pregnancy, moderation in the consumption of caffeine is advisable.

Exercise

Exercise is a routine part of many women's daily activities. For a normal pregnancy, a low-impact exercise regimen may be continued throughout pregnancy. Additionally, studies also show that women may increase their levels of fitness during pregnancy without problems. There are no data to indicate that pregnant women must decrease the intensity of their exercise or lower their target heart rates. However, physiologic changes of pregnancy may alter the effect of various exercises on the body or may limit the body's ability to perform certain types of exercise. Body position as a modulator of cardiac output is particularly important in the third trimester, when either motionless standing or the supine position can result in decreased venous return and cardiac output. In some instances, this will result in hypotension or syncope.

Both oxygen uptake and baseline oxygen consumption are increased during pregnancy. Deep breathing is more difficult, particularly in later pregnancy, due to uterine size and decreased diaphragmatic excursion. These changes combine to make less oxygen available for aerobic activity, thereby decreasing maximum exercise performance.

Exercise is not a means of weight control in pregnancy. Women who seek to exercise to keep from gaining weight or losing their prepregnancy shape should be counseled regarding normal pregnancy body changes.

Data regarding the fetal response to maternal exercise are reassuring. Moderate (submaximal) exercise has never been shown to increase maternal core body temperature and thus, fetal temperature. Studies of the fetus following submaximal maternal exercise (65% to 70% aerobic capacity) have not shown any associated changes in the fetal heart rate. Exercise-induced effects on the fetus, including malformations, increased miscarriage rates, retardation, or growth restriction, have not been demonstrated in human pregnancies. Women who exercise strenuously throughout pregnancy, such as elite athletes, may deliver infants as much as 300 to 400 g smaller in weight than women who do not exercise as strenuously. This, however, is not considered deleterious.

Recommendations Women who exercise regularly before pregnancy may be encouraged to continue. They may be counseled that performance capacity tends to fall, but this is not a sign that they should forgo regular moderate exercise. Indeed, exercise may relieve stress, diminish anxiety, and increase self-esteem. Some studies have also shown that women who exercise regularly have shorter labors. For most women with gestational diabetes, regular exercise has been shown to be helpful for glucose control. Specific exercise regimens should be individualized and patients who have not been physically active prior to pregnancy are advised to proceed slowly. General recommendations include the following:

- Exercise should be regular rather than sporadic and intermittent.
- Exercise should be stopped if signs and symptoms of oxygen deprivation, such as extreme fatigue, dizziness, or extreme shortness of breath, occur.
- To avoid becoming overheated, pregnant women should exercise in a cool area, stay well hydrated, and wear appropriate clothing.
- Exercise that requires prolonged time in the supine position should be avoided during the second and third trimesters.
- The form of exercise chosen should not be one with significant risk of trauma (especially to the abdomen) or falls.
- Caloric intake should be increased in direct proportion to the additional energy requirements of exercise.

Contraindications Relative contraindications to exercise during pregnancy include the following:

- evidence of IUGR
- persistent vaginal bleeding
- incompetent cervix or cervical cerclage placement
- risk factors for preterm labor
- rupture of membranes
- pregnancy-induced hypertension
- chronic medical conditions that might be adversely impacted by vigorous exercise.

Nausea and Vomiting

Recurrent nausea and vomiting during the first trimester occurs in over one half of pregnancies. While the term *morning sickness* is well known, it is a misnomer, as these symptoms can occur at any time throughout the day or night. Symptoms usually begin in weeks 6 to 8, peak during weeks 12 to 14, and are significantly resolved by week 22. The etiology of this problem is not clear. Hormonal, as well as emotional, factors have been investigated without consistent results. Symptoms can be mild or so severe that the patient becomes dehydrated and risks electrolyte imbalance and caloric malnutrition. Nonpharmacologic measures often suffice to alleviate, if not completely relieve, the symptoms. These include avoidance of fatty or spicy foods, eating small, more frequent meals, drinking ginger teas, inhaling peppermint oil vapors, wearing motion sickness bands on the wrists, and increasing rest periods each day. In severe cases of emesis, various pharmacologic agents have been used with varying success. These include pyridoxine, a variety of antihistamines, promethazine, metoclopramide, trimethobenzamide, methylprednisolone, and droperidol. Because supplemental vitamin and mineral preparations may exacerbate symptoms of nausea, they should be stopped until the symptoms have resolved. Women and their families may be reassured that minimal weight gain in the first 18 weeks is common.

Ptyalism

Ptyalism is the increased production of saliva, probably induced by the consumption of starch. There is no cure, although reducing carbohydrate intake may be helpful. The problem is often self-limiting.

Heartburn

Heartburn is usually caused by reflux esophagitis from both mechanical factors (enlarging uterus displacing the stomach above the esophageal sphincter) and hormonal factors (progesterone causing a relative relaxation of the esophageal sphincter). Treatment consists of eliminating acidic and spicy foods, decreasing the amount of food and liquid at each meal, limiting food and liquid intake before bedtime, sleeping in a semi-Fowler position or propped up on pillows, and use of antacids. Liquid forms of antacids and H_2-receptor inhibitors provide the most consistent relief of symptoms. Patients should be cautioned that antacids containing aluminum may cause constipation, while diarrhea may be associated with use of those containing magnesium.

Constipation

Progesterone-induced relaxation of the intestinal smooth muscle slows peristalsis and increases bowel transit time. Dietary management of this common condition includes increased fluids and liberal intake of high-fiber foods. Iron salts may exacerbate the problem. Over-the-counter (OTC) products containing psyllium draw fluid into the intestine and promote a more rapid transit time. Enemas and strong cathartics should be avoided.

Fatigue

Pregnant women will usually have an increased sense of fatigue during pregnancy. This is a normal symptom. A sense of breathlessness is also normal. A significant

increase in fatigue or breathlessness however should alert the clinician to possible pathology.

Varicosities and Hemorrhoids

Varicosities most often occur in the lower extremities but may be seen in the vulva as well. Contributing factors include genetic predisposition, advanced maternal age, increased parity, and prolonged standing. Manifestations can range from mild cosmetic effects to chronic pain and superficial thrombophlebitis. Treatment includes avoidance of garments that constrict at the knee and upper leg, support stockings, and increased periods of rest with the legs elevated.

Hemorrhoids, varicosities of the rectal veins, are due to mechanical compression by the enlarging uterus, as well as from constipation and straining at stool. Treatment includes OTC preparations, witch hazel, topical preparations, cool sitz baths, and stool softeners. If thrombosis of a hemorrhoid occurs, the clot can be excised to relieve pain and swelling.

Leg Cramps

Almost half of all pregnant women suffer from recurrent painful spasms of the muscles of the lower extremities, especially the calves. Leg cramps are more frequent at night and usually occur during the third trimester. Various prophylactic and therapeutic options have been suggested, most notably, calcium lactate and high potassium foods, such as banana, kiwi, or cantaloupe, but there are no data from controlled trials to show benefit over placebo for any of these. Massage, heat, and stretching the affected muscle(s) relieves the cramps when they occur.

Backache

Most pregnant women experience lower backaches as pregnancy progresses. These are usually alleviated by minimizing the amount of time spent standing, by increasing rest, by wearing a specially designed support belt over the lower abdomen, and by taking an analgesic such as acetaminophen. Exercises to increase muscular strength of the back and abdomen are sometimes helpful. Shoes with good support and avoidance of high heels that exaggerate the lordotic posture are essential. Increasingly severe or abrupt-onset back pain requires orthopedic consultation. Rhythmic cramping pains originating in the back may be a sign of preterm labor and necessitate appropriate evaluation.

Round Ligament Pain

This pain most frequently occurs during the second trimester when women report sharp, bilateral, or unilateral groin pain. It has been called “round ligament pain”, though it is not known if round ligament stretch is the true etiology. The pain may be increased with sudden movement or change in position. Resolution of unremitting ligament pain is sometimes achieved by having the patient assume a position on the hands and knees and lower the head to the floor, while keeping the buttocks in the air.

Headache

Generalized headaches are not uncommon during the first trimester of pregnancy. Muscle tension headaches may occur intermittently. The frequency and intensity of migraine headaches may increase or decrease during pregnancy. Headaches during the second and third trimesters are not an expected symptom of pregnancy. Pathologic headaches that occur with preeclampsia are discussed in Chapter 16.

Emotional Changes

Pregnancy is a time of significant psychological stress. Changes in hormonal levels, changes in relationships to partners, family and friends, and changes in body image all lead to increased psychological stress. Increased levels of placental corticotropin-releasing hormone toward the end of pregnancy also affect the maternal hypothalamic–pituitary axis and other brain loci involved in stress responses. There is a corresponding shift in most women toward primary process. Dreams become more vivid and dramatic. Emotional lability is common. It is very helpful to counsel the pregnant woman and her partner about these normal changes. Women with social stressors or with a history of depression may develop signs of atypical depression, necessitating counseling and medications.

Sexual Relations

Coital activity during normal pregnancy need not be restricted. The couple can be counseled regarding changing positions to achieve better comfort. Deep penetration may be more uncomfortable as pregnancy progresses. It is common for women to have changes in sexual desire over the course of gestation. Many women achieve orgasm easier during pregnancy; however libido often decreases in the first and third trimesters. Nipple stimulation, vaginal penetration, and orgasm can cause uterine contractions secondary to the release of prostaglandins and oxytocin. However, there are no proven adverse effects on the fetus or the onset of labor. The question of the effect of coitus in women at risk for preterm labor or early spontaneous pregnancy loss remains unanswered. Couples at risk may prefer to avoid sexual relations to minimize any feelings of guilt or responsibility if a problem occurs subsequently.

There are two concrete interdictions to coitus during pregnancy. The first is that intercourse should not occur after membrane rupture or in the presence of known placenta previa. The second is that forceful introduction of air into the vagina should be avoided because of the risk of fatal air embolism.

Employment

Most patients are able to continue to work throughout their pregnancy. In general, work activities that increase the risk of falls or trauma, especially to the abdomen, should be avoided. Hazardous toxic or chemical exposures should be identified early and avoided. Strenuous physical activity, including repetitive lifting and prolonged standing for more than 5 hours, has been associated with a greater rate of adverse outcomes, and work routines should be modified accordingly.

Urinary Frequency

Patients often experience urinary frequency during the first 3 months of pregnancy, as the enlarging uterus compresses the bladder, and again during the last weeks, as the fetal head descends into the pelvis. If frequency occurs in conjunction with dysuria, hematuria, or urgency/hesitancy, the patient should be evaluated for a urinary tract infection.

Skin Changes

Hair growth has variable patterns in pregnancy, although many women experience increased growth during pregnancy and hair loss postpartum. Skin commonly darkens over the face and median ventral line of the abdomen in many women. Any nevi that change color should be excised.

Leukorrhea

An increase in the amount of vaginal discharge is physiologic and expected during pregnancy. Discharge accompanied by itching or burning, or a malodorous discharge, should be evaluated and treated accordingly. Douching has no place in the treatment or management of leukorrhea in pregnancy. Increased watery discharge may precede preterm labor and should be evaluated.

Syncope

Venous pooling in the lower extremities increases as the pregnancy progresses. This can lead to dizziness or lightheadedness, especially after standing upright abruptly or for long periods of time. Other causes of syncope include dehydration, hypoglycemia, and the shunting of blood flow to the stomach after eating a large meal. Syncope during exercise is a sign of overexertion. In general, syncopal episodes resolve rapidly and should be managed acutely, just as in a nonpregnant patient. Syncope in the supine position is avoidable by resting in the lateral recumbent position, right or left, thereby relieving uterine compression of the vena cava.

X-rays/Ionizing Radiation

The adverse effects on the fetus of ionizing radiation are dose-dependent. While there is no single diagnostic procedure that results in a dose of radiation high enough

to threaten the fetus or embryo, cumulative exposures or multiple procedures should be avoided, especially during the first trimester when the fetus is at highest risk for possible anomalies. Patients may undergo dental x-rays as needed, provided that the abdomen is fully covered by a lead apron. Studies using radioactive isotopes are best avoided. As in all diagnostic procedures, the risks and the potential benefits must be evaluated and individualized for each patient. Exposure to video display terminals is safe in pregnancy.

Travel

Most issues concerning travel involve the comfort of the mother. When prolonged sitting is involved, the patient should try to stretch her legs and walk for 10 minutes every 2 hours to decrease the risk of thrombosis that can occur secondary to the hypercoaguable pregnancy state and mechanical compression of venous blood flow from the extremities. Dependent edema may also be more pronounced after prolonged sitting. If the patient will be away from home for a significant period of time, she should take a copy of her medical record with her. Pregnant women can and should always wear seat belts when riding in a car. Travel in a pressurized airplane presents no additional risk to pregnant women. In traveling abroad, especially to underdeveloped countries, the usual precautions should be taken regarding ingestion of unpurified drinking water and uncooked fruits and vegetables.

Immunizations

Four immunizations using vaccines containing live viruses are relatively contraindicated during pregnancy. These are measles, mumps, rubella, and yellow fever. However, in certain circumstances, risk/benefit assessment may lead to receiving the immunizations. The risks for the fetus from the administration of rabies vaccine are unknown and each case must be considered individually, since the indications for prophylaxis are not altered by pregnancy. Tetanus toxoid, if needed, is acceptable in pregnancy. Flu vaccine is recommended for pregnant women. Women who are receiving hepatitis B vaccine may continue receiving it during pregnancy. Immune globulin for acute exposures to hepatitis A is considered safe also.

PREPARING FOR CHILDBIRTH

Prenatal Education Classes

Few empiric studies have examined the impact of prepared childbirth education on perinatal outcomes, but such education is generally believed to be helpful and valuable. The landmark volume *Birth of a Child* by Grantley Dick-Read, published in 1958, changed the modern face of childbirth education. Formal childbirth classes evolved rapidly in a multiplicity of settings. The goals of these classes are to educate and to answer questions in an environment conducive to the woman's new state of being, so that both the patient and her partner have the opportunity to decrease their anxiety level and increase their knowledge. Classes are designed to be an empowering experience, helping the parent(s) become a part of the process rather than the object of the actions of others. The content of childbirth classes varies but usually includes topics such as normal labor and delivery, anesthesia, breathing and concentration techniques, obstetric complications and interventions, and obstetric operations. Many instructors encourage patients to formulate a “birth plan” and to put this in writing and share it with their clinician. This can facilitate communication between the parents themselves and between patient and caregiver.

Certain decisions are best considered and made prior to delivery. These include issues such as breast-feeding, postpartum contraception, return to work, and circumcision of a male infant. It is helpful if parents are given information in a nonjudgmental, nonthreatening environment so that they may make appropriate, well-considered, and informed decisions.

Signs of Labor

The final element in preparing for childbirth is knowledge of when labor is occurring and when it is appropriate to notify the health care provider. Patients should be given a 24-hour phone number to call for assistance. A course of action should be made clear to the patient and her partner. As has been reinforced throughout pregnancy, any warning signs of potential adverse outcomes mandate an immediate telephone call.

CONCLUSION

The future of effective and efficient prenatal care in the United States depends largely on access, our ability to demonstrate clear benefit for patients and the incorporation of evidence-based data and practices that have well-defined outcomes and use cost-effective methods.

Of equal importance to the content of prenatal care is the manner in which it is delivered. A crucial determinant of effective prenatal care is the clinician–patient relationship. Virtues of trust, honesty, and ethical treatment are integral to achieving the goal of prenatal care, which emphasizes allowing patients to be active in their health care. The skill of a caregiver can prevent the alienating experience of a bad outcome, but caregivers who look for a solution to their own powerlessness in the domination of patients or the domination of natural processes can make good outcomes alienating experiences for their patients. Caregivers must be aware of cultural diversity and assess the care they give, not in terms of their own needs or the needs of a profession or a medical organization, but in terms of those who have entrusted them with care.

SUMMARY POINTS

- Pregnancy is a normal physiologic event in a woman's life and most pregnancies are normal. Pregnancy is a time of significant psychological transitions that are experienced in varied ways by each mother.
- The preconception visit is a focused visit that allows systematic identification of potential risks and the implementation of early interventions.
- The appropriate content of the first prenatal visit and subsequent prenatal care is contained in formalized published forms.
- A firm scientific foundation for the content and timing of prenatal care visits and the relationship of such care to maternal and newborn outcomes is under continued review.
- Pregnancy is a time of change, expectation, anticipation, concern, and uncertainty for many women and their families; the provision of direct, concise, and accurate information in a compassionate and reassuring manner by the clinician is therapeutic.
- Each prenatal visit should evaluate and address interval history, maternal changes, fetal growth, specific interventions, and general patient concerns.

SUGGESTED READINGS

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Appendix I

Figure. ACOG ANTEPARTUM RECORD (FORM A).

Figure. ACOG ANTEPARTUM RECORD (FORM B).

Figure. ACOG ANTEPARTUM RECORD (FORM C).

Figure. ACOG ANTEPARTUM RECORD (FORM D).

Figure. ACOG ANTEPARTUM RECORD (FORM E).

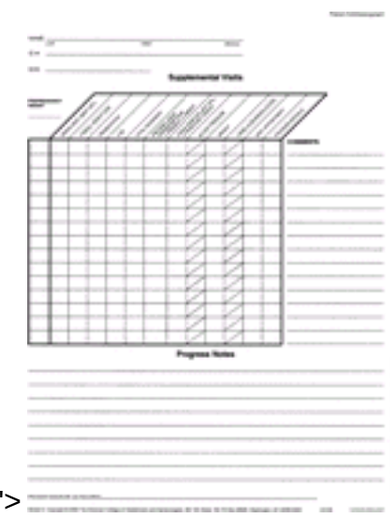

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Figure. ACOG ANTEPARTUM RECORD (FORM F).

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Figure. OBSTETRIC MEDICAL HISTORY.

Appendix II

The following table shows the body mass index (BMI) for weight and height. From the bottom line: Every number below the first dark line is “underweight.” Every number between the first and second dark line is “nomal weight.” Every number between the second and third dark line is “overweitht.” The rest of the chart above the third dark line represents “obese.”

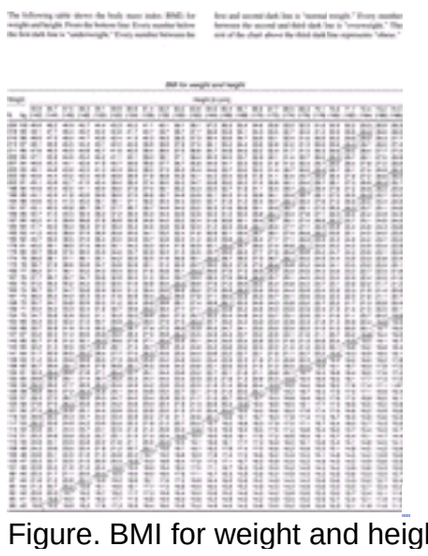

Figure. BMI for weight and height.

Appendix III

Maternal and child health care currently accounts for a large proportion of health care dollars spent annually in the United States. This is due to the large number of patients and the numerous procedures performed during pregnancy and the first months of life.

The effectiveness of prenatal care is still often measured in terms of finite outcomes such as maternal and infant mortality. While these end points do not take into account such parameters as patient satisfaction, emergency interventions, length of hospitalization, and degree of access, they are used as a crude measure of quality of care of mothers and infants and are often cited in comparisons between states and countries, even when the actual data and methodologies for obtaining them are diverse and incomparable. The definitions currently used by the National Center for Health Statistics when collecting data on maternal and infant mortality and morbidity are given here.

- Live birth: the complete expulsion or extraction from the mother of a product of human conception, regardless of the duration of the pregnancy, that then breathes or shows any other evidence of life, whether or not the umbilical cord has been cut or the placenta is attached.
- Fetal death (stillbirth): death before the complete expulsion or extraction from the mother of a product of human conception, regardless of the duration of the pregnancy. This definition excludes terminations of pregnancy.
- Early neonatal death: death of a live-born infant during the first 7 days of life.
- Late neonatal death: death of an infant after 7 days but before 29 days of life.
- Fetal death rate: the number of stillborn infants per 1000 infants born.
- Neonatal mortality rate:the number of infant deaths before 29 days of life per 1000 live births.
- Perinatal death rate: a combination of fetal and neonatal deaths per 1000 total births.
- Birth rate: the number of births per 1000 members of the population.
- Fertility rate: the number of live births per 1000 female members of the population between the ages of 15 and 44 years.
- Maternal mortality: the death of a woman from any cause related to or aggravated by pregnancy or its management, regardless of duration or site of pregnancy (but not from accidental or incidental causes), occurring during the pregnancy or up to 42 days after the pregnancy. It includes direct and indirect obstetric deaths.
- Direct obstetric death: the death of a woman from obstetric complications of pregnancy, labor, or the puerperium, resulting from interventions, omissions, or treatment, or from a chain of events resulting from any of these.
- Indirect obstetric death: the death of a woman resulting from a previously existing disease or a disease that developed during pregnancy, labor, or the puerperium that was not related to direct obstetric causes, although the physiologic effects of pregnancy were partially responsible for the death.
- Maternal mortality rate: maternal deaths per 100,000 live births.

Chapter 2

Dwight J. Rouse and Elaine St. John

Normal Labor, Delivery, Newborn Care, and Puerperium

LABOR
Labor Progress
MANAGEMENT OF LABOR AND DELIVERY
Antepartum Instructions
Admission
Management of the First Stage of Labor
Management of the Second Stage of Labor
Management of the Third Stage of Labor
Management of the “Fourth Stage” of Labor
Postpartum Care
PUERPERIUM
Complications of the Puerperium
Breast-feeding
Nursing Problems
NEWBORN CARE
Immediate Assessment and Resuscitation
Meconium
The Apgar Score
General Evaluation and Treatment
Early Onset Sepsis
Hyperbilirubinemia and Discharge Planning
SUMMARY POINTS

SUGGESTED READINGS

LABOR

Labor is defined as regular uterine contractions that lead to effacement and dilation of the cervix. If the estimated gestational age is accurate, labor usually begins within 2 weeks of the estimated date of confinement (EDC), which is 280 days (i.e., 40 weeks after the first day of the last menstrual period). However, because only 3% to 5% of patients actually deliver on their EDC, it has been suggested that EDCs be framed in terms of a range (e.g., from 38 to 42 weeks). Conceptualizing EDCs in this manner, it has been argued, might lessen the pressure for date-predicated interventions such as induction of labor.

Prior to the onset of true labor, there is a general softening and stretching of pelvic ligaments and the soft tissues of the vagina. There is also shortening and dilation (ripening) of the cervix. Braxton Hicks contractions (weak, irregular, regional contractions) usually occur for weeks before the onset of actual labor. The normal stimulus for the biochemical cascade that finally results in labor is unknown. Corticotropin-releasing factor (CRF) plays a role. It is released into the maternal circulation early in the second trimester, and its concentration rises exponentially as pregnancy advances. CRF regulates the secretion of adrenal cortisol, which can increase the strength of uterine contractions. CRF also stimulates production of oxytocin by the fetus and prostaglandins by the placenta.

Other factors probably play a role. For instance, progesterone inhibits and estrogen stimulates uterine contractility. Like CRF, estrogen also stimulates the production of oxytocin receptors in the uterus. Thus, as progesterone levels decline near term, estrogen may stimulate myometrial contractility. Mechanical stretch can also increase uterine contractility, as occurs with twin gestations and pregnancies complicated by polyhydramnios. Once labor is initiated, the process is thought to involve multiple positive feedback loops. For instance, contractions stretch the cervix. Stretching of the cervix elicits a reflex contraction by the uterus, pushing the fetal head against the cervix to stretch it more, and so on.

Labor Progress

Clinically recognizable labor is typically divided into three stages, each with statistically derived normative rates and durations. Many normative labor values were derived from the investigations of Emanuel Friedman, who studied thousands of normal and abnormal labors and plotted cervical dilation and fetal descent against time. The resulting graphic labor curve can be used to recognize individual labor patterns which deviate from normal and to guide the nature and timing of interventions. In a World Health Organization study of 35,484 women, use of a partogram (Fig. 2.1) and an agreed upon labor management protocol was associated with a reduction in the percentage of prolonged labors, the proportion of labors requiring augmentation, and postpartum sepsis.

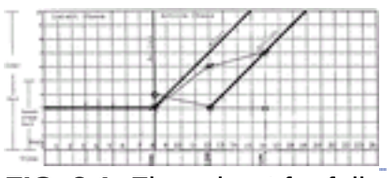

FIG. 2.1. Flow sheet for following labor progress. (From Chua S, Arulkumaran S. Poor prognosis in labor, including augmentation, malpositions and malpresentations. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. High risk pregnancy, second ed. London: Harcourt Brace, 1999:1105; with permission.)

The first stage of labor begins with the onset of regular uterine contractions and ends with complete cervical dilation. This stage is further divided into three phases: latent, active, and deceleration, although the existence of the last phase has been questioned. During the latent phase, contractions become progressively stronger, longer, more frequent, and better coordinated. The mother's discomfort may be minimal or it may be severe. The latent phase is considered prolonged if it lasts longer than 20 hours in a nullipara, or 14 hours in a parous woman. The active phase commences when the slope of cervical dilation reaches its maximum. Typically, and especially in the nullipara, this occurs at 3 to 4 cm of dilation. During the active phase, contractions are usually strong and regular, occurring every 2 to 3 minutes. The active phase ends with complete (10 cm) cervical dilation. This phase of labor is generally quite painful. The length of the active phase is more predictable than the latent, lasting, on average, about 5 hours in nulliparas, and 2 hours in multiparas. Without labor epidural analgesia, respective minimum (fifth percentile) rates of dilation are 1.2 cm per hour and 1.5 cm per hour. With epidural, the rates are slower. Progressive descent of the fetal head into the maternal pelvis occurs to a variable degree during the active phase.

The second stage is defined as the period from complete cervical dilation to complete delivery of the baby. During the second stage, contractions are strong and regular, with a frequency of every 1 to 3 minutes. The baby's head descends more deeply into the pelvis, and in women without regional anesthesia, each contraction stimulates a strong urge to push. In combination, uterine contractions and maternal expulsive efforts effect delivery of the baby. The second stage typically lasts about 50 minutes in nulliparas and 20 minutes in multiparas, but is often longer in women with regional anesthesia. The third stage of labor is defined as the period from delivery of the baby to delivery of the placenta. Regardless of parity, the third stage of labor is usually brief (under 10 minutes). The third stage of labor is prolonged if it persists beyond 30 minutes.

The three classic determinants of the progress of labor are:

- *Power*—uterine contractions and, in the second stage, maternal expulsive efforts
- *Pelvis*—the bony pelvis and the overlying maternal soft tissues
- *Passenger*—the fetus and its lie, presentation, and position.

The power of labor can be assessed clinically by uterine palpation or with the use of an intrauterine pressure catheter. Assessment of the pelvis involves manual

evaluation of the pelvic inlet, midpelvis, and outlet.

- *Pelvic inlet*—The transverse diameter of the pelvic inlet averages 13 cm. It cannot be measured clinically, but a narrow transverse inlet is a very rare cause of abnormal labor progress. The anteroposterior (AP) diameter of the inlet is more important. It is estimated clinically by determining the distance between the lower margin of the symphysis pubis and the sacral promontory (Fig. 2.2). This value is known as the diagonal conjugate. The obstetric conjugate—or true AP diameter—is 1.5 to 2.0 cm shorter. The pelvic inlet is an adequate size for a normal fetus if the diagonal conjugate is 12 cm or greater.

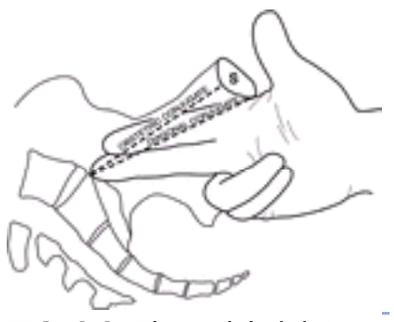

FIG. 2.2. The pelvic inlet anteroposterior diameter is estimated from the diagonal conjugate.

- *Midpelvis*—The specific diameters of the midpelvis cannot be measured clinically. Contraction of the midpelvis is suspected if the ischial spines are quite prominent (or the sacrosciatic notch is less than two fingerbreadths wide), the pubic arch is narrow, the pelvic side walls converge, or the sacral concavity is quite shallow (Fig. 2.3).

FIG. 2.3. The transverse diameter of the midpelvis is estimated by evaluating the distance between the ischial spines.

- *Pelvic outlet*—The transverse diameter of the pelvic outlet should be greater than 8 cm. This diameter can be estimated by placing a fist on the perineum to measure the distance between the ischial tuberosities. The AP diameter is estimated by noting the angle made by the pubic rami. A contracted outlet is rarely the sole cause of dystocia; however, it is often associated with midpelvis contraction.

Consideration of these measurements allows assignment to one of the various pelvic types, and thus an appreciation of how and where labor may be stalled if the pelvis is not favorable for childbirth (Fig. 2.4). Careful evaluation of the midpelvis is most important, as those women found to have a contracted midpelvis are poor candidates for forceps-assisted vaginal delivery. However, because the fetal skull has the ability to mold, borderline pelvimetry is not a contraindication to a trial of labor.

FIG. 2.4. Pelvic types. **A:** Gynecoid pelvis—most common, round to oval inlet, ischial spines not prominent, curved sacrum, wide pubic arch; best suited for childbearing. **B:** Android pelvis—heart-shaped inlet, narrow midpelvis with anterior sacrum, prominent ischial spines, convergent side walls, narrow pubic arch. **C:** Platypelloid pelvis—least common, decreased anteroposterior dimensions at all levels with wide transverse dimensions. **D:** Anthropoid pelvis—narrow inlet, midpelvis, and pubic arch.

From the perspective of the passenger (fetus), labor involves movement progressively downward through the pelvis by the following *cardinal movements* (Fig. 2.5).

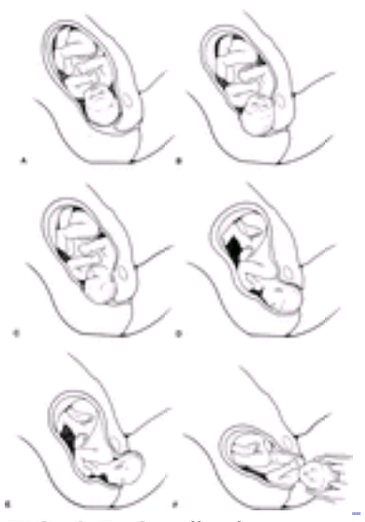

FIG. 2.5. Cardinal movements of labor. **A:** Engagement. **B:** Flexion. **C:** Descent and internal rotation. **D, E:** Extension. **F:** External rotation.

- *Engagement* occurs days to weeks prior to labor for primigravidas and at the onset of labor for multigravidas.
- *Flexion* of the neck allows the occiput to lead, thus the smallest possible diameter of the fetal head travels downward through the pelvis.
- *Descent* is progressive as the cervix thins, and the lower uterine segment lengthens.
- *Internal rotation* occurs during descent. The vertex rotates from transverse to either a posterior or anterior position to pass the ischial spines.
- *Extension* occurs as the fetal head distends the perineum and the occiput passes beneath the symphysis.
- *External rotation* of the head after delivery to a transverse position allows the shoulders to rotate internally to an AP position.

MANAGEMENT OF LABOR AND DELIVERY

Antepartum Instructions

All women should be advised of the circumstances that should prompt them to seek evaluation for labor. These include (a) possible rupture of the membranes, (b) regular uterine contractions, (c) bleeding per vagina, and (d) back, pelvic, or abdominal pain greater than they are anticipating. Nulliparas are more likely to confuse false labor or Braxton Hicks contractions with true labor. Although distinguishing the two can be problematic, the contractions of false labor tend to be irregular both in intensity and in interval, and the associated discomfort, if any, is typically limited to the lower abdomen and groin. The contractions of false labor usually abate with time, analgesia, or sedation. With true labor, the contractions progressively increase in intensity. They occur every 2 to 4 minutes and cause discomfort in the abdomen and back with the associated sensation of increasing pelvic pressure. For many women labor will be preceded, by several hours or even days, by the passage of bloody show (a small amount of bloody mucous discharge from the cervix). In 10% of pregnancies, chorioamnion rupture precedes the onset of labor, and amniotic fluid leaks through the cervix and out of the vagina. Optimal management for such women has recently been clarified. A randomized trial of over 5000 women with

prelabor rupture of membranes at term demonstrated that induction of labor with oxytocin (as opposed to expectant management, or induction with prostaglandins) resulted in the lowest rate of neonatal infection and maternal postpartum fever, and did not increase the cesarean delivery rate. In many cases, the only way to confirm the diagnosis of true labor is observation over several hours and examination of the cervix for change.

Admission

If the woman is having contractions, their time of onset and frequency should be recorded. Questions should focus on spontaneous rupture of the membranes, presence or absence of bleeding, and fetal activity. A review of the patient's prenatal record should take specific note of her EDC and its reliability, as well as her past medical and surgical history, and details of previous pregnancies: number, gestation, fetal size, duration of labor, and any complications (e.g., shoulder dystocia). Prenatal laboratory data should be reviewed, including blood type, hematocrit, Rh_0(D) immune globulin requirements, VDRL test, rubella immunity, and hepatitis and human immunodeficiency virus (HIV) status.

The admission physical examination should include vital signs (temperature, pulse, blood pressure), auscultation of the heart and lungs, and a brief neurologic examination. Leopold maneuvers should be performed to assess fetal position (Fig. 2.6), and the uterus should be palpated, or a tocodynamometer employed, to determine the frequency, intensity, and duration of uterine contractions. Fundal height should be evaluated and a clinical assessment of fetal weight should be performed. Fetal heart tones should be assessed, either by auscultation or via electronic monitoring, with specific attention to the response of the fetal heart rate (FHR) to the uterine contractions.

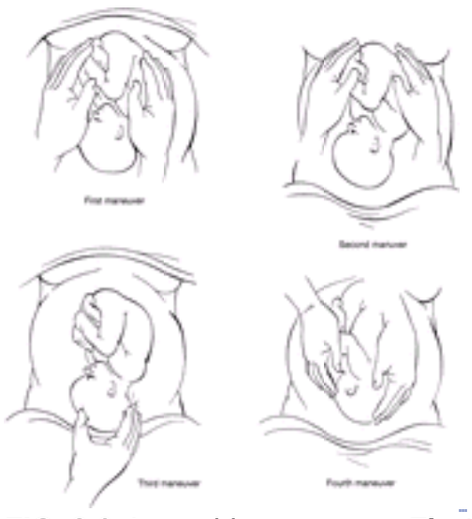

FIG. 2.6. Leopold maneuvers. **First maneuver:** The uterine contour is outlined; the fundus is palpated, allowing identification of the fetal parts. **Second maneuver:** By palpation of the sides of the maternal abdomen, the location of the fetal back is determined. **Third maneuver:** The presenting part is grasped, identified, and evaluated for engagement. **Fourth maneuver:** With palpation toward the pelvis, the identity of the presenting part is confirmed, and flexion or extension of the fetal head is evaluated.

The vulva should be examined for herpetic lesions. If membrane rupture is suspected, it should be confirmed (or ruled out). Several signs support rupture, including pooling of amniotic fluid in the vagina (observed by sterile speculum examination) or direct visualization of fluid leakage through the cervix. The pH of the pooled fluid can be checked with nitrazine paper, which turns blue in the presence of amniotic fluid (but also in the presence of blood), and an air-dried sample (on a slide) of the fluid can be examined under a microscope for the characteristic “fern” pattern that confirms the presence of amniotic fluid (Fig. 2.7). Since cervical mucus and maternal serum can demonstrate a fern pattern, care must be taken in collection of this sample. Palpation of the cervix includes attention to the following:

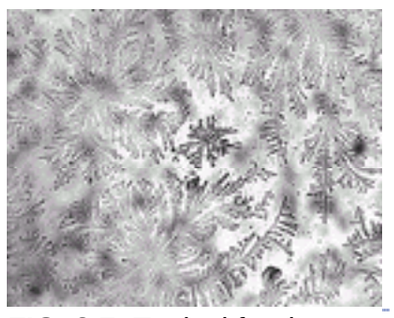

FIG. 2.7. Typical fern pattern of dried amniotic fluid (400×). (Original photo, courtesy of Dr. Dwight Rouse.)

- assessment of consistency (soft or firm)
- degree of effacement (Fig. 2.8)

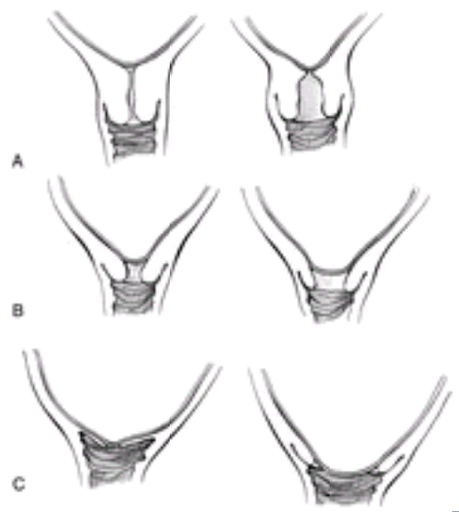

FIG. 2.8. Degree of cervical effacement. **A:** No effacement. **B:** 75% effacement. **C:** 100% effacement.

- dilation of the cervical os
- location of the cervical os with respect to the vaginal axis (posterior, midplane, or anterior).

The presenting part should be identified by palpation. Station is determined by noting the position of the fetal presenting (bony) part relative to the ischial spines (Fig. 2.9). The fetal position is determined by noting the orientation of occiput relative to the maternal pelvis (Fig. 2.10). The attitude of the fetal head is the position of the fetal head relative to the fetal chest and any lateral flexion of the head (Fig. 2.11, Fig. 2.12 and Fig. 2.13). Pelvimetry should be performed as previously described.

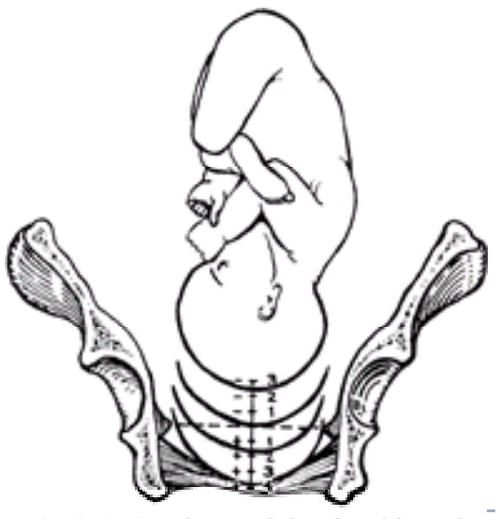

FIG. 2.9. Stations of the fetal head. At the 0 station, the fetal head is at the bony ischial spines and fills the maternal sacrum. Positions above the ischial spines are referred to as -1 through -5, referring to the number of centimeters that the head is positioned above the spines. As the head descends past the ischial spines, the stations are referred to as +1 through +5 (head visible at the introitus).

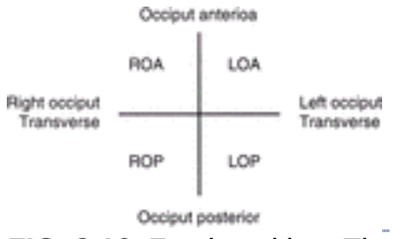

FIG. 2.10. Fetal position. The orientation of the presenting vertex within the maternal pelvis.

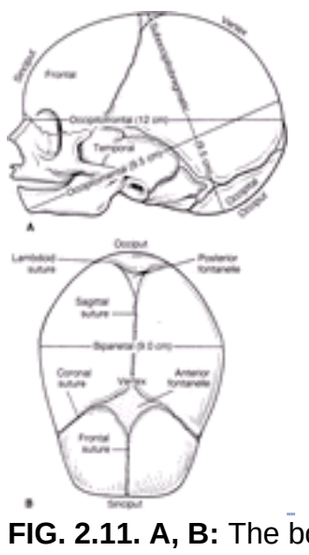

FIG. 2.11. A, B: The bones, sutures, fontanelles, and clinically important diameters of the fetal head.

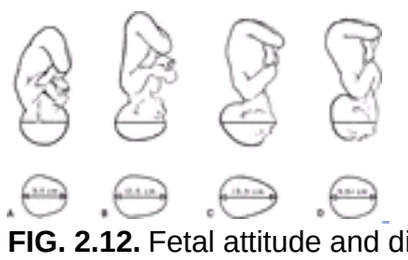

FIG. 2.12. Fetal attitude and dimensions of a term-size fetus. **A:** Full flexion presents the smallest circumference of the fetal head to the narrower planes of the pelvis. **B:** Military attitude usually changes to full flexion with descent into the pelvis. **C:** Brow presentation usually converts to full flexion or a face presentation, as the occipitomental diameter is too large for all except the largest pelves to accommodate. **D:** Face presentation shows dimensions that allow descent through the pelvis, unless the chin is posterior. Persistent mentum posterior must be delivered by cesarean section.

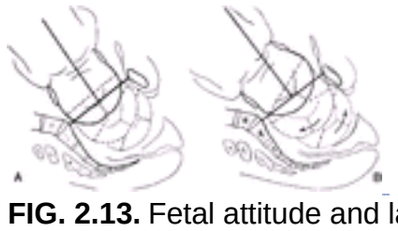

FIG. 2.13. Fetal attitude and lateral flexion of the fetal head. **A:** Synclitism—The plane of the biparietal diameter is parallel to the plane of the inlet. **B:** Asynclitism—Lateral flexion of the fetal head leads to anterior parietal or posterior parietal presentation.

In women at term with rupture of the membranes prior to the onset of labor, it is appropriate to defer digital examination of the cervix until they are in active labor, to decrease the risk of chorioamnionitis. It is important, however, to confirm the baby's presentation, and an ultrasound examination should be performed if the presentation is not clear.

Management of the First Stage of Labor

A variety of management approaches to the first stage of labor have been employed and evaluated, and no single approach is clearly superior. The primary management goals are to monitor fetal well-being, support the woman through what can be a lengthy, uncomfortable period, and offer intervention as it may become appropriate. Support of the woman through labor includes allowing her to assume whatever position is most comfortable (or least uncomfortable) for her. All forms of monitoring, be it intermittent auscultation, external fetal monitoring, or internal monitoring, can be accomplished in a lying, sitting, or upright position. In most normal labors, the only time a healthy woman's movements must be limited is after she has received analgesia and would not be steady on her feet. Uterine blood flow is maximal in the lateral recumbent position, and this should be the initial position adopted if there is concern over fetal well-being. Because of impaired venous return and reduced maternal cardiac output, the supine position is usually best avoided. With these considerations in mind, women should be free to position themselves as they like.

Vital signs should be monitored at least every 4 hours, or more frequently as clinically indicated. By consensus of the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists (ACOG), all women whose 35-37 week rectovaginal group B streptococcus (GBS) culture was positive should receive intrapartum antibiotic prophylaxis for the prevention of early onset neonatal GBS disease. Acceptable prophylactic antibiotic regimens include intravenous penicillin G 5 million units initially, and then 2.5 million units every four hours until delivery, or intravenous ampicillin 2 gm initially, followed by 1 gm every 4 hours until delivery. For women allergic to penicillin, clindamycin, erythromycin, vancomycin, or, in women without a urticarial or anaphylactoid response to penicillin, a first

generation cephalosporin may be substituted.

Irrespective of rectovaginal culture results, women with GBS bacteriuria during the pregnancy and those who have previously delivered an infant with early onset GBS disease should also receive antibiotic prophylaxis. If an appropriate rectovaginal GBS culture was not performed or is not available, prophylaxis should be based on the following risk factors: threatened pre-term delivery (< 37 weeks), GBS bacteriuria at any time in the current pregnancy, fever (= 38.0°C), rupture of membranes for at least 18 hours, or delivery of a prior infant with early onset GBS disease. Separate from the issue of GBS prophylaxis, if a woman develops an intrapartum fever, defined by some authorities as a temperature of at least 37.8°C (100.0°F) and by others as at least 38.0°C (100.4°F), evaluation and treatment for chorioamnionitis may be indicated.

Placement of an intravenous line is not necessary for all women in labor. However, women who are dehydrated may benefit from intravenous hydration. It seems prudent to establish intravenous access for administration of fluids and medication, should they be necessary, in women at increased risk of postpartum hemorrhage (i.e., those with prior postpartum hemorrhage, prolonged labor, or overdistended uterus).

In most women, laboratory evaluation upon presentation in labor can be minimized. Although in many units it is customary to perform routine admission blood type and antibody screen, hemoglobin and hematocrit, and syphilis serology, the necessity and cost-effectiveness of repeating these tests in healthy women who have received adequate prenatal care is debatable. Certainly, if a woman has hypertension on admission, she should be evaluated for possible preeclampsia. In women who have not had any prenatal care, it is advisable to order a hemoglobin and hematocrit, blood type, and Rh status, an antibody screen, a rubella titer, and syphilis, hepatitis, and HIV screens.

The benefits of continuous caregiver support (by nurses, midwives, or laypeople) throughout labor have been established by multiple randomized trials. Salutary effects of such support include reduced pain medication requirements, lowered rates of operative vaginal and cesarean delivery, and a diminution in the frequency of 5-minute Apgar scores below 7. Thus, to the extent possible, all women should have access to continuous caregiver support throughout labor.

No evidence-based criteria are available to direct how often the cervix should be examined during the first stage of labor. In general, frequent examinations in the latent phase of labor serve little purpose. They may unrealistically increase a woman's expectation for progress in labor and in addition, are uncomfortable and increase risk for infectious morbidity. However, during observation, if the membranes rupture, the cervix should be examined and the FHR evaluated if the presenting part was not well applied to the cervix on previous examination. These measures should enhance the detection of umbilical cord prolapse. In the active phase of labor, monitoring the progress of labor with cervical examinations every 2 hours allows identification of those women who are not making normal progress and who should therefore be evaluated for oxytocin augmentation.

During labor, the FHR should be monitored. For most women, both intermittent auscultation and intermittent or continuous electronic monitoring are acceptable (see Chapter 9). While artificial rupture of membranes (amniotomy) may shorten the duration of labor by 1 to 2 hours and reduce the use of oxytocin, it may also increase the risk of cesarean delivery by 25%. Thus, in most women, amniotomy should be reserved for such indications as placement of internal fetal monitoring devices for better assessment of the FHR pattern, or for abnormal labor progress. To avoid umbilical cord prolapse, amniotomy is best performed when the presenting part is well applied to the cervix, and preferably during a contraction (or with fundal pressure) to minimize the chance for dislodging the fetal head. Although typically performed with a thin, plastic, hook-ended tool designed specifically for the purpose, amniotomy may be achieved simply by placing a fetal scalp electrode. In cases of excess amniotic fluid, or when the vertex is not well applied, a spinal or pudendal block needle may be used to create a small opening in the membranes to allow the gradual egress of amniotic fluid, thereby avoiding umbilical cord prolapse or the rapid decompression of the uterus and the associated risk of placental abruption.

Meconium staining of the amniotic fluid occurs in up to one-fifth of deliveries. Meta-analysis of randomized trials performed in settings of standard perinatal surveillance demonstrates that with moderate or severe meconium staining, amnioinfusion of 500 to 1000 mL (or more, depending on the protocol) of sterile saline into the uterus (through an intrauterine catheter) will reduce variable heart rate decelerations and may lower the risk of cesarean delivery. In settings of limited perinatal surveillance, amnioinfusion reduces the risk of meconium aspiration syndrome, neonatal hypoxic ischemic encephalopathy, neonatal ventilation or intensive care unit admission, and perhaps perinatal mortality.

Management of the Second Stage of Labor

The onset of the second stage of labor with complete dilation of the cervix is usually noted by the woman as the presenting part descends into the vagina and she experiences the urge to push with contractions. However, regional anesthesia may partially or completely blunt this urge. The cervix should be examined at this time to confirm complete dilation, and the position and station of the presenting part should be ascertained. Whether nulliparous women with regional anesthesia should begin expulsive efforts in the absence of an urge to push was the subject of a multicenter, randomized clinical trial. In the trial, women allocated to immediate pushing were less likely to have intrapartum fever (4.5% vs. 8.5%). Moreover, their second stages were one hour shorter. However, difficult deliveries (defined as midpelvic operative vaginal deliveries, low-pelvic rotational deliveries, or second stage cesarean delivery) were less common (18% vs. 23%) in the delayed pushing group, who were instructed to not push until the urge was irresistible or the head was on the perineum. Neonatal outcomes were equivalent between the groups. This trial thus supports individualization in the timing of maternal expulsive efforts.

Support of a woman in the second stage involves allowing her to find the most comfortable and effective position for pushing, as well as encouraging her efforts. Preparations for delivery should be made when the presenting part begins to distend the perineum and often sooner for multigravidas. Local or pudendal anesthesia, if necessary, should be administered at this time.

An episiotomy is an incision in the perineum used to facilitate vaginal delivery. It is useful for patients in whom the perineum does not readily stretch and when delivery must be expedited. In the past, routine episiotomy was advocated to prevent subsequent pelvic relaxation; however, there is no evidence that it does so. Meta-analysis of randomized episiotomy trials, in which restrictive episiotomy use (˜ 30% of women underwent episiotomy) was compared to liberal use (˜70% episiotomy rate), reveals the following. Restrictive use of episiotomy lowers the risk of posterior perineal trauma, lessens the need for suturing, and is associated with fewer healing complications. However, restrictive use of episiotomy increases the risk of anterior perineal trauma. There is no difference between the two policies in severe vaginal or perineal trauma, or subsequent dyspareunia, urinary incontinence, or perineal pain.

There are two basic types of episiotomy: midline and mediolateral. The benefits of a midline episiotomy include anatomic end results, easy repair, and lower incidence of postpartum pain or dyspareunia. A mediolateral episiotomy is less likely to extend into the anal sphincter or rectal mucosa, but is generally believed to result in more pain, dyspareunia, and excessive blood loss. Episiotomy should not be performed until delivery is imminent. A midline incision is made with scissors from the midpoint of the posterior fourchette directly backward toward the rectum (Fig. 2.14). The midline episiotomy is subdivided as follows:

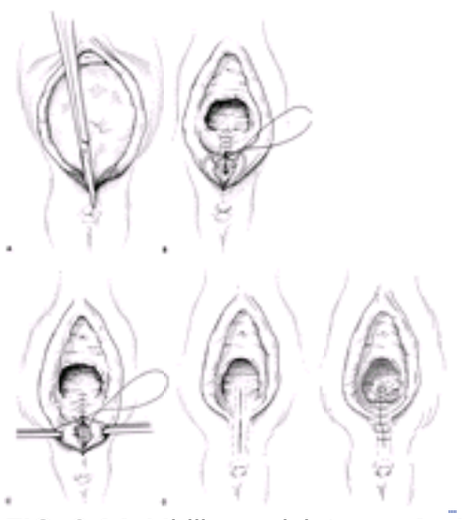

FIG. 2.14. Midline episiotomy. **A:** As the fetal head distends, with the perineum under adequate anesthesia, the episiotomy is cut through the perineal body and the tissues of the vagina and the rectovaginal septum. **B:** The episiotomy is repaired by reapproximating the vaginal mucosa in a running fashion with a delayed absorbable suture. **C:** The submucosal tissue of the vagina and the subcutaneous tissue and fascia of the perineal body are then closed. **D:** The skin is then reapproximated with a running subcuticular suture.

- first degree—through the mucosa only

- second degree—through the mucosa and subcutaneous tissues, including the muscles of the perineal body
- third degree—into or through the anal sphincter
- fourth degree—through the rectal mucosa.

A mediolateral incision is made with scissors from the midpoint of the posterior fourchette at a 45-degree angle laterally on either side.

Regardless of use of an episiotomy, tears and extensions into the rectum are best prevented by keeping the baby's head well flexed until the occiput passes beyond the subpubic arch. As the vertex appears beneath the symphysis, the perineum is supported by direct pressure from a draped hand over the coccygeal region. As the head delivers, it will rotate to a transverse position; the mother should be encouraged to continue to push to achieve delivery of the anterior shoulder. A quick evaluation for the presence of the umbilical cord around the baby's neck (nuchal cord) should be carried out. A nuchal cord can usually be slipped around the baby's head. Occasionally, it must be double-clamped and cut if it is too tight to reduce. Maternal pushing efforts can be assisted by placing gentle downward traction on the baby's head. With delivery of the anterior shoulder, a moment can be taken to bulb suction the baby's nose and mouth. Renewed pushing by the mother in combination with gentle upward traction by the obstetrician will achieve delivery of the posterior shoulder. The baby's body generally delivers easily following the shoulders. Care must be taken to support the baby's head and ensure that the baby does not slip from one's grip. After confirmation of good respiration and normal heart rate (easily checked at the cord insertion at the umbilicus), the baby may be given to the mother to cradle. The cord is then double-clamped and cut, and cord blood collected. The baby should be dried and wrapped soon following delivery to maintain its body temperature.

Management of the Third Stage of Labor

The third stage of labor begins following the delivery of the baby and ends with the delivery of the placenta. Signs of spontaneous placental separation include an apparent lengthening of the umbilical cord, a gush of vaginal bleeding, and a change in shape of the uterus from discoid to globular along with a rise in fundal height. Active management of the third stage of labor, which involves prompt umbilical cord clamping and cutting, administration of an oxytocic agent, and gentle umbilical cord traction, reduces maternal blood loss and the frequency of postpartum hemorrhage, and lessens the risk that the third stage will be prolonged. Cord traction should be used only against fundally applied counter-traction (Fig. 2.15) to lessen the potential for uterine inversion and catastrophic hemorrhage. If at any time heavy bleeding occurs during the third stage of labor or if the placenta is not delivered within 30 minutes of the birth, the placenta should be manually removed. The anesthesiologist should be alerted at this time, as general anesthesia may be required for women who have no regional anesthesia, and curettage may be necessary if the placenta does not readily separate from the uterine wall. Manual removal is accomplished by developing a cleavage plane with the intrauterine hand between the maternal surface of the placenta and the uterine wall, while simultaneously fixing the uterus with the abdominal hand, and progressively peeling the placenta free. To ensure complete placental removal, a 4-inch by 4-inch gauze may be wrapped around the hand and used to abrade the uterine wall. The placenta should then be carefully inspected for cord insertion, confirmation of a three-vessel cord (infants with only two cord vessels have a higher rate of malformations and warrant closer evaluation by the newborn caregiver), and completeness of the placenta and membranes. If any portion of the placenta or the membranes is missing, the uterine cavity should be manually explored. Some advocate routine exploration of the uterine cavity to reduce the risk of infection and bleeding from retained placental fragments. In most women, especially those without regional anesthesia, the benefit of manual exploration is outweighed by the discomfort it causes, as well as the increased risk for uterine infection.

FIG. 2.15. Stage three of labor: delivery of the placenta. **A:** Spontaneous separation of the placenta is confirmed. **B:** With gentle traction on the umbilical cord and suprapubic palpation of the fundus, the placenta and membranes are delivered. **C:** If spontaneous separation of the placenta does not occur or bleeding ensues, the placenta is manually separated from the wall of the uterus and removed.

The uterus should be frequently palpated following delivery of the placenta to ensure that it remains well contracted. Oxytocin, 10 to 20 U administered intramuscularly or as a dilute intravenous solution, has been demonstrated to decrease the incidence of postpartum hemorrhage secondary to uterine atony. The birth canal, including the cervix, vagina, and perineum should be inspected for lacerations requiring repair. During this time, under most circumstances and after drying and swaddling, the baby should be kept with the family and, for women planning to breast-feed, placed to the breast to nurse within the first 10 to 20 minutes after birth. This first suckling not only stimulates endogenous oxytocin release but also begins the process of milk production and successful breast-feeding.

Management of the “Fourth Stage” of Labor

Because many complications of birth occur or become evident during the first hour after delivery, this time has been referred to as the “fourth stage” of labor, though it is not officially defined as a labor stage. The new mother should be seen at least every 15 minutes by a trained labor and delivery nurse to assess vital signs and look for evidence of uterine atony or postpartum hemorrhage. The perineum should be inspected for any signs of hematoma formation, which may be signaled by inordinate vulvar or rectal pain. The newborn should undergo its initial assessment at this time and be observed closely for any signs of compromise.

Postpartum Care

After the first 24 hours, postpartum recovery is rapid. A regular diet can be offered to most women as soon as they request food, sometimes shortly after delivery. Because of their risk to require general anesthesia, it is prudent to delay feeding women who have experienced, or are at risk for, significant postpartum hemorrhage. Full ambulation is encouraged as soon as possible. Exercises to improve tone and strengthen abdominal muscles may be started after 1 day. The perineum should be cleansed with warm water two or three times daily after voiding or bowel movements. Both showers and baths may be taken, but vaginal douching is prohibited during the early puerperium to avoid the risk of introducing infection into the uterus. Pain from an uncomfortable perineal laceration or episiotomy can be relieved with warm sitz baths and an analgesic (e.g., acetaminophen, 650 mg, with or without codeine or ibuprofen, 600 to 800 mg) (Table 2.1).

Oxytocin, 10 U i.m.
Bed rest and vital signs every 15 min for 1 h postpartum then every 4 h
Regular diet
Ambulation as tolerated when stable
Ice pack to the perineum
Tucks to the perineum as required
Sitz baths t.i.d. and at bedtime, as needed
Maintain i.v. line (if present): discontinue when vital signs are stable and uterine bleeding is normal
Urethral catheterization if unable to void in 6 h
Breast binder, ice packs if not nursing
Hemoglobin and hematocrit on postpartum day 1
Type and crossmatch for $Rh_0(D)$ immunoglobulin if indicated
Medications
Vitamins: continue prenatal vitamins; additional ferrous sulfate if anemic
Pain: ibuprofen, 400–600 mg p.o. every 4–6 h, for cramping/pain
Bowels: docusate sodium, 100 mg p.o. BID, milk of magnesia, 30 mL/d p.o., as needed; bisacodyl, 10 mg p.o. or per rectum, as needed

TABLE 2.1. *Examples of orders after routine vaginal delivery: immediately postpartum*

When regional anesthesia is used, care must be taken to avoid problems with urinary retention and bladder overdistention. Women should be encouraged to void every 2 to 3 hours, even if they are not aware of any sensation of bladder fullness, as rapid diuresis may occur following delivery, especially when oxytocin is discontinued.

Prior to discharge, a hemoglobin or hematocrit should be checked if there is any concern that a woman has experienced heavier than normal postpartum bleeding, or if she entered labor significantly anemic. In addition, seronegative women should be immunized against rubella on the day of discharge. If the mother is Rh-negative, is not sensitized, and has an Rh-positive infant, she should be given $Rh_0(D)$ immune globulin to prevent sensitization from occurring. As discharge from the hospital now

occurs anywhere from 12 to 48 hours following an uncomplicated birth, most women have not begun milk production prior to their discharge. To support breast-feeding, it is critical to advise women of the availability of assistance, should they experience any difficulty with nursing. Binding and avoiding any stimulation of the breasts are advised if the mother does not plan to breast-feed. She should also take aspirin, acetaminophen, or ibuprofen if engorgement becomes uncomfortable.

The length of inpatient hospitalization following childbirth has changed remarkably over the past two decades, reflecting the decreasing risk of postpartum complications and changing medical and societal attitudes toward birth, as well as pressures from third-party payors. Numerous reports, including three randomized, controlled trials have shown early discharge, 12 to 24 hours postdelivery, *with* appropriate follow-up in the home results in a low and acceptable rate of readmission of mothers and babies. Several studies show that longer hospital stays improve maternal postpartum adjustment and breast-feeding success. Stays of 12- to 24-hours are only acceptable when patients have adequate help in the home and the community has a home care nursing program with 24-hour coverage, 7 days a week. Home care services, while not always necessary, can be very helpful and appear to increase the safety of early discharge. All women and their babies discharged within 24 hours of birth should be offered a minimum of one home visit or an appointment for outpatient follow-up in the first few days following discharge.

PUERPERIUM

The puerperium is the 6 to 8 weeks following delivery of the placenta, in which the uterus returns to its normal state. Following delivery of the placenta, the uterus rapidly contracts to half of its predelivery size. The involution that then occurs over the next several weeks is most rapid in women who breast-feed their newborns. Postpartum vaginal discharge, or lochia, changes as the uterus involutes. Initially, the discharge is grossly bloody (lochia rubra), persisting for 3 to 4 days. It then decreases in volume and changes to pale brown and becomes thinner (lochia serosa), persisting for 10 to 12 days. Finally, the discharge becomes yellowish white, occasionally tinged with blood (lochia alba), and may persist for several weeks. The total volume of lochia is about 250 mL, and women are usually encouraged to use external pads to absorb it, rather than intravaginal tampons, in order to minimize the risk of infection. When followed closely, a woman's hematocrit may actually rise due to diuresis following delivery and autotransfusion occurring as the uterus involutes. After 1 week, the uterus is firm and nontender and extends to about midway between the symphysis and the umbilicus. By 2 weeks postpartum, the uterus should no longer be palpable abdominally. The contractions of the involuting uterus may be painful, especially during the first few days following delivery. These “after pains” are usually relieved with acetaminophen or ibuprofen.

Prior to discharge, women should receive instructions regarding what they can expect during the puerperium and recommendations for activity. In general, women should be encouraged to rest as they feel necessary and gradually increase their activity following delivery. They do not need to be restricted in terms of ambulation, but should be cautioned that driving in the early postpartum may not be advisable if perineal discomfort is distracting, or would cause a delay in reaction in case of an emergency. Women can resume a regular diet, and, if nursing, should be encouraged to keep well hydrated. Perineal pain should gradually diminish. If it does not, or it worsens, women should be instructed to seek evaluation for possible infection or hematoma. Normal bladder function should resume, but women should be cautioned that they may experience some difficulty with stress and urge incontinence, which can be expected to gradually improve in the months following delivery.

Parents should receive information regarding lochia, expected volume, changes, and duration; activities; care of the breasts, perineum, and bladder; and dietary and, specifically, fluid requirements. The specific signs of complications should be stressed, including fever, chills, leg pain or swelling, episiotomy pain or drainage, and abnormal duration or amount of bleeding.

Couples should be advised that they can safely resume coitus when desired and comfortable; however, abstaining for at least 2 weeks following the birth is often recommended. They should be forewarned of potential discomfort of the perineum and problems with vaginal dryness due to atrophic vaginitis, as well as the potential for transient changes in libido related to pregnancy and delivery.

For women who are breast-feeding, ACOG has summarized hormonal contraceptive options (Table 2.2). Women who are not nursing and desire a combination oral contraceptive can safely have this method initiated 1 to 2 weeks following delivery. Long-acting progestin contraception such as medroxyprogesterone acetate (Depo-Provera) injections or levonorgestrel implants (Norplant System) can be started or placed anytime following delivery. A diaphragm should be fitted only after complete involution of the uterus at 6 to 8 weeks postpartum. In the meantime, condoms and spermicidal foam or jelly should be used. Intrauterine devices can be placed immediately following delivery of the placenta; however, insertion at this time is associated with an increased risk of expulsion. Thus, waiting until 6 to 8 weeks postpartum may be preferable.

◊ Progestin-only oral contraceptives prescribed or dispensed at discharge from the hospital to be started 2–3 wks postpartum (e.g., the first Sunday after the newborn is 2 wks old)
◊ Depot medroxyprogesterone acetate initiated at 6 wks postpartum[a]
◊ Hormonal implants inserted at 6 week postpartum[a]
◊ Combined estrogen–progestin contraceptives, if prescribed, should not be started before 6 wks postpartum, and only when lactation is well established and the infant's nutritional status well-monitored

[a]There are certain clinical situations in which earlier initiation might be considered.
Source: American College of Obstetricians and Gynecologists. *Breast-feeding: maternal and infant aspects.* ACOG Educational Bulletin No. 258, July 2000.

TABLE 2.2. *ACOG recommendations for hormonal contraception if used by breast-feeding women*

In nonlactating women, ovulation usually occurs about 6 weeks postpartum. The first menses following delivery is often an anovulatory cycle; however, conception has been reported as early as 2 weeks postpartum, so contraception must be advised even in the early postpartum period. While women who exclusively breast-feed their babies usually do not ovulate for at least 3 months following delivery, an occasional nursing mother will ovulate early, and thus contraception use should be advised. Women who receive rubella immunization, which is a live vaccine, are advised to delay pregnancy for at least a month. Women should be cautioned about postpartum depression. Instructions from the pediatrician regarding care of the neonate should be reinforced, as well as encouraging follow-up should any problems occur.

Although its value is open to question, it is customary to schedule an office visit 4 to 6 weeks postpartum. At this visit, inquiries should be made regarding breast-feeding, continued bleeding, resumption of sexual intercourse, use of appropriate contraception, and any difficulty with regard to voiding or bowel movements. A focused physical examination can be performed, and a Pap smear obtained, if indicated. Women should be counseled regarding emotional lability in the postpartum period and reassured that intervention is available should she experience clinically significant depression.

Complications of the Puerperium

Puerperal Infection Fever (a temperature of at least 38°C or 100.4°F) is the most commonly observed sign of puerperal infection. The differential diagnosis includes infections of the perineum, vagina, uterus, parametrium, bladder, kidneys, or breast. Noninfectious causes of fever such as thrombophlebitis and breast engorgement must also be considered. After vaginal delivery, endometritis is infrequent but may be presaged by chorioamnionitis. Various obstetric factors increase the risk of endometritis; two of the most consistent are prolonged rupture of the membranes and prolonged labor, both of which are often associated with multiple intrapartum cervical examinations, which also add to the risk. Endometritis is usually caused by normal vaginal flora, including *Escherichia coli*, ß-hemolytic streptococci, facultative organisms such as *Streptococcus faecalis*, and anaerobes such as *Peptostreptoccus, Bacteroides*, and *Prevotella* species. Most infections involve mixed flora, but progression to an anaerobic infection is a particular risk following cesarean delivery. Women suffering with serious puerperal infection of the reproductive tract frequently complain of chills, headache, malaise, and anorexia. Physical examination usually reveals tachycardia and often pallor. If the uterus is involved, it is usually tender and may be large and boggy. Lochia may be diminished if the cervix is blocked, or it may be profuse and malodorous. Parametrial involvement, peritonitis, and pelvic thrombophlebitis may complicate the illness. Endotoxic shock or a virulent puerperal sepsis may develop in a relatively short time and can be fatal. Prompt and aggressive management with broad-spectrum antibiotics—and potentially surgery—is mandatory (see Chapter 19).

Postpartum Hemorrhage Postpartum hemorrhage has been defined as a blood loss of greater than 500 mL during or after the third stage of labor. This definition is somewhat paradoxical, as careful measures of blood loss following delivery indicate that the *average* is approximately 500 mL. After hypertensive disorders and embolism, postpartum hemorrhage is the major cause of maternal mortality for women who reach the second trimester. The major cause of postpartum hemorrhage is uterine atony, or failure of the uterus to contract sufficiently after delivery. This failure inhibits the major hemostatic mechanism of the postpartum uterus—myometrial contraction with constriction of placental bed arteries and veins. Risk factors for uterine atony include prolonged or oxytocin-augmented labor, uterine overdistension (as with polyhydramnios, fetal macrosomia, or multiple gestation), chorioamnionitis, grand multiparity, and a history of postpartum hemorrhage. Halogenated anesthetic agents also inhibit uterine contractility, and very rapid labors have been associated with failure of the uterus to contract adequately after delivery. Additional causes of postpartum hemorrhage are vaginal or cervical lacerations, and retained products of conception. Most serious hemorrhages occur within the first 24 hours after delivery but may occur even weeks after delivery. If hemorrhage occurs, and uterine atony is the presumptive cause, bimanual uterine compression (using a fist in the anterior vaginal fornix and the other hand on the abdomen, open and compressing the posterior uterine wall) should be performed and dilute intravenous oxytocin (40 to 80 units per L) administered. Large bore intravenous access should be secured. If bleeding persists, the vagina and cervix should be inspected for bleeding lacerations, and these should be sutured if found. The uterus should be manually explored for retained placental fragments or membranes. Intramuscular injection of methylergonovine maleate (0.2 mg) or prostaglandin F_2 (0.25 mg) can aid in stimulating contraction of the atonic uterus. Both may exacerbate or provoke

hypertension. Preparation should be made to replace blood and blood products as necessary to prevent the development of a consumptive coagulopathy. If contractions cannot be stimulated in a refractory atonic uterus, laparotomy with uterine artery ligation, hypogastric artery ligation (if a skilled, experienced surgeon is available and the woman is hemodynamically stable) or hysterectomy may be required. If bleeding from a vaginal wall laceration is persistent, packing, angiography, and selective embolization may be helpful.

Depression Many mothers (at least half) feel an emotional letdown during the first few days after delivery. These “maternity blues” are characterized by bouts of sadness, crying, and lability of mood. This state is usually, but not always, short-lived and seldom persists beyond 2 weeks. No specific therapy other than emotional support is indicated. More seriously, up to 20% of women may experience a major postpartum depression, characterized by such symptoms as insomnia, pessimism, lethargy, feelings of inadequacy, inability to cope, and fatigue. In women with these symptoms, it is important to rule out postpartum hypothyroidism. Both counseling and medication (usually with a selective serotonin reuptake inhibitor) may be indicated. Profound, persistent depression or that associated with lack of interest in the infant, suicidal or homicidal thoughts, hallucinations, or psychotic behavior should prompt psychiatric consultation. The recurrence risk for postpartum depression is high, and prophylactic therapy beginning 2 to 3 weeks before delivery may be indicated. An earlier postpartum visit should be considered for women at risk of postpartum depression including those with a prior history of depression not associated with pregnancy. Puerperal psychosis (hallucinations, suicidal impulses) is unusual but may complicate as many as 1 in 500 pregnancies. It is an emergency which should be immediately attended to by a psychiatrist to prevent the mother from harming herself or her infant.

Breast-feeding

Breast-feeding has undergone somewhat of a renaissance in the United States over the past 30 years: in 1971 only one-fourth of mothers breast-fed at hospital discharge, versus almost two thirds in 1998. In 1997, the AAP summarized the manifest benefits of breast-feeding for the infant (Table 2.3).

Research in the United States, Canada, Europe and other developed countries, among predominantly middle-class populations, provides strong evidence that human milk feeding decreases the incidence and/or severity of diarrhea, lower respiratory infection, otitis media, bacteremia, bacterial meningitis, botulism, urinary tract infection, and necrotizing enterocolitis. There are a number of studies that show a possible protective effect of human milk feeding against sudden infant death syndrome, insulin-dependent diabetes mellitus, Crohn's disease, ulcerative colitis, lymphoma, allergic diseases, and other chronic digestive diseases. Breast-feeding has also been related to possible enhancement of cognitive development. (American Academy of Pediatrics, Work Group on Breast-feeding. Breast-feeding and the use of human milk. *Pediatrics* 1997;100:1035–1039 [Paragraph includes 39 citations]).

Source: American College of Obstetricians and Gynecologists. Breast-feeding: maternal and infant aspects. ACOG Educational Bulletin No. 258, July 2000.

TABLE 2.3. *Research on established and potential protective effects of human milk and breast-feeding on infants*

Breast-feeding mothers benefit as well. Suckling-triggered oxytocin release promotes uterine contractions and leads to diminished blood loss. Oxytocin and prolactin levels are elevated in breast-feeding mothers, enhancing feelings of attachment and relaxation. Women who breast-feed face lower risks of ovarian and premenopausal breast cancer, and are less subject to pregnancy-induced obesity. By delaying ovulation, breast-feeding contributes to longer interpregnancy intervals.

Almost all women may breast-feed. However, some women should not. According to the ACOG, these include women who:

- take street drugs or do not control alcohol use
- have an infant with galactosemia
- are infected with HIV
- have active, untreated tuberculosis
- take certain medications
- are undergoing treatment for breast cancer.

Additionally, women with active varicella infections, herpes simplex virus infections of the breast, and active hepatitis A and B (until the infant has been passively and actively vaccinated) should refrain from breast-feeding. The list of medications contraindicated in breast-feeding is not extensive. It includes bromocriptine, cocaine, cyclophosphamide, cyclosporine, doxorubicin, ergotamine, lithium, methotrexate, phencyclidine, phenindione, and radioactive iodine and other radiolabeled elements. Women who want to breast-feed but who receive radioactive elements on a one-time or short-term basis (as for a diagnostic study) can pump and discard their milk until the radioactivity has cleared their bodies.

Premature infants can be breast-fed, but may have special nutritional requirements, especially those born very prematurely. Consultation is necessary to ensure adequate nutrition for such babies. Mothers whose babies are temporarily unable to breast feed may pump their breasts (which is most efficiently done with an electric pump) and the milk may be administered to the baby or stored for later use (frozen unless use is planned within 2 days).

Lack of education and knowledge, both on the part of caregivers and mothers, is the biggest barrier to breast-feeding. To redress this deficiency, ACOG has compiled two lists of resources (Table 2.4, Table 2.5). It is incumbent upon obstetric and pediatric care providers to provide education, support, and assistance to allow women to begin and maintain successful breast-feeding. These activities should begin at the first prenatal visit (or even sooner, e.g., routine gynecologic health visits) and continue throughout the pregnancy and postpartum period. Hospital protocols and care delivery should be conducive to breast-feeding, and specific practices to support breast-feeding have been enumerated (Table 2.6). Since most women are discharged before their milk comes in, most questions and problems with breast-feeding are handled on an outpatient basis. Therefore, to achieve successful, sustained breast-feeding among their patients, physicians and their office staff must have the ability to field questions and promptly correct problems with nursing.

Breast-feeding your baby. Wlashington, DC: American College of Obstetricians and Gynecologists; 1997. Patient Education Pamphlet APO29. *Breast-feeding: loving support for a bright future. Q & A. Physicians' breast-feeding support kit.* Tampa, FL: Best Start Social Marketing, 1998. *Working & breast-feeding. Can you do it? Yes, you can!* Alexandria, VA: National Healthy Mothers, Healthy Babies Coalition, 1997. *Ten steps to support parents' choice to breast-feed their baby.* American Academy of Pediatrics Task Force on Breast-feeding. Elk Grove Village, IL: AAP, 1999.

Source: American College of Obstetricians and Gynecologists. Breast-feeding: maternal and infant aspects. ACOG Educational Bulletin No. 258, July 2000.

TABLE 2.4. *Patient breast-feeding education materials*

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Source: American College of Obstetricians and Gynecologists. *Breast-feeding: maternal and infant aspects*. ACOG Educational Bulletin No. 258, July 2000.

TABLE 2.5. *References for health care workers and patients seeking in-depth information about breast-feeding*

- Maintain a written breast-feeding policy that is communicated to all health care staff.
- Train all pertinent health care staff in skills necessary to implement this policy.
- Inform all pregnant women about the benefits of breast-feeding.
- Offer all mothers the opportunity to initiate breast-feeding within 1 hour of birth.
- Show breast-feeding mothers how to breastfeed and how to maintain lactation even if they are separated from their infants.
- Give breast-feeding infants only breast milk unless medically indicated.
- Facilitate rooming-in; encourage all mothers and infants to remain together during their hospital stay.
- Encourage unrestricted breast-feeding when baby exhibits hunger cues or signals or on request of mother.
- Encourage exclusive suckling at the breast by providing no pacifiers or artificial nipples.
- Refer mothers to established breast-feeding and mothers' support groups and services, and foster the establishment of those services when they are not available.

[a]The 1994 report of the Healthy Mothers, Healthy Babies National Coalition Expert Work Group recommended that the UNICEF-WHO Baby Friendly Hospital initiative be adapted for use in the United States Breast-feeding Health initiative, using the adapted ten steps above.

Source: Randolph L, Cooper L, Fonseca-Becker F, et al. *Baby Friendly Hospital initiative feasibility study: final report*. Healthy Mothers, Healthy Babies National Coalition Expert Work Group. Alexandria, VA: HMHB, 1994; and American College of Obstetricians and Gynecologists. *Breast-feeding: maternal and infant aspects*. ACOG Educational Bulletin No. 258, July 2000.

TABLE 2.6. *Ten hospital practices to encourage and support breast-feeding* [a]

Women who make an informed decision not to breast-feed should be reassured that milk production will gradually diminish over the first few days after delivery. During this time, a properly fitted bra, ice packs, and oral analgesics should minimize the discomfort of breast engorgement. Medical therapies to hasten this process are no longer advised.

Other than encouraging breast-feeding women to follow a well-balanced, varied diet, and to keep adequately hydrated, no specific dietary modifications are necessary. It is reasonable to recommend a multivitamin with iron supplementation to all nursing women, especially strict vegetarians and those who do not eat dairy products.

Nursing women have a greater delay in resumption of intercourse, compared to those who bottle-feed. In some women, this is clearly attributable to discomfort due to relative vaginal atrophy and decreased lubrication from low estrogen levels. If lubrication during intercourse does not provide relief, women with a well-established milk supply may benefit from vaginal estrogen cream.

Not working, or working part-time, is associated with a longer period of breast-feeding. However, working is rarely the reason given by women for not breast-feeding. The barriers to breast-feeding while working include lack of a flexible or part-time work schedule, inadequate maternity leave and job security, lack of on-site day care, and lack of an appropriate place to pump or breast-feed. Often, the most significant problem facing a mother trying to work and breast-feed is the people around her who do not understand her choice to nurse. Increasingly, however, societal attitudes, and social policies and laws have become more favorable to, and supportive of, breast-feeding.

Nursing Problems

Evaluating problems with nursing requires the observation of the mother and baby while nursing, to which the office setting may not be conducive—and thus the advantage of lay assistance and lactation specialists. Adequate rest is important, and encouragement to rest should accompany almost all calls about problems with nursing.

Concerns about Insufficient Milk Supply The most common reason women give for discontinuing breast-feeding is a concern over insufficient milk supply. Milk letdown can be inhibited by cold, pain, and emotional stress and is sometimes difficult to achieve using a breast pump. A quiet, private setting and pictures of the baby to look at may help. Thus simple supportive measures and environmental modification may be all that is required. If the problem proves refractory, oxytocin in nasal-spray form may be helpful. The spray contains 40 USP units (IU) per milliliter, which is administered into one or both nostrils 2 to 3 minutes prior to nursing or pumping.
Painful Nipples Painful nipples are usually caused by problems with positioning and latching on. For some women, comfort will be gained by leaving their nipples exposed and using either a lamp or hair dryer to dry their nipples after feedings. Additionally, breast shields and purified lanolin cream may help provide relief.
Mastitis One to two percent of breast-feeding women will develop mastitis, which can occur any time, but is most frequent in the first through fifth week of breast-feeding. Typical symptoms are unilateral breast pain, chills, and malaise. Signs include fever, and an erythematous, indurated segment of breast. *Staphylococcus aureus* is the most common agent, although a broad- spectrum of bacteria may be causative. In women not allergic or sensitive to penicillin, a 7- to 10-day course of oral dicloxacillin, 500 mg q.i.d., is usually curative. Oral hydration is advised and antipyretics may lessen discomfort and fever. For penicillin-intolerant women, erythromycin may be substituted. Breast-feeding should continue, as drainage of the breast has therapeutic value. Neglected or recurrent infections and infections with resistant organisms can lead to a breast abscess. Treatment of an abscess usually involves intravenous antibiotics and aspiration or surgical drainage.

NEWBORN CARE

Immediate Assessment and Resuscitation

The transition from fetus to newborn infant is the most dramatic physiologic change that occurs in the human life span. The fetus that received all of its oxygen and nutritional needs via the placenta must now use two entirely different, essentially dormant organ systems to meet these needs. The circulation is rerouted and the pulmonary bypass paths (ductus arteriosus, foramen ovale, and umbilical circulation) are no longer used. The lungs and left side of the heart that once handled about 15% of the circulation must now deal with 100% of the circulation in series with the right heart and remainder of the body. The fluid-filled, unexpanded lungs must be inflated and cleared of fluid to allow gas exchange, as they are now the sole source of oxygen for the infant.

Resuscitation in the delivery room is geared toward helping the infant accomplish this transition. The AAP Neonatal Resuscitation Program (NRP) is a training course that all those specializing in pediatrics complete and is strongly encouraged for all individuals who deliver infants or attend deliveries; in fact, many institutions now require current certification for delivery room personnel. The resuscitation algorithm from the current NRP is shown in Figure 2.16.

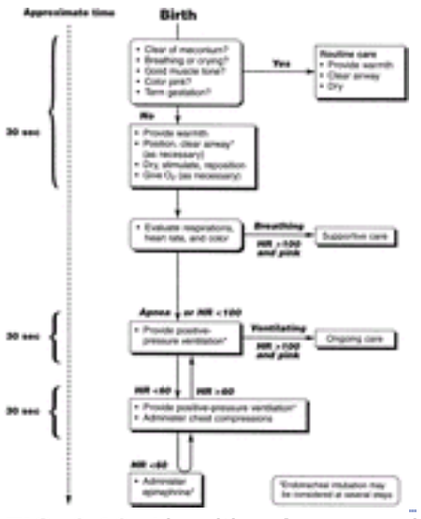

FIG. 2.16. Algorithm for resuscitation of the newly born infant. (From American Academy of Pediatrics © 2000; with permission.)

While every delivery should be attended by personnel trained in newborn resuscitation, the presence of personnel experienced in resuscitation is most desirable for deliveries where the need for resuscitation is more likely. Examples of these situations are summarized in Table 2.7.

TABLE 2.7. *Antepartum factors and intrapartum factors*

Meconium

Meconium passage prior to birth occurs in up to 20% of term deliveries and is a common reason for neonatal resuscitation. In the 1970s it was recognized that early suctioning by the obstetrician or pediatrician decreased the incidence of meconium aspiration syndrome (MAS). In the 1980s, routine suctioning of the oropharynx at the perineum or endotracheal suctioning were standard practice; however, it became clear that not all cases of MAS could be prevented and that aspiration in utero could occur. In the 1990s, many neonatologists were concerned that vigorous babies with thin meconium had a very low risk of MAS, and might actually do better if not intubated for tracheal suctioning. Unfortunately, the majority of studies pertinent to this issue have not been prospective, randomized, or controlled. The most recent Cochrane Library review concluded that until further evidence is available, endotracheal suctioning for meconium should be reserved for those infants who are depressed or have respiratory difficulties.

The Apgar Score

In 1952, Dr. Virginia Apgar devised a 0 to 10 scale scoring system intended to focus attention on the newborn and allow the systematic assessment of its condition and immediate needs (Table 2.8). Since that time, Apgar scores have become a mainstay in immediate newborn assessment. The Apgar score is a useful tool to guide those charged with assessment and care of the newborn. It provides an overall picture of infant status, and has been used in clinical research to correlate later outcomes with initial appearance. It cannot be used to predict neurologic outcome without other tests or examinations, nor is it a validated tool for determining asphyxia. Moreover, it was never intended for use in premature infants. Scores are assigned at 1 minute of age, and every 5 minutes thereafter until the score is over 7, or until 20 minutes of age. Clearly, resuscitation should begin if necessary prior to the 1-minute score.

TABLE 2.8. *Apgar mnemonic*

General Evaluation and Treatment

Every newborn infant should have a thorough physical examination. The newborn exam is focused on identification of congenital abnormalities, birth trauma, and signs of transitional difficulties (Table 2.9). Although infants of 35 or more weeks and over 2 kg will generally be able to maintain their temperature and feed successfully, all infants born prior to 37 weeks may require more frequent monitoring of temperature and blood glucose. Infants who are large or small for their delivery dates are at higher risk for hypoglycemia. If dates are uncertain, a Dubowitz or Ballard examination may be performed, ideally between 24 to 48 hours of age. In addition to monitoring blood sugar prior to established feeding, routine laboratory work often includes blood type, Coombs test, and hematocrit. A positive Coombs test can be caused by Rh or ABO incompatibility. Hematocrit levels between 40% to 65% are acceptable. Most states screen for phenylketonuria (PKU) and congenital hypothyroidism. Other tests used by some states include screens for congenital adrenal hyperplasia, cystic fibrosis, and other inborn errors of metabolism. These tests may be initiated prior to discharge according to state mandates. Infants born in U.S. hospitals are given either dilute silver nitrate drops or erythromycin ophthalmic ointment to prevent *Neisseria gonorrhoeae* conjunctivitis, which was once the most common cause of congenital blindness. Vitamin K is administered intramuscularly to prevent vitamin K deficiency bleeding (VKDB). Factors that can contribute to this deficiency include low vitamin K stores at birth, poor placental transfer of vitamin K, low levels of vitamin K in breast milk, and sterility of the gut. Because standard commercial infant formulas contain supplemental vitamin K, VKDB is almost exclusively a problem of breast-fed infants. The most common sites of bleeding are the umbilicus, mucous membranes, gastrointestinal tract, the penis after circumcision, and skin (from venipuncture). Intracranial bleeding can occur and is the main cause of mortality and long-term morbidity. In the United States, all infants are actively immunized against hepatitis B, the initial dose of which is generally given on the day of birth. If the mother is positive for hepatitis B surface antigen or if her status cannot be determined within a few days, the infant should also receive passive immunization within 7 days in the form of hepatitis B immune globulin.

TABLE 2.9. *Examination of the newborn*

Early Onset Sepsis

One of the most serious problems encountered in the immediate newborn period is early onset sepsis, defined as occurring in the first 5 days after birth. The current estimated rate in the United States is 1 to 2 per 1000 live births. Group B streptococci (GBS) remain the most common causal organisms, but with the routine use of intrapartum antibiotic prophylaxis for GBS, *Escherichia coli* now constitutes a larger proportion of causative organisms. The symptoms of neonatal sepsis include respiratory distress, lethargy, poor feeding, hypotonia, seizures, and shock. The management of infants with symptoms of sepsis includes blood and, if indicated, cerebrospinal fluid cultures, followed by the administration of broad-spectrum intravenous antibiotics, generally a penicillin in combination with an aminoglycoside. The management of asymptomatic infants of mothers with risk factors for neonatal sepsis is less clear and has become a topic of considerable debate since the routine use of intrapartum GBS chemoprophylaxis. Based on expert opinion and limited data the following general approach has been recommended. Because of an increased risk for early-onset GBS septicemia and greater difficulty in assessing symptoms, asymptomatic infants born prior to 35 weeks gestation should be evaluated with a complete blood count and blood culture, and observed in the hospital without empirical antimicrobial therapy for at least 48 hours. In infants born at and beyond 35 weeks, clinical assessment is more dependable. Routine laboratory evaluation is not recommended in these infants. They should, however, be observed in-hospital for at least 48 hours.

Hyperbilirubinemia and Discharge Planning

Timing of newborn discharge has been a topic of controversy for nearly 20 years. Prior to and during much of this time, the traditional stay was 3 days for a vaginally delivered baby and 5 days for those delivered by cesarean (due to the mother's extended stay). This minimum of 3 days allowed detection of the most common serious problems of the newborn, such as ductal-dependant congenital heart disease, early onset sepsis, hyperbilirubinemia, and failure to establish adequate breast-feeding. Discharges at 24 hours (or less) became popular in the late 1980s, a practice driven largely by third-party payors. While numerous small studies were performed to assess the safety of early discharge, most suffered from insufficient numbers to rule out an increase in adverse outcomes that, individually, are relatively uncommon. Bilirubin encephalopathy, a disorder rarely seen for the past 30 to 40 years, has recently been reported to be on the rise. Bilirubin peaks at 5 days in formula-fed infants but may peak as late as 7 to 10 days in breast-fed infants. Breast milk production is minimal in the first 48 hours after delivery and does not reach 80% of full volume until 4 days postpartum. Because of this time frame, it is not easy to predict at 3 days of age which breast-fed infants with a negative Coombs test will be at risk of dangerously high bilirubin levels (>25 mg/dL), and it is nearly impossible to do so at less than 48 hours. In recognition of these issues, the pendulum appears to be swinging back to a 3-day stay for most breast-fed infants. Infants readmitted after discharge prior to 48 hours are most likely breast-fed and jaundice is the most common reason for admission. In addition to insufficient breast milk intake, hyperbilirubinemia can result from relative polycythemia, bruising, cephalohematoma, or be idiopathic. The current AAP guidelines for management of term infants with nonhemolytic jaundice are given in Table 2.10.

TABLE 2.10. *American Academy of Pediatrics hyperbilirubinemia treatment guidelines: total serum bilirubin (mg/dL)*

SUMMARY POINTS

- Labor is defined as regular uterine contractions that lead to effacement and dilation of the cervix.
- Labor can be conceptualized as depending on the *Power*, the *Passage*, and the *Passenger*.
- A variety of management approaches to labor have been employed and evaluated, and no single approach is clearly superior.
- Both infection and hemorrhage can complicate normal labor and delivery, and caregivers must be vigilant for these complications and competent in their management.
- Encouraging and providing support for breast-feeding has significant benefits for both infants and mothers.
- Every delivery should be attended by personnel trained in newborn resuscitation.
- Newborn hospital stays shorter than 3 days may compromise the detection of hyperbilirubinemia in breast-fed infants.

SUGGESTED READINGS

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Chapter 3

Joy L. Hawkins

Obstetric Analgesia and Anesthesia

PAIN OF PARTURITION
SYSTEMIC ANALGESIA AND SEDATION
Use of Systemic Medications
Systemic Narcotics
Patient-controlled Intravenous Analgesia
Narcotic Antagonists
Sedative Drugs
Inhalational Agents
REGIONAL ANALGESIA
Local Anesthetic Agents
Side Effects of Local Anesthetic Drugs
Use of Regional Anesthetic Blocks
Complications of Regional Block Analgesia
OTHER METHODS OF PAIN RELIEF
Prepared Childbirth
Hypnosis
Acupuncture
Biofeedback
Transcutaneous Electrical Nerve Stimulation
Intracutaneous Nerve Stimulation
ANESTHESIA FOR CESAREAN DELIVERY
Epidural Anesthesia
Subarachnoid or Spinal Anesthesia
General Anesthesia
Analgesia after Cesarean Section
SUMMARY POINTS

REFERENCES

The purpose of this chapter is to acquaint the obstetrician with the various techniques of obstetric analgesia (pain relief) and anesthesia (for surgical procedures) and to describe their indications, advantages, disadvantages, and complications. The technical aspects, including the methods of administration, will not be described in detail. Readers seeking specific information on how to perform the various obstetric anesthetic techniques are referred to one of the basic obstetric anesthesia textbooks ([1]).

Obstetric analgesia or anesthesia refers to the multiple techniques useful for the alleviation of the pain associated with labor, delivery, or surgery. The choice of an appropriate analgesic technique must be made by the patient, the obstetrician, and the anesthesiologist and should take into consideration the patient's anatomy and physiology, the status of her fetus, the obstetric plan for delivery, and the pharmacology of the drugs to be employed ([2]). Most women now request some form of analgesia during childbirth (Table 3.1).

	≥1500 Births			<500 Births		
	1981	1992	1997	1981	1992	1997
None (%)	27	11	11	45	33	17
Parenteral (%)	52	48	39	37	48	50
Paracervical (%)	5	2	2	6	7	6
Regional (%)	22	55	66	9	21	42

Source: Adapted from Hawkins JL, et al. Obstetric anesthesia work force survey, 1981 versus 1992. *Anesthesiology* 1997;87:135, and Hawkins JL, et al. *Anesthesiology* 1999;91:A1060.

TABLE 3.1. *Types of labor analgesia provided by size of hospital in three time periods*

PAIN OF PARTURITION

Increasing dilation of the cervix, contraction and distention of the uterus, and distention or tearing of the vagina, vulva, and perineum causes the pain that occurs during labor and delivery. Pain may be generated through stretching or application of pressure to adjacent pelvic organs.

The pain that occurs in the first stage of labor increases in severity as the cervix becomes more dilated. The onset of pain lags approximately 15 to 30 seconds behind the onset of the uterine contraction and is first perceived when the intraamniotic pressure reaches 15 mm Hg above that of resting tonus. In the second stage of labor, sharp pain occurs as the tissues of the vagina and perineum are stretched. Stretching stimulates the second, third, and fourth sacral nerve roots, which carry nociceptive information to the spinal cord through the sensory fibers of the pudendal nerve. Adnexal pressure and traction on the bladder, urethra, rectum, and peritoneum also contribute to the pain of parturition. Compression of the lumbosacral plexus by the fetal head, particularly in the occiput posterior position, may cause pain even before the onset of labor.

The pain of uterine contractions is conducted through small sensory nerve fibers of the paracervical and inferior hypogastric plexuses to join the sympathetic nerve chain at L2-3. The ascending fibers enter the spinal cord through the nerve roots of T-10 to T-12, with a variable contribution from L-1 (Fig. 3.1). Because the cutaneous branches of the lower thoracic and upper lumbar nerves migrate caudally for a considerable distance before they innervate the skin, the pain of uterine contractions is often referred to the area over the upper sacrum and the lower lumbar spine.

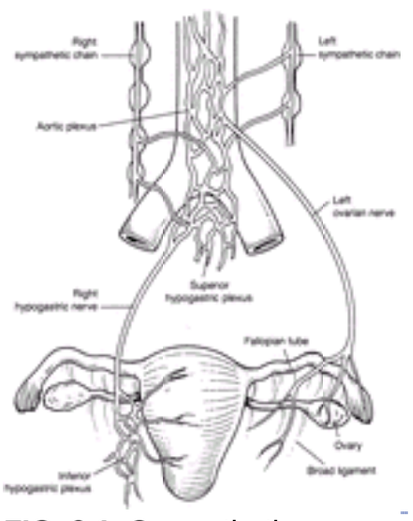

FIG. 3.1. Sympathetic nerve supply of the uterus from the pelvic and abdominal distribution. The uterine nerves arise from the upper part of the uterus (i.e., upper uterine segment), the contraction of which contributes to pain; from the lower part of the uterus (i.e., lower uterine segment), the distention of which contributes to pain; and from the cervix, the dilation of which contributes to pain. The ovarian nerve supplies the ovary, fallopian tube, broad ligament, round ligament, and the side of the uterus, and it communicates with the uterine plexus. The sympathetic efferent and afferent fibers are shown together. (Adapted from Abouleish E. *Pain control in*

obstetrics. Philadelphia: JB Lippincott Co, 1977.)

Pain from the uterus and cervix is transmitted through the small-diameter myelinated d-A fibers and unmyelinated C fibers. Because there are relatively fewer nociceptive afferent nerves from visceral structures than from somatic structures, visceral pain is perceived as being diffuse and difficult to localize. These visceral afferents also synapse on and excite the same dorsal horn neurons as afferents from somatic structures. This arrangement is responsible for the phenomenon of referred pain.

The gate theory of Melzack and Wall holds that stimulation of the large cutaneous ß-A nerve fibers closes a “gate” in the substantia gelatinosa of the spinal cord, preventing pain impulses from being carried rostrally by the d-A and C nerve fibers. This theory forms the basis for the use of acupuncture, transcutaneous electrical nerve stimulation, and intracutaneous nerve stimulation with sterile water injections for the relief of pain associated with parturition.

Pregnancy appears to reduce anesthetic requirements. It has been postulated that high progesterone levels lead to increased quantities of endogenous endorphins, which may increase the maternal threshold to pain. One study correlated pain intensity during labor and plasma levels of ß-endorphin. The lowest endorphin levels were found after abolition of labor pain by epidural analgesia. The highest concentrations were observed in the first few minutes after delivery, immediately after cessation of the severe pain of expulsive labor.

The nature of the pain of labor varies in intensity with the stages of labor. The intensity of pain is related to physical factors such as the strength and duration of uterine contractions, the rapidity of cervical dilation, the degree of distention of the vaginal and perineal tissues, the requirement for operative delivery, and the size, presentation, and position of the infant. Augmentation of labor with oxytocin increases the strength and pain of uterine contractions. The primiparous woman may perceive greater pain than the multipara who enters labor with more advanced cervical dilation and who may also be more psychologically prepared (Fig. 3.2). Exhaustion, psychological factors, and protracted nausea and vomiting may also increase the parturient's perception of labor pain.

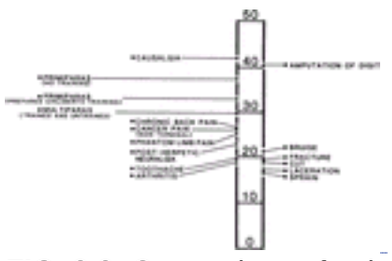

FIG. 3.2. Comparison of pain scores obtained from women during labor and from patients in a general hospital pain clinic or emergency department using the McGill pain questionnaire. (From Melzack R. The myth of painless childbirth. *Pain* 1984;19:321–37.)

Pain management is an important part of modern obstetric care. The obstetrician should appreciate the importance of providing pain relief during labor through the use of nonpharmacologic techniques, systemic analgesics, or regional block analgesia. During the second stage of labor, additional analgesia may also be needed through perineal extension of a segmental epidural or through the use of pudendal or spinal blocks.

SYSTEMIC ANALGESIA AND SEDATION

In the management of labor pain, systemic narcotics are usually considered to be the first step beyond the less invasive or “natural” methods such as massage, water baths, and birth attendants (doulas). They may also be necessary for patients who are not candidates for regional analgesia. Research indicates the analgesic effects of parenteral agents used in labor is limited and the primary mechanism of action is heavy sedation ([3]). Although narcotics may be effective for some patients in relieving the pain of labor, their side effects prohibit the use of large doses. The physician must balance maternal and neonatal respiratory depression with effective relief of the pain of labor. Because the pain of labor occurs intermittently with contractions, maternal hyperventilation during a contraction leads to hypoventilation for the 2 to 3 minutes between contractions, especially when narcotics have depressed the carbon dioxide response curve. There are advantages and disadvantages of all available narcotics, and a drug should be chosen with knowledge of its side effects and pharmacokinetics (Table 3.2).

TABLE 3.2. *Parenteral medications for labor analgesia*

Use of Systemic Medications

Because the use of systemic narcotics and tranquilizers does not require special training or the availability of anesthesia personnel, they are used extensively in the United States to provide labor analgesia (see Table 3.1). These compounds do not induce fetal heart rate (FHR) abnormalities other than changes in variability and rarely sinusoidal heart rate patterns, nor do they cause fetal acidosis. The drug-related adverse maternal effects of narcotics can include nausea, vomiting, pruritus, sedation, decreased gastric motility, loss of protective airway reflexes, and hypoxia due to respiratory depression. The adverse neonatal effects of these agents include central nervous system (CNS) depression, respiratory depression, impaired early breast-feeding, altered neuroadaptive behavior, and decreased ability to regulate body temperature. To minimize these side effects, the lowest effective dosage should be employed, and the timing with respect to delivery must be carefully considered. Resuscitation equipment should be kept at hand, and naloxone, used to antagonize opioids, should be readily available. Benzodiazepine effects may be reversed with flumazenil (Romazicon).

Systemic Narcotics

Meperidine Meperidine (Demerol) has achieved wide popularity for systemic analgesia during labor. It is preferred over morphine because it produces less emesis and does not depress the newborn carbon dioxide response curve as much as morphine. It can be administered intravenously or intramuscularly during labor. Current usage most often consists of small, incremental intravenous doses of 25 to 50 mg. Small doses can also be used to treat shivering. Placental transfer of meperidine occurs rapidly. Maximal depression of the infant occurs when delivery takes place 2 to 4 hours after maternal intravenous or intramuscular administration. Delivery of the infant within 1 hour of administration produces little evidence of newborn depression. A study using meperidine for labor analgesia by a patient-controlled infusion device found 5% of infants required naloxone at delivery ([4]). Meperidine has as its principal metabolite the compound normeperidine, which is equipotent with meperidine in its ability to produce respiratory depression and can also cause seizures. Repeated intravenous administration of small doses of meperidine leads to increasing maternal and fetal levels of normeperidine. Meperidine has an elimination half-life in neonatal blood of 22.7 hours, and that of normeperidine is measured in days, reflected in abnormal neurobehavioral scores for up to 3 days.

Morphine Morphine is pharmacologically more potent than meperidine by a factor of approximately 10. Morphine depresses the newborn carbon dioxide response curve more than meperidine, perhaps due to greater permeability of the infant brain to morphine. Because of this reputation, morphine has virtually disappeared from the armamentarium of analgesic drugs used by the obstetrician for the management of labor.

Fentanyl Fentanyl (Sublimaze) is a potent synthetic narcotic with analgesic activity approximately 100 times that of morphine. Its onset of action is rapid, and its duration of activity is short (i.e., 20–30 minutes) because of its rapid distribution from plasma. The terminal drug elimination half-life after a single small dose is 1 to 2 hours. Fentanyl is highly bound to protein, which may limit its placental transfer. It has no active metabolites. Fetal–maternal blood concentration ratios average 0.31 over the first 10 minutes after intravenous administration. Fentanyl produces moderate analgesia and mild sedation. There may be a brief period of decreased FHR variability, but no other disturbing FHR patterns have been reported. Comparative studies with meperidine indicate that the need for newborn naloxone (Narcan) administration is greater after use of meperidine than after administration of fentanyl.

Nalbuphine Nalbuphine (Nubain) is a potent narcotic agonist–antagonist agent which, at equianalgesic doses, produces respiratory depression equivalent to that of morphine. The advantage and disadvantage of nalbuphine is that as the dosage is increased, a ceiling effect is seen for respiratory depression, and unfortunately also for analgesia. Maximal respiratory depression occurs with a dose of 30 mg in a 70-kg adult. Sedation and dysphoric reactions may also occur. Reversal of other opioid effects may precipitate withdrawal in a susceptible patient. A possible transient depressive effect of nalbuphine on the fetal CNS has been identified.
Butorphanol Butorphanol (Stadol) is another synthetic narcotic with agonist–antagonist properties. It is five times more potent than morphine and 40 times more potent than meperidine. It has achieved moderate popularity in the United States in the management of the pain of the first stage of labor. It is usually administered intravenously in doses of 1 to 2 mg. Butorphanol exhibits the same ceiling effect for analgesia and respiratory depression as nalbuphine. Maternal side effects may include sedation, dysphoric reactions, and reversal of other opioid effects.
Newer Opioids Sufentanil and remifentanil, the newer synthetic opioids, have not been studied extensively for systemic analgesia during labor.

Patient-controlled Intravenous Analgesia

Intravenous patient-controlled analgesia (PCA) is widely available and provides pain relief through self-administration of intravenous opioids. Fentanyl, remifentanil, and meperidine are the analgesics most commonly employed with this technique. The infusion pump is programmed so that the patient receives an incremental dose when she pushes the button, followed by a lockout interval when additional requests by the patient will not be administered. An hourly maximum may also be programmed. A basal infusion is rarely used in labor because of the risk of respiratory depression between contractions. The actual settings are dictated by the pharmacokinetics of the narcotic chosen. The main advantage of PCA is improved patient satisfaction due to a feeling of control and not having to wait for a nurse to bring pain medication. Use of PCA may also decrease nursing staffing requirements.

In a study by Rosenblatt and colleagues ([5]), metoclopramide (Reglan) was used as an analgesic adjunct to PCA for patients undergoing prostaglandin induction of labor for second-trimester termination of pregnancy. Patients were given intravenous metoclopramide, 10 mg, or saline placebo followed by PCA-administered morphine. Those receiving metoclopramide used 54% less morphine and had lower pain scores.

Narcotic Antagonists

Naloxone Because all narcotics cross the placenta and can produce respiratory depression in the neonate, availability of an effective antagonist is essential. Naloxone reverses opioid-induced respiratory depression without producing side effects of its own. Because it also reverses analgesia, its prophylactic use is not advised. Naloxone may be administered to the parturient as an intravenous bolus of 0.1 to 0.4 mg to treat maternal respiratory depression. Care must be taken to *titrate* naloxone to the desired effect, since large doses have been implicated in the causation of myocardial infarction, pulmonary edema, and severe hypertension. Naloxone, 0.01 mg per kg, may also be administered intravenously, intramuscularly, or through the endotracheal tube to the newborn to reverse the respiratory depressant effects of placentally transferred narcotics. The effect is usually apparent within a few minutes and persists for as long as 2 hours. The neonate must be carefully observed for evidence of renarcotization, because the half-life of naloxone is less than that of most narcotics.

Sedative Drugs

Benzodiazepines The principal benzodiazepine drugs are diazepam (Valium) and midazolam (Versed). Diazepam has been used extensively in other parts of the world for seizure prophylaxis in patients with severe preeclampsia. However, because of its side effects on the newborn, it has found little favor in the United States. Newborns exposed to diazepam characteristically exhibit hypotonicity, hypoactivity, and impaired temperature regulation and metabolic response to cold stress. Midazolam is a newer benzodiazepine anxiolytic, a sedative drug with significant amnestic properties. It is five times more potent than diazepam and is soluble in water, a property that reduces pain associated with intravenous administration. Midazolam crosses the sheep placenta, achieving a fetal–maternal concentration ratio of 0.15. Its metabolites are inactive, and the drug is excreted more rapidly than diazepam. Midazolam has been used as an induction agent for cesarean delivery, but because of its ability to cross the placenta, it has produced neonatal respiratory depression and decreased body tone and temperature. Midazolam has not been recommended for use as a tranquilizer-sedative in labor, because its amnestic properties are unacceptable to most parturients.
Barbiturates Barbiturates may be used in the latent phase of labor. Although they cause maternal sedation and decreased anxiety, barbiturates lack analgesic properties and may increase the perception of pain when given without concomitant administration of a narcotic. Most barbiturates have long elimination half-lives and readily cross the placenta. Prolonged neonatal effects have led to the virtual elimination of these drugs from use during labor.
Other Sedatives Phenothiazine derivatives, such as promethazine (Phenergan), have been used in obstetrics and provide sedation and decrease nausea. Hydroxyzine, although not a phenothiazine, has similar properties when used in combination with narcotics. Maternal sedation is achieved without significant maternal or newborn side effects. It is important to remember that none of these drugs provide analgesia, and some parturients may object to the heavy sedation they cause. In addition, both medications are very painful intramuscular injections. They should have little place in the management of labor analgesia. Ketamine (Ketalar), when administered intermittently at low doses (10–15 mg), can produce analgesia in parturients without causing maternal loss of consciousness or neonatal respiratory depression. An improvement on this technique using low-dose ketamine infusion has been described by Maroof and associates ([6]). In this study, patients were given an intravenous bolus of ketamine, 0.5 mg per kg, upon achieving 4 cm of cervical dilation. This was followed by an infusion of ketamine at 0.25 mg per kg per hour. Patients served as their own controls, evaluating labor with and without the benefit of ketamine. Pain scores were significantly better with ketamine. The authors concluded that ketamine infusion produced acceptable analgesia throughout labor and was not associated with delirium or loss of consciousness in any patient. In addition, neonatal respiratory depression was not noted. The profound amnesia and potential for dysphoria or other psychomimetic effects when using ketamine limit its general use for labor analgesia. It is most useful for short painful procedures such as urgent forceps delivery or manual removal of the placenta.

Inhalational Agents

Nitrous oxide can be inhaled periodically with contractions in a 50% mixture with oxygen. During a painful contraction, the mother breathes from a mask connected to the regulator valve of a breathing circuit. A scavenging system is required by the Occupational Safety and Health Administration (OSHA) to eliminate exhaled waste anesthetic gases. Unfortunately, when it is breathed at the onset of a contraction, maximal analgesia is achieved only after the contraction has ended. When nitrous oxide is used in conjunction with narcotics, maternal oxygen saturation may decrease. Use of a pulse oximeter to ensure adequate maternal oxygenation is recommended. In practical terms, since almost all deliveries in the United States now take place outside the operating room, an anesthesia machine will probably not be available to safely administer inhalational agents.

REGIONAL ANALGESIA

Local Anesthetic Agents

Most local anesthetic agents share a common structure consisting of a hydrophilic amino group connected by an intermediate chain to a lipophilic aromatic residue. Their presumed mechanism of action is to block exchange of sodium and potassium ions across the cell membrane, probably through mechanical interruption of ion flow through cell wall channels.

Local anesthetic drugs are manufactured as chloride salts. The nonionized base is able to diffuse across tissues, while the ionized form is actually the active component. The amounts of nonionized (mobile) and ionized (active) drug depend on the pK_a of the local anesthetic and tissue pH.

After injection of lidocaine (Xylocaine), the sensory nerve action potential decreases more sharply in pregnant women than in nonpregnant women. This implies that pregnant women have an increased susceptibility to the effects of local anesthetic agents ([7]).

Local anesthetics belong principally to two groups, those of ester and amide configurations. Ester drugs are generally characterized by their rapid onset of action, short duration, and low toxicity. Chloroprocaine (Nesacaine) is a representative of this group. It is rapidly metabolized by serum pseudocholinesterase, forming paraaminobenzoic acid. Lidocaine, bupivacaine, ropivacaine, and levobupivacaine are representatives of the amide group. These drugs are more highly bound to protein and have a slower onset and a longer duration of action. They are metabolized in the liver. Toxicity is usually greater for amides than for drugs of the ester group (Table 3.3).

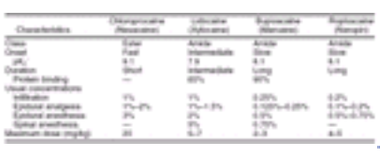

TABLE 3.3. *Characteristics of local anesthetics commonly used in obstetric anesthesia*

Local anesthetic drugs are absorbed systemically. Distribution to the fetus depends on maternal tissue uptake, maternal blood concentration, uterine blood flow, and maternal and fetal metabolism and excretion. Fetal-tissue drug distribution is also affected by asphyxia. Fetal asphyxia leads to increased P_aCO_2, which results in cerebral and coronary vessel dilation and increased brain and myocardial blood flow. The increased perfusion of these organs with anesthetic drug leads to greater toxicity. The decrease in pH seen with fetal asphyxia results in increased ionized (active) drug in the fetal circulation and tissues, a phenomenon referred to as ion trapping. The clinical significance of this is unclear.

Side Effects of Local Anesthetic Drugs

Systemic Toxicity Systemic complications involving the use of local anesthetics include toxic blood levels of the drug and allergic reactions, as well as reactions due to epinephrine that is often added to local anesthetic solutions to retard systemic absorption and prolong duration of action. Maximal safe doses for healthy young adults are 7 mg per kg (300 mg) of lidocaine, 2 to 3 mg per kg (175 mg) of bupivacaine, and 20 mg per kg (1000 mg) of chloroprocaine (see Table 3.3). The most common reason for high blood levels of local anesthetic drugs is accidental intravascular injection. This most commonly occurs when an epidural catheter has been placed or migrated into a vein. To minimize accidental intravenous injection, gentle aspiration should be undertaken before each injection. Injection should be done slowly and incrementally with only 2 to 5 mL of local anesthetic drug to reduce the chance of a sudden increase in plasma levels. A marker such as epinephrine may be added to the local anesthetic solution so that intravascular injection will manifest as tachycardia. The infiltration of a local anesthetic agent into an area rich in vessels, such as the region of the uterine artery (e.g., paracervical block), pudendal vessels, or the epidural space may be associated with absorption of the drug through blood vessel walls. The serum levels tend to rise slowly, and toxic manifestations usually occur only after multiple injections. Repeated injections of slowly metabolized local anesthetic drugs, such as the amides, may lead to accumulation in the serum such that toxic levels are achieved. This phenomenon does not occur readily with esters such as chloroprocaine, which are rapidly metabolized (maternal serum half-life of 21 seconds and fetal serum half-life of 43 seconds for chloroprocaine). To minimize the likelihood of producing high serum levels, care should be taken to record the amount and concentration of local anesthetic solution and to limit use to approximately 25% less than the maximal safe dose. Signs and symptoms of local anesthetic drug toxicity include, in order of their appearance, a relaxed feeling, drowsiness, lightheadedness, tinnitus, circumoral paresthesias, metallic taste, slurred speech, blurred vision, unconsciousness, convulsions, and cardiac dysrhythmias and arrest. In 1983, the U.S. Food and Drug Administration issued an advisory, warning that 0.75% bupivacaine should no longer be used in obstetrics because of reports of bupivacaine-induced cardiac arrest occurring at blood levels of only 3 to 5 µg per mL. The advisory stated that the resuscitation in these cases had been “difficult or impossible despite apparently adequate preparation and appropriate management.” Inadvertent intravascular injection causes high serum levels, which produce cardiac arrest through blockade of the cardiac sodium channels, inhibiting repolarization of the nerve cell membranes of the conduction system of the heart. Bupivacaine has been found to bind avidly to nonspecific cardiac protein–binding sites, slowing the conduction of impulses arising in pacemaker cells and causing a dose-dependent reduction in the strength of myocardial contractility, leading to cardiac arrest. Management is best accomplished through prevention, as described previously. Therapy is symptomatic. Initial treatment includes the use of mask oxygen, a reliable intravenous line, and measures to ensure and protect the airway. These include use of cricoid pressure to occlude the esophagus, the availability of adequate suction, and the capability to perform endotracheal intubation, if needed. Adequacy of respirations must be ensured, if necessary by means of positive pressure ventilation with 100% inspired oxygen. The patient should be hyperventilated to help correct metabolic acidosis caused by seizure activity and decreased cardiac output. CNS hyperreactivity and convulsions are treated with thiopental (Pentothal) in small, incremental doses of 25 to 50 mg given intravenously, or with 1 to 5 mg of midazolam given intravenously. In the event of cardiovascular depression, elevate the lower extremities and verify left uterine displacement. Vasoactive drugs such as ephedrine, phenylephrine, epinephrine, and calcium may be employed to support the circulation. If cardiopulmonary resuscitation is indicated, the fetus should be delivered within 5 minutes to relieve maternal central venous compression and advanced cardiac life support (ACLS) protocols should be followed.

Use of Regional Anesthetic Blocks

Local Infiltration of the Perineum Local infiltration of the perineum is commonly performed when an episiotomy is needed and time or fetal head position does not allow a pudendal block to be administered. An average of 10 to 20 mL of local anesthetic solution is employed. The preferred drugs are lidocaine 1% or chloroprocaine 2%.

Pudendal Block The pudendal block provides analgesia of the vaginal introitus and perineum. There are several advantages of this analgesic technique. Because the elapsed time between administration and delivery is short, there is relatively little systemic absorption and therefore little opportunity for the drug to directly affect the fetus. The block is easy to accomplish and provides analgesia of the perineum only. The disadvantages include the need for large drug doses (i.e., 10 mL on each side) and the potential for local anesthetic toxicity, hematoma, and the possibility of infection leading to retropsoas or subgluteal abscess. With the transvaginal approach, the ischial spine must first be identified. Through a guide, a needle is inserted into the vagina and directed laterally and posteriorly to the ischial spine. A submucosal wheal is made, and the needle is advanced into the sacrospinous ligament, where resistance is felt. As the needle passes the ligament, a loss of resistance is felt. The needle has now entered the pudendal canal, which contains the pudendal nerve and associated vessels (Fig. 3.3). After aspirating the needle for blood, 3 to 5 mL of local anesthetic solution (usually lidocaine 1%) is injected, and the needle is advanced another 0.5 to 1 cm. If aspiration is again negative, 5 to 7 mL of solution is injected. A total of 10 mL is injected on each side. Approximately 10 minutes are required for anesthesia to occur. Chloroprocaine 1% to 2% may also be used for this block. Analgesia with chloroprocaine lasts less than 1 hour, but lidocaine analgesia is more prolonged.

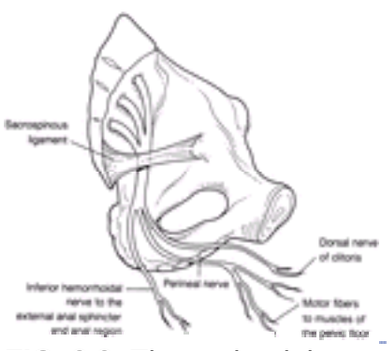

FIG. 3.3. The pudendal nerve and its branches. The inferior hemorrhoidal nerve can arise higher up from the pudendal nerve or separately from the sacral plexus. (Adapted from Abouleish E. *Pain control in obstetrics.* Philadelphia: JB Lippincott Co, 1977.)

Paracervical Block Paracervical block (PCB) anesthesia may be used when the active phase of labor begins, and it can be employed until approximately 8 cm of dilation has been achieved. Although formerly popular, this block has fallen into relative disuse since the description of bradycardia after PCB and its proven association with fetal acidosis. The PCB is useful when anesthesia personnel are unavailable and parenteral narcotics are inadequate. The PCB relieves the pain associated with uterine contractions, but it is not effective for pain associated with distention of the pelvic floor. The two drugs of choice are chloroprocaine and lidocaine in 1% concentrations. Typically, 6 mL of drug is administered superficially, just under the vaginal mucosa, at the 4- and 8-o'clock positions (Fig. 3.4). In this way, bradycardia, which occurs in 10% to 30% of cases, is less likely to appear. The landmark study by Baxi and colleagues ([8]), using a transcutaneous oxygen electrode attached to the fetal scalp, demonstrated that bradycardia is related to decreasing fetal oxygenation, which becomes marginal approximately 10 minutes after injection. This research has been corroborated by the study of isolated human uterine artery segments and by work in animals, indicating that direct uterine artery vasoconstriction and uterine hypertonus in response to the injection of a local anesthetic drug diminish uterine blood flow and fetal oxygenation.

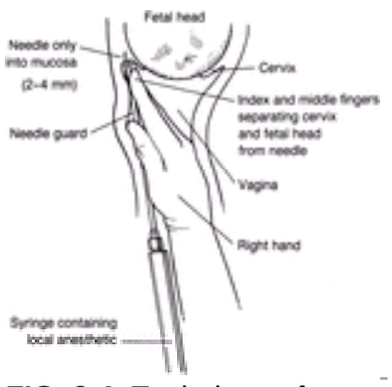

FIG. 3.4. Technique of paracervical block. Notice the position of the hand and fingers in relation to the cervix and fetal head and the shallow depth of the needle insertion. No undue pressure is applied at the vaginal fornix by the fingers or needle guide. (Adapted from Abouleish E. *Pain control in obstetrics.* Philadelphia: JB Lippincott Co, 1977.)

Lumbar Epidural Analgesia

Standard Technique Lumbar epidural analgesia was first performed in 1884 by Corning, who recognized that analgesia could still occur when attempted spinal analgesia failed. In 1921, Pages applied the technique to surgery. Obstetric applications were made by Graffagnino and Seyler in 1935. The most commonly used

anesthetic agents for lumbar epidural analgesia for labor are bupivacaine 0.0625% to 0.25% and ropivacaine 0.1% to 0.2%. The technique of lumbar epidural analgesia involves the insertion of a 17- or 18-gauge hollow-bore needle through the ligamentum flavum into the epidural space at the L4-5, L3-4, or L2-3 interspace. Although the hanging-drop technique for identification of the epidural space is generally effective, most physicians prefer the loss-of-resistance technique as the one that affords the least risk of penetration of the dura. Use of air or saline may be used to identify the epidural space. A 20-gauge catheter is passed through the epidural needle for a distance of 3 to 5 cm within the epidural space. This catheter is securely taped in place and serves as an avenue for intermittent or continuous infusion of local anesthetic agents or opioids.

Combined Spinal–Epidural Analgesia The combined spinal–epidural (CSE) technique adds a subarachnoid injection of an opioid with or without a small dose of local anesthetic in a needle-through-needle technique to provide a faster onset with a smaller dose of medication than is possible using epidural medications alone ([9]). The epidural catheter is still available for additional analgesia. A prospective, double-blinded, randomized study compared CSE analgesia with standard epidural analgesia in spontaneously laboring nulliparous parturients. There was no difference in the rate of progress of labor, the amount of epidural local anesthetic required, and the incidence of instrumental deliveries between the CSE and the standard epidural analgesia groups. However, analgesia was more complete and there was higher patient satisfaction in the CSE group than in the epidural analgesia group.

Patient-controlled Epidural Analgesia Patient-controlled epidural analgesia (PCEA) is a technique by which the patient self-administers on-demand doses of an analgesic mixture via an epidural catheter, whenever she perceives discomfort. To avoid overdosage, a lockout period follows each self-administration. This technique is associated with a decreased use of local anesthetic solution and less demand on staff time compared to continuous epidural infusion (CEI). Most studies have found patients will self-administer less local anesthetic solution than continuous infusions provide and that anesthesia workforce needs are reduced by about 40% ([10]). Quality of analgesia, complications, and amount of motor block are similar between the two techniques.

Epidural Medications in Labor Epidural injection of opioids alone has been shown to be of limited value for the relief of labor pain. High doses of morphine (7.5 mg) have provided satisfactory analgesia, but only during the first stage of labor. Because of its slow onset of action (often 1 hour or more) and high incidence of side effects (nausea and pruritus), morphine is not a satisfactory agent for this use. Fentanyl and sufentanil used alone can provide analgesia for early labor, but require high doses—100 µg fentanyl or 30 µg sufentanil. In contrast, *spinal* injection of opioids alone provides excellent, although time-limited analgesia for labor in small doses—10 to 25 µg fentanyl or 5 to 10 µg sufentanil. Fortunately, the addition of opioids to dilute concentrations of epidural local anesthetics has been proven to be quite effective in the relief of labor pain. The combination is a rational one because local anesthetic solutions relieve somatic pain preferentially, whereas opioids are more effective in relieving visceral pain. By combining a lipid-soluble opioid such as fentanyl or sufentanil to bupivacaine or ropivacaine, the concentration of local anesthetic can be dramatically decreased and motor block can be minimized. The addition of fentanyl or sufentanil approximately doubles the analgesic efficacy of any concentration of bupivacaine or ropivacaine, while shortening the time to complete analgesia. *Opioid and Chloroprocaine Mixtures*. Mixtures of morphine with chloroprocaine have not been shown to be useful, as chloroprocaine appears to antagonize the analgesic effects of the opioid, while increasing its side effects, particularly nausea and pruritus. The mechanism of this unfavorable interaction is unknown. Chloroprocaine may also prolong the onset of morphine analgesia and decrease the effectiveness of bupivacaine if used before these agents. The most satisfactory analgesia appears to be produced when opioids are combined with amide local anesthetics. The beneficial effects of epidural opioids in labor appear to be the following:

- reduction in motor block, allowing improved mobility of the patient
- reduction in shivering
- decreased incidence of hypotension
- use of lower doses of local anesthetic agents
- greater maternal satisfaction with the analgesia that they provide.

Effects of Epidural Analgesia on Uterine Blood Flow Studies investigating changes in intervillous blood flow and mean arterial pressure with lumbar epidural analgesia in adequately preloaded patients have demonstrated only a negligible reduction in these parameters with the onset of effective analgesia. Well-hydrated patients with preeclampsia have experienced improvement in intervillous blood flow along with a slight decrease in blood pressure.

Advantages and Disadvantages of Lumbar Epidural Analgesia There are three principal advantages of lumbar epidural analgesia:

- the parturient remains awake and cooperative.
- the incidence of complications is very low when the technique is used correctly.
- once an epidural catheter is in place, it can be used to provide analgesia or anesthesia for a vaginal or cesarean delivery.

The disadvantages of lumbar epidural analgesia include:

- the possibility of poor perineal analgesia
- the presence of “hot spots”, where analgesia is insufficient
- delayed onset of action
- technical difficulty
- intravascular injection
- accidental dural puncture
- hypotension. Technical failure occurs in approximately 4% of cases.

Indications and Contraindications for Lumbar Epidural Analgesia Indications for lumbar epidural analgesia include pain in labor, management of the patient with preeclampsia who does not have a coagulation abnormality, management of labor in patients with certain cardiac lesions, and management of breech delivery. A joint statement by the American College of Obstetricians and Gynecologists (ACOG) and the American Society of Anesthesiologists (ASA) ([11]) notes that: “Labor results in severe pain for many women. There is no other circumstance in which it is considered acceptable for a person to experience untreated severe pain, amenable to safe intervention, while under a physician's care. In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor. Of the various pharmacologic methods of pain relief used in labor and delivery, regional analgesia techniques—spinal, epidural and combined spinal epidural (CSE) are the most flexible, effective, and least depressing to the CNS, allowing for an alert, participating mother and an alert neonate.” There are absolute and relative contraindications to the induction of lumbar epidural analgesia. Absolute contraindications include the following: patient refusal, hemodynamic instability, infection at the anticipated site of puncture, and absence of resuscitation equipment. Relative contraindications may include fever, preexisting CNS disease, hypovolemia, hypotension, lack of experience by the anesthetist, and blood coagulation defects. Although an arbitrary platelet count of 100,000 per mm ^{3} has been advocated as the lower limit for safe lumbar epidural analgesia, successful blocks without epidural bleeding complications have been obtained with platelet counts as low as 50,000 per mm ^{3}. In one report, Beilin and colleagues ([12]) described a study of 80 women who presented for labor and delivery and had platelet counts less than 100,000 per mm ^{3} during the peripartum period. Of these 80, 30 were given an epidural anesthetic. The range of platelet counts was 69,000 to 98,000 per mm ^{3}. No patient had any documented neurologic complication. These authors concluded that regional anesthesia should not necessarily be withheld when the platelet count is less than 100,000 per mm ^{3}. However, given that the risk of epidural hematoma is extremely rare, a study this small would be unlikely to reveal a problem. The underlying cause of the thrombocytopenia is also important and must be considered along with any absolute number. For example, the patient with idiopathic thrombocytopenic purpura or gestational thrombocytopenia is much less likely to bleed at a low platelet count than the patient with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome. The best indicator of potential bleeding is a patient history of bruises, contusions, petechiae, bleeding from the gums, and so on.

Subarachnoid Analgesia Subarachnoid or spinal analgesia for labor has become increasingly popular. The major advantages of spinal analgesia include (a) use of a very low dose of local anesthetic or narcotic analgesic drug and (b) the excellent analgesia provided. Onset of action is rapid, and uterine activity is not affected. The disadvantages include (a) the possibility of postdural puncture headache (PDPH) which is increasingly rare with the use of pencil-point needles and (b) the time-limited nature of a single-shot technique. For this reason spinal analgesia is commonly combined with an epidural catheter as a CSE technique. Indications and contraindications are similar to epidural analgesia. Morphine and fentanyl can provided analgesia during labor when administered intrathecally in small doses. Labor analgesia usually lasts for 4 to 8 hours and is not accompanied by motor block. The major disadvantages include pruritus and nausea. Pruritus can be antagonized with small doses of intravenous naloxone or oral naltrexone. PDPH can be minimized through the use of 22- to 27-gauge Whitacre, Sprotte, or other pencil-point needles. A 28-gauge microcatheter can be passed through 22-gauge spinal needles, permitting the use of continuous spinal analgesia in labor and surgery. These catheters were withdrawn from the market because of associated cauda equina syndrome, probably related to local anesthetic neurotoxicity.

Complications of Regional Block Analgesia

Hypotension Hypotension is common, occurring in 10% to 20% of patients undergoing epidural analgesia for labor and 50% to 80% for cesarean delivery. It often occurs despite left uterine displacement and administration of an adequate vascular preload. Treatment should consist of the following steps:

1. Ensure or verify left uterine displacement.
2. Increase intravenous fluid infusion to the maximal available rate.
3. Administer oxygen by facemask.
4. If hypotension does not immediately resolve, administer ephedrine intravenously in 5- to 10-mg increments until hypotension resolves.

Phenylephrine, an a-agonist, has been avoided in the past because of concerns about compromising uterine blood flow, but more recent work has shown no adverse clinical effects and higher fetal pH values than ephedrine alone ([13]).

Postdural Puncture Headache When a large-bore epidural needle (e.g., 18-gauge Tuohy) penetrates the dura and arachnoid membranes, the incidence of PDPH is greater than 50%. Other factors governing the incidence of PDPH include the number of times the dura has been punctured, the direction of the bevel, and the type of needle used. PDPH occurs because a decrease in cerebrospinal fluid (CSF) volume causes compensatory cerebral vasodilation and traction on the pain-sensitive blood vessels and meninges. Assumption of the erect position increases traction on these structures and aggravates the pain. Therefore, the main diagnostic criterion of PDPH is that it is postural. Ocular and auditory symptoms, such as vertigo, ataxia, and sixth cranial nerve palsy may be associated with PDPH. Many different treatment regimens have been employed for this condition, including administration of saline through the epidural catheter, the use of abdominal binders, the administration of intravenous or oral caffeine (as a cerebral vasoconstrictor), bed rest, analgesics, and epidural blood patches. The most effective of these is the epidural blood patch. Evidence suggests that prophylactic epidural blood patch can substantially reduce the incidence and severity of PDPH. In a study by Lowinwirt and associates ([14]), patients with accidental dural puncture with 16- or 17-gauge needles were randomized and allocated to two treatment groups. In one group, patients received 15 to 20 mL of autologous blood through the indwelling epidural catheter at least 5 hours following the last dose of local anesthetic and just before catheter removal. Patients in the control group were managed conservatively with intravenous hydration, bed rest, theophylline, or caffeine. Eighty-three percent of patients receiving the prophylactic epidural blood patch avoided PDPH. Only 4% of patients treated conservatively avoided PDPH. Use of a prophylactic epidural blood patch was not associated with any complications.

Chronic Back Pain Low-back pain is a common complaint in the postpartum period. A controversy exists as to the role that epidural analgesia for labor and delivery might play in the subsequent development of low-back pain. Whereas several retrospective studies have demonstrated an association, other prospective studies have shown no increased risk of acute low-back pain after epidural use. A study by Loughnan and colleagues ([15]) examined the risk of low-back pain 6 months after delivery in patients who received epidural analgesia, as compared with those who did not. This prospective follow-up study showed no difference in the prevalence of low-back pain at 6 months after delivery. Therefore, it seems unlikely that epidural analgesia makes any significant contribution to the 19% to 33% prevalence of low-back pain among postpartum women.

Neurologic Complications Neurologic complications of epidural and spinal analgesia are rare, occurring in about 1 per 10,000 blocks. Many postpartum neurologic sequelae are related to intraoperative positioning problems. An example is foot drop associated with pressure on the lateral popliteal nerve and caused by an improperly placed stirrup. In the lithotomy position, pressure applied on the femoral cutaneous nerve by the inguinal ligament may cause pain and numbness in the lateral thigh. Pain and numbness in the distribution of the sciatic nerve may result from forceps delivery or passage of the baby's head through the pelvis. Spinal nerve root neuropathy may be caused by traumatic insertion of a spinal needle or an epidural needle or catheter. In this case, pain and paresthesias along the distribution of the nerve are perceived immediately, but they tend to disappear when the needle or catheter is removed. Rarely, symptoms may appear as long as 2 days after the procedure. Recovery usually occurs in 1 to 2 weeks, but injury can be permanent. Accidental injection of an irritant solution (e.g., thiopental) or a prep solution into the CSF may produce adhesive arachnoiditis, which can cause permanent loss of spinal cord function. Epidural abscess usually is caused by hematogenous spread and not by injection of contaminated anesthetic solutions. Epidural hematoma is a serious complication that, although rare, may occur in conjunction with coagulopathy. A hematoma should be suspected if recovery from the block is slow or absent or if neurologic function worsens after a period of initial recovery. The primary symptoms are pain and weakness, which may progress rapidly to paralysis. Early surgical drainage provides the only chance for recovery of neurologic function.

Effects of Epidural Analgesia on Progress of Labor Whether use of regional analgesic techniques is associated with an increased risk of cesarean delivery remains controversial, but that concern is mainly based on results from small retrospective studies. There is definitely an *association* between use of epidural analgesia for labor and cesarean delivery, but the problem is that nulliparous women with longer and more painful labors are the patients more likely to choose epidural analgesia, and they are also those who are at higher risk to have a cesarean delivery regardless of their choice of labor analgesia. The presence of severe pain during early labor signals an increased risk for prolonged labor and operative delivery ([16]). Also, regional analgesia is often recommended to women in whom operative or instrumental delivery is thought to be likely. Designing a study to remove that bias or association has proven difficult, both for the ethical reason you cannot refuse a treatment available to a patient if requested (i.e., if a patient is randomized to receive “no epidural” but she later requests it because of inadequate pain relief she must be allowed to cross over) and because there is no other form of pain relief to offer that provides equivalent analgesia (i.e., a “control group”). For this reason, many studies done prior to the last decade were methodologically flawed. More recent studies have attempted to control for the fact that women already at increased risk for an operative delivery are more likely to choose epidural analgesia, and have *not* found regional analgesia to be associated with cesarean delivery ([17]). There are different methodological ways to accomplish this. Several retrospective, population-based studies have found that the introduction of an epidural analgesia service or the increased use of epidural analgesia did not increase the cesarean delivery rate. In a “natural” experiment, a military hospital went from a 1% to 84% epidural analgesia rate in one year while other conditions remained unchanged ([18]). A review of singleton, nulliparous, term patients in spontaneous labor before and after the change found no differences in rates of cesarean delivery overall and for dystocia, no change in instrumental delivery rates, no change in duration of first and active stages of labor, but an increase in the second stage of labor by about 25 minutes. At the National Maternity Hospital in Dublin, the epidural rate increased from 10% to 57% over 3 years with no effect on cesarean delivery rates ([19]). These clinicians suggested use of active management of labor and use of oxytocin in the second stage of labor to overcome increases in instrumental vaginal delivery rates. Other studies have used generous doses of narcotics in the control group to prevent crossover to the epidural analgesia group. A review of 802 nulliparous patients randomized to epidural analgesia or intramuscular meperidine using standardized labor management found similar cesarean delivery rates in an intent-to-treat analysis ([20]). The spontaneous vaginal delivery rate was also similar between groups. A randomized trial of 715 women who received epidural analgesia or patient-controlled meperidine found no difference in cesarean delivery rates and lower pain scores in the epidural group ([4]). Pain relief is a worthy goal unto itself! Obstetric management must also influence the cesarean delivery rate. Even randomized trials cannot blind the obstetrician to the type of analgesia being used, and the obstetrician makes the decision regarding the need for cesarean delivery. If epidural analgesia has an influence on the risk of cesarean delivery, then those obstetricians with a higher use should have a higher cesarean delivery rate. In contrast, a review of 110 obstetricians in a single hospital practice found no relationship between frequency of epidural analgesia use and rate of cesarean section for dystocia across practitioners ($R^2 = 0.019$) ([21]). They concluded that after accounting for a number of known patient risk factors, obstetric practice style appears to be a major determinant of rates of cesarean delivery. As noted earlier, the intensity of labor pain may be predictive of an increased risk of cesarean delivery for dystocia. A secondary analysis of women randomized to receive patient-controlled intravenous meperidine analgesia for labor found that those who required higher doses of narcotic had higher pain scores initially, longer labors (9 vs. 5 hours), and more cesarean deliveries for dystocia (14% vs. 1.4%) ([22]). Thus, it would appear that there are many variables with the potential to affect the risk of cesarean delivery besides choice of analgesia during labor. These would include patient-related factors such as parity, induction, level of pain, labor pattern, and oxytocin use, as well as obstetrician-related factors such as active or passive management. An editorial suggested that “Perhaps the time has now come to look at the problem in a different way and to ask why labor is prolonged and spontaneous delivery less likely in some units than in others. The realization that labor with regional analgesia is not the same as that without and that management must be modified will hopefully result in improvements in outcome” ([23]). Chestnut ([24]) has made some astute comments on the current state of affairs regarding anesthesia in labor:

1. Use of dilute solutions of local anesthetics in labor may be less likely to have an effect on progress of labor.
2. Administration of epidural analgesia should be delayed until labor is well established; however, it is unnecessary to wait until an arbitrary cervical dilation, such as 5 cm.
3. Studies on patients attempting vaginal birth after cesarean delivery have not shown an increase in cesarean delivery rates when epidural analgesia is used, and good analgesia may encourage some women to attempt vaginal delivery.
4. Use of epidural analgesia during labor may decrease the use of general anesthesia with its attendant risks if emergency cesarean delivery is required.
5. Maternal administration of high doses of narcotics may result in substantial neonatal effects such as respiratory depression ([25]).
6. Maternal–fetal factors and obstetric management, not epidural analgesia, are the most important determinants of the cesarean delivery rate.

OTHER METHODS OF PAIN RELIEF

Prepared Childbirth

Prepared childbirth techniques are based on the belief that pain can be eliminated or reduced by conditioned reflexes of controlled relaxation and that education about the birth process can diminish the pain resulting from fear of the unknown. Parturients and significant others are offered a series of five to ten weekly lectures and are educated about pregnancy, labor, and the delivery process. The parturient is taught how to relax and engages in exercises to strengthen her back and abdominal muscles. She also learns specific breathing patterns to be used while she experiences the discomfort of uterine contractions. All parturients should have access to emotional support, whether by her husband, a family member, a birth attendant (doula), or professional hospital staff. Insurance companies are beginning to pay for doulas as the literature has supported the beneficial effect on decreasing interventions ([26]). Effective courses also teach pregnant women that additional methods of pain relief are available and that these do not cause harm to the fetus. The pregnant woman should be advised that to ask for these other methods does not imply that she is a failure.

Hypnosis

Hypnosis is a state of altered consciousness that requires deep concentration. The patient is not asleep, but she initiates a trance as labor begins and continues it until delivery is completed. The patient must undergo a time-consuming series of training sessions with a hypnotist, and this technique is not always successful ([27]).

Acupuncture

Acupuncture has been used to help control labor pain in China and the Far East for many years. Since the early 1970s, mixed reports of its efficacy have been published in the West. Some studies indicate that acupuncture can significantly lower pain scores and may decrease the duration of the first stage of labor. Although enthusiasm for the technique varies in Western countries, the Chinese continue to report 99% rates of excellent and good success. When acupuncture is used for

cesarean section in conjunction with intravenous meperidine and local anesthetic infiltration, blood pressure, pulse rate, and respirations are stable, and the degree of patient acceptance is reported to be high.

Biofeedback

Biofeedback is provided by a portable electromyographic device through an audible sound and visual monitor. Electrodes placed over the maternal abdomen monitor tension of the abdominal musculature. This technique may be helpful during the first stage of labor and may reduce its duration.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) analgesia is based on the observation that application of a mild electric current to the skin can result in reduction of pain. Activation based on the gate theory and release of enkephalins are possible modes of action. Studies evaluating the effectiveness of TENS suggested that, although the method does no harm, it probably does little good and should not be advocated for widespread use for labor analgesia ([28]).

Intracutaneous Nerve Stimulation

Trolle and colleagues ([29]) evaluated the analgesic effect of intradermal sterile water blocks in women complaining of severe low-back pain during labor. Saline solution was used as a control. Sterile water or saline (0.1 mL) was injected at four different spots in the low-back area, approximately corresponding to the borders of the sacrum. Eighty-nine percent of women in the sterile water group reported an analgesic effect, compared with 45% in the saline group. However, meperidine use in the two groups was similar, as were the rates for oxytocin use and dystocia. The cesarean section rate in the sterile water group was significantly lower due to more cephalopelvic disproportion and malposition of the occiput in the saline group. This technique is free of adverse effects and enjoys a high degree of patient acceptance although the mechanism is unclear.

ANESTHESIA FOR CESAREAN DELIVERY

There are three anesthetic choices for cesarean delivery. Selection of one over the others depends on the patient's desires, medical status, and the urgency of the operation. Regional anesthesia is strongly preferred in the United States (Table 3.4).

	≥1500 Births			<500 Births		
	1981	1992	1997	1981	1992	1997
Epidural (%)	29	54	43	12	29	29
Spinal (%)	33	35	49	37	49	63
General (%)	35	12	8	46	22	8

Source: Adapted from Hawkins JL, et al. Obstetric anesthesia work force survey, 1981 versus 1992. *Anesthesiology* 1997;87:135, and Hawkins JL, et al. *Anesthesiology* 1999; 91:A1060.

TABLE 3.4. *Types of cesarean anesthesia provided by size of hospital in three time periods*

Epidural Anesthesia

Epidural anesthesia accounts for approximately 40% of anesthetics used for cesarean section. It offers the advantages of unlimited duration, minimizing the risks of airway management, and providing a route for postoperative pain management.

To carry out a cesarean delivery, a sensory dermatome level of at least T-4 is required. Anesthesia to this level eliminates proprioception from the respiratory muscles of the chest wall, and the parturient may experience a subjective sensation of dyspnea. Reassurance will usually allay this fear. The patient should be placed on the operating table with the uterus displaced laterally through elevation of the right hip or by tilting of the operating table, to prevent aortocaval compression.

A vascular preload of 1000 to 1500 mL of a non–glucose-containing crystalloid solution should be administered before dosing of the epidural needle or catheter with the anesthetizing solution. A surgical concentration of a local anesthetic (often 2% lidocaine) with or without added opioid is administered through the catheter in 3- to 5-mL increments. The patient should be given oxygen by nasal cannula or by mask. One study failed to reveal any differences in the clinical condition of neonates, as assessed by Apgar scores and blood gas analyses, when oxygen administration by these two modalities was compared.

Epidural opioids have been useful for relieving pain of visceral origin, which affects as many as one-third of the women who have cesarean sections under epidural anesthesia. Visceral pain occurs primarily during bladder retraction, exteriorization of the uterus, and suturing of the peritoneum. The addition of fentanyl or sufentanil to the local anesthetic reduces the time of onset of analgesia, decreases the incidence of nausea, and increases the quality of analgesia without depressing the neurobehavioral status of the newborn.

Studies of fentanyl concentrations in neonates demonstrate that fentanyl crosses the placenta. Even high maternal doses (e.g., 100 µg) of fentanyl yield safe levels in the newborn. Morphine 2 to 4 mg is often administered through the epidural catheter after delivery to provide 12 to 24 hours of postoperative analgesia, although the incidence of associated pruritus and nausea can be high. Use of epidural morphine may reactivate herpetic labialis (herpes simplex virus-1) infections ([30]).

There are several advantages to using epidural analgesia for cesarean section delivery:

- if an epidural catheter is already in place, it can be used expeditiously for the cesarean section delivery.
- maternal hypotension may be less pronounced and slower in onset with epidural than with spinal anesthesia.
- headache is usually avoided, unless the patient sustains an accidental dural puncture.
- the length of anesthesia is controllable in case surgery is prolonged.
- the technique is adaptable for postoperative pain relief.

The disadvantages include:

- the slower onset of analgesia
- the requirement for a larger amount of anesthetic solution with its attendant increased risk of systemic toxicity
- the lower success rate than that experienced with subarachnoid block.

An unexpectedly high level of anesthetic block may be achieved with epidural or spinal anesthesia and, as a result, this should be monitored. The likelihood of inadvertent spinal anesthesia while attempting epidural block can be minimized through gentle aspiration of the catheter combined with using a test dose of sufficiently small volume that it is unlikely to produce a high block. A total spinal block generally occurs within 90 seconds after injection, but it may be delayed for as long as 20 minutes. Dyspnea, hypotension, unconsciousness, and apnea are signs and symptoms of total spinal block. Treatment includes ventilation through an endotracheal tube and, if needed, circulatory support.

Subarachnoid or Spinal Anesthesia

A subarachnoid block provides excellent anesthesia for cesarean section delivery. Over 50% of cesarean deliveries are performed using this technique (see Table 3.4). Prehydration is administered with 1500 to 2000 mL of a non–glucose-containing crystalloid solution. A 22- to 27-gauge pencil-point spinal needle is inserted into the subarachnoid space, which is identified by the characteristic feel of the needle penetrating the dura and observing CSF in the needle. Bupivacaine 0.75%, 10 to 12 mg, with dextrose, is most commonly used. Analgesia of shorter duration is obtained with the use of lidocaine 5% in 7.5% dextrose.

Opioids may also be administered intrathecally to improve quality of analgesia, decrease nausea, and improve cardiovascular stability by allowing a lower dose of local anesthetic. Spinal (as well as epidural) narcotics are associated with a high incidence of pruritus, as well as the rare but real potential for delayed respiratory depression. Fentanyl may be administered to improve intraoperative analgesia while the addition of morphine can provide postoperative analgesia that may last for 18 to 24 hours.

Contraindications to spinal anesthesia are the same as for epidural anesthesia and include patient refusal, septicemia, infection of the puncture site, acute or chronic hypovolemia, and abnormal clotting parameters. Spinal anesthesia is usually avoided in pregnant women with acute CNS disease.

The most common complication of spinal anesthesia is hypotension. This should be treated promptly with fluid administration and intravenous ephedrine (5- to 10-mg bolus). Oxygen should be given, and the parturient's oxygen saturation should be monitored with a pulse oximeter. In the event of a high spinal block which compromises ventilation or airway control, cricoid pressure should be applied and endotracheal intubation performed to prevent aspiration of gastric contents.

With the increasing use of spinal and epidural narcotics, pruritus is becoming a commonplace adverse effect. Its incidence approaches 60% when spinal or epidural morphine is employed. The cause seems to be related to stimulation of opioid receptors rather than to release of histamine. Naloxone can be used to control pruritus, but the dose must be titrated carefully to avoid antagonism of analgesia. Nalbuphine may also be used and is less likely to antagonize analgesia.

Approximately 23% of women experience shivering during normal labor and delivery, and the rate increases to approximately 68% with epidural analgesia. Shivering can be diminished or abolished through epidural injection of opioids (e.g., fentanyl 100 µg) or small intravenous doses of meperidine (e.g., 12.5 mg).

General Anesthesia

General anesthesia is used for cesarean delivery when the patient refuses regional analgesia or has a contraindication to regional analgesia, or when a need exists for rapid delivery because of fetal distress, cord prolapse, shoulder dystocia, or maternal hemorrhage.

The American College of Obstetricians and Gynecologists in the fifth edition of *Guidelines for Perinatal Care*, cites the risk factors for failed intubation and urges obstetricians to be alert to the presence of the factors that place parturients at increased risk for complications from emergency general anesthesia. Among these are marked obesity, severe facial and neck edema, extremely short stature, short neck, difficulty opening the mouth, a small mandible, protuberant teeth, arthritis of the neck, anatomic abnormalities of the face or mouth, a large thyroid gland, asthma, serious medical or obstetric complications, and a history of problems with anesthetics. If any of these factors is identified, a member of the anesthesia team should be consulted to prepare for the unexpected need to induce general anesthesia. If the anesthesiologist has concerns about his or her ability to intubate the patient, early placement of a regional anesthetic should be planned or arrangements for an awake intubation should be made.

Pneumonitis resulting from aspiration of gastric contents has long been feared as a complication of general anesthesia for obstetrics, but is extremely rare. One review compared the incidence of aspiration in obstetric and gynecological patients ([31]). The incidence of clinically significant aspiration was 0.11% in women undergoing cesarean delivery compared to 0.01% in gynecology inpatients. No patient died, but morbidity was significant. The prudent anesthetist administers a nonparticulate oral antacid, such as sodium citrate, given prophylactically to increase the gastric pH. If time allows, an H_2-blocker (e.g., ranitidine 50 mg intravenously) should be administered. Intravenous metoclopramide, 10 mg, hastens gastric emptying, increases gastroesophageal sphincter tone, and may decrease nausea.

Before induction of anesthesia, the patient should be preoxygenated with 100% oxygen by mask for at least 3 minutes. Induction is commonly carried out using thiopental (3–4 mg per kg i.v.). Propofol (Diprivan) has also been used. Propofol is associated with a blunted hypertensive response to endotracheal intubation and has yielded similar and satisfactory Apgar scores, neurologic and adaptive capacity scores, and umbilical cord blood gas analyses. If propofol infusion is used for maintenance of anesthesia for a prolonged time before delivery, neonatal blood levels are high, and neurologic and adaptive capacity scores may be impaired. If the patient is hemodynamically unstable, ketamine 1 mg per kg or etomidate 0.3 mg per kg may be used.

Intubation is facilitated by use of succinylcholine. Cricoid pressure is maintained during induction of anesthesia until the endotracheal tube is in place, the cuff has been inflated, respirations have been auscultated, and end-tidal carbon dioxide has been seen. After successful intubation, a mixture of equal parts of nitrous oxide and oxygen may be administered, and a low dose of an inhalational agent, such as desflurane 3%, sevoflurane 1% or isoflurane 0.75%, is administered to optimize maternal analgesia and amnesia. These low concentrations have minimal effects on uterine contractility and are not associated with postpartum hemorrhage. After delivery of the infant, the nitrous oxide concentration may be increased to 70%, and narcotics may be given intravenously to supplement the anesthesia. Midazolam may be used to decrease the risk of maternal recall.

The advantages of general anesthesia include:

- reliability of the technique
- rapidity of induction of anesthesia
- avoidance of sympathetic blockade and hypotension.

The disadvantages include:

- the risks of maternal aspiration of gastric contents
- failed intubation
- maternal awareness
- hypertension during manipulation of the larynx.

If the cords are poorly visualized during laryngoscopy, no more than three attempts at endotracheal intubation should be made before beginning a failed intubation drill ([32]). The initial maneuver in the failed intubation drill depends on the obstetric indication for cesarean section. If the operation is not emergent, the patient should be awakened and an epidural or spinal block performed. If a regional anesthetic cannot be accomplished, an awake fiberoptic intubation should be considered. In an obstetric emergency where surgery must proceed, the patient must be ventilated with bag and mask or laryngeal mask airway, and anesthesia may be maintained with inhalational or intravenous agents throughout the remainder of the cesarean section. The continuation of cricoid pressure is important to reduce the maternal risk of aspiration. If it should prove impossible to ventilate the patient with bag and mask, an emergency maneuver such as cricothyroidotomy must be performed. Use of an esophageal gastric tube airway (Combitube) or laryngeal mask may enable adequate ventilation.

Inability to intubate has been estimated to occur seven times more commonly in the obstetric patient than in the general operating room, and continues to contribute significantly to anesthetic causes of maternal mortality ([33]). Anticipation of a difficult intubation allows the anesthesia team to be prepared to avoid general anesthesia or plan an awake intubation.

Analgesia after Cesarean Section

Considerable advances have been made in the management of pain after cesarean section. The availability of spinal and epidural narcotics has enabled the anesthesia team to provide the postsurgical patient with effective, long-term analgesia. Morphine is the most commonly used neuraxial opioid because of its long duration and lack of motor block compared to local anesthetic infusions. The most feared complication is respiratory depression. The rate of analgesia-related respiratory depression is approximately 0.09%. Because this complication is rare, patients receiving postoperative neuraxial opioid analgesia may be safely nursed on the general ward, if the nurses are appropriately educated in monitoring the degree of somnolence and the respiratory rates of their patients. Patients who did not receive regional anesthesia may receive intravenous PCA. Combining narcotics and nonsteroidal antiinflammatory medications such as ketorolac or ibuprofen improves the quality of analgesia and allows reduced doses of narcotics. Naloxone should be readily available to antagonize respiratory depression.

SUMMARY POINTS

- Pain management is an important part of modern obstetric care. Most women will request some form of analgesia during childbirth.
- Parenteral narcotics for labor analgesia may be administered by intermittent injection or patient-controlled intravenous infusion. There are advantages and disadvantages of all opioids.
- High systemic blood levels of local anesthetic caused by intravascular injection or excessive absorption may lead to convulsions and cardiac arrest. Resuscitation equipment must be immediately available whenever regional blocks are used.
- Modern techniques of regional analgesia for labor (dilute concentrations of epidural local anesthetics, combined spinal–epidural analgesia and patient-controlled epidural infusions) emphasize pain relief with minimal motor block. Studies indicate these techniques do not impact progress of labor.
- Although modern anesthetic care for cesarean delivery is extremely safe (anesthesia-related maternal mortality = 1.1 per million live births), general anesthesia complications are more common than regional anesthetic complications because of difficulties with airway management.

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Chapter 4

D. Ware Branch and James R. Scott

Early Pregnancy Loss

EPIDEMIOLOGY
ETIOLOGY
Embryonic Factors
Parental Factors
PATHOLOGY
CLINICAL FEATURES AND TREATMENT
Threatened Miscarriage
Inevitable and Incomplete Miscarriage
Complete Miscarriage
Missed Miscarriage
Septic Miscarriage
RECURRENT MISCARRIAGE
Known and Suspected Causes of Recurrent Miscarriage
Recommendations for Recurrent Miscarriage
SUMMARY POINTS
SUGGESTED READINGS

The term *spontaneous abortion*, which has a negative connotation to many patients, is gradually being replaced by the word *miscarriage.* Both terms originally defined pregnancy losses prior to 20 weeks gestation, but they are more commonly used by physicians to describe first-trimester losses. These arbitrary time limits have become less useful with advances in developmental biology and diagnostic sonography. The preembryonic period is defined as conception through the first 5 weeks of pregnancy from the first day of the last menstrual period. The embryonic period encompasses 6 to 9 weeks gestation, and the fetal period is from 10 weeks until delivery.

EPIDEMIOLOGY

Human reproduction is relatively inefficient, and miscarriage is the most common complication of pregnancy, with an overall incidence of approximately 15% among clinically recognized pregnancies. The rate of miscarriage is, however, heavily dependent upon the past obstetric history, being higher among women with prior miscarriages and lower among women whose past pregnancy(ies) ended in live births.

Histologically defective ova found in hysterectomy specimens (Fig. 4.1) and data on early pregnancies detected with sensitive ß-human chorionic gonadotropin (ß-hCG) assays indicate that the very early and often unrecognized pregnancy loss rate is two to three times higher than that of recognized pregnancy. The prevalence of miscarriage also increases with maternal age from 12% in women younger than 20 years of age to over 50% in women older than 45 years of age (Fig. 4.2).

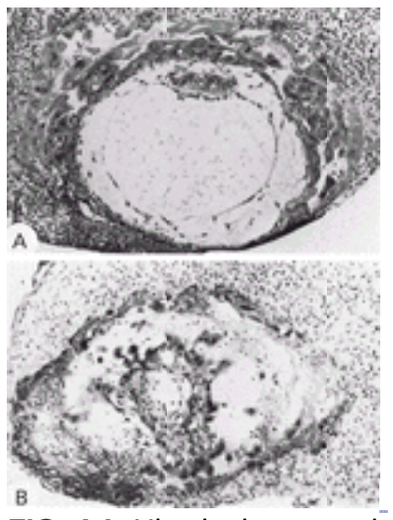

FIG. 4.1. Histologic comparison of **(A)** a morphologically normally implanted human ovum estimated to be about 11 to 12 days of age with **(B)** an abnormal conceptus, showing a defective trophoblast with pathologically large lacunae and an empty chorionic sac that is destined to abort. (From Hertig AT, Rock J, Adams EC. *Am J Anat* 1956;98:435, with permission.)

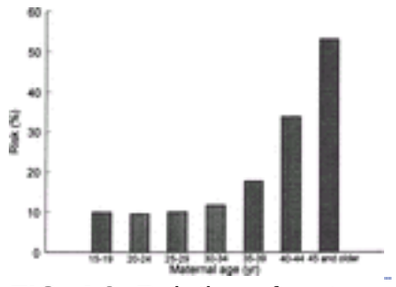

FIG. 4.2. Relation of maternal age to the risk of spontaneous abortion. (Data from Warburtin D, Kline J, Stein Z, et al. Cytogenetic abnormalities in spontaneous abortions of recognized conceptions. In: Porter IH, ed. *Perinatal genetics: diagnosis and treatment.* New York: Academic Press, 1986:133.)

ETIOLOGY

In view of the complicated genetic, hormonal, immunologic, and cellular events requiring precise integration for fertilization, implantation, and embryonic development, it is remarkable that successful pregnancy occurs so often. When early pregnancy loss occurs, it can be due to a number of embryonic and parental factors.

Embryonic Factors

Most single, sporadic miscarriages are caused by nonrepetitive intrinsic defects in the developing conceptus, such as abnormal germ cells, chromosomal abnormalities in the conceptus, defective implantation, defects in the developing placenta or embryo, accidental injuries to the fetus, and probably other causes as yet unrecognized. Fifty percent of women presenting with spotting or cramping already have a nonviable conceptus by sonogram, and many of these embryos are morphologically abnormal. About one-third of abortus specimens from losses occurring before 9 weeks gestation are anembryonic. Some cases of empty gestational sacs or “blighted ova” actually represent pregnancy failures with subsequent embryonic resorption. The high proportion of abnormal aborted concepti is apparently the result of a selective process that eliminates about 95% of morphologic and cytogenetic errors.

The frequency of chromosomally abnormal spontaneously aborted products of conception in the first trimester is approximately 60% and decreases to 7% by the end of week 24 (Fig. 4.3). The rate of genetic abnormalities is even higher in anembryonic miscarriages. Autosomal trisomies are the most common (51.9%) and arise de novo as a result of meiotic nondisjunction during gametogenesis in parents with normal karyotypes. The relative frequency of each type of trisomy differs considerably.

Trisomy 16, which accounts for about one-third of all trisomic abortions, has not been reported in live-born infants and is therefore uniformly lethal. Trisomy 22 and 21 follow in frequency. The next most common chromosomal abnormalities, in decreasing order, are monosomy 45,X (the single most common karyotypic abnormality), triploidy, tetraploidy, translocations, and mosaicism.

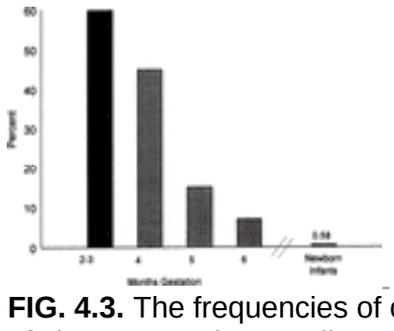

FIG. 4.3. The frequencies of chromosomal anomalies among 3040 spontaneously aborted fetuses related to the duration of pregnancy. For comparison, the frequency of chromosomal anomalies among 54,749 newborn infants is shown. (Data from Shiota K, Uwabe C, Nishimaura H. High prevalence of defective human embryos at the early implantation period. *Teratology* 1987;35:309; Boue J, Boue A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. *Teratology* 1975;12:11; Lauritsen JG. Aetiology of spontaneous abortion: a cytogenetic and epidemiological study of 288 abortuses and their parents. *Acta Obstet Gynecol Scand Suppl* 1976;52:1; and Creasy MR, Crolla JA, Alberman ED. A cytogenetic study of human spontaneous abortions using banding techniques. *Hum Genet* 1976;31:177.)

Parental Factors

In a small percentage of cases, one member of the couple is the carrier of a balanced translocation, and the offspring of these parents may be repeatedly aborted. Media publicity tends to give the impression that a variety of agents such as infections, video display terminals, cigarette smoking, coffee, ethanol, chemical agents, and drugs (see Chapter 7) markedly increase the risk of miscarriage. In reality, there is little credible evidence that extrinsic factors account for anything other than a very small proportion of early pregnancy loss.

PATHOLOGY

Most miscarriages occur within a few weeks after the death of the embryo or rudimentary analog. Initially, there is hemorrhage into the decidua basalis, with necrosis and inflammation in the region of implantation. The gestational sac is partially or entirely detached. Uterine contractions and dilation of the cervix usually result in expulsion of most or all of the products of conception. When the sac is opened, fluid is often found surrounding a small macerated embryo, or there may be no visible embryo in the sac. Histologically, hydropic degeneration of the placental villi caused by retention of tissue fluid is common.

CLINICAL FEATURES AND TREATMENT

An unrecognized pregnancy episode should always be considered a possibility in any woman of reproductive age with abnormal bleeding or pain. Each new pregnant patient should also be instructed to notify her physician promptly about vaginal bleeding or uterine cramps. Since management depends on a number of factors, it is convenient to consider the clinical aspects of miscarriage under the following subgroups.

Threatened Miscarriage

Any bloody vaginal discharge or uterine bleeding that occurs during the first half of pregnancy has traditionally been assumed to be a threatened miscarriage. Because as many as 25% of pregnant women have some degree of spotting or bleeding during the early months of gestation, it is a common diagnosis.

Bleeding associated with threatened miscarriage is typically scanty, varies from a brownish discharge to bright red bleeding, and may occur repeatedly over the course of many days. It usually precedes uterine cramping or low backache. On pelvic examination, the cervix is closed and uneffaced, and no tissue has passed. The differential diagnosis includes ectopic pregnancy, molar pregnancy, vaginal ulcerations, cervicitis with bleeding, cervical erosions, polyps, and carcinoma.

A viable conceptus can be detected with modern ultrasound as early as 5.5 weeks of gestation. The ability to visualize the embryo and embryonic heart motion has made evaluation and management of threatened miscarriage more precise. However, accurate knowledge of gestational age is necessary for proper interpretation. Ultrasound findings are unreliable at 3 to 4 weeks gestation, and what appears to be an empty uterus can be misinterpreted as an abnormal intrauterine or ectopic pregnancy when it is actually a normal early gestation. If there is any doubt of normalcy, it is best to perform serial ß-hCG measurements and a follow-up sonogram. From 5 to 6 weeks, the yolk sac and gestational sac are visible by transvaginal ultrasound, and the embryo with cardiac activity is seen soon after that. Abnormal gestational sac and yolk sac size, an embryo small for dates, and slow embryonic heart rates suggest impending pregnancy loss. The presence of an appropriately sized embryo with a normal cardiac rate is encouraging, even in the setting of uterine bleeding, and more than two thirds of these will survive. In the absence of signs of miscarriage, more than 95% of pregnancies continue if a live embryo is demonstrated ultrasonically at 8 weeks gestation. These embryos have a very low mortality rate during the next few weeks, and the subsequent pregnancy loss rate is only 1% if a live fetus is seen at 14 to 16 weeks gestation.

Although there is no convincing evidence that any treatment favorably influences the course of threatened miscarriage, a sympathetic attitude by the physician along with continuing support and follow-up are important to patients. This includes a tactful explanation about the pathologic process and favorable prognosis when the pregnancy is viable. An optimistic but cautious approach is prudent, since a few of these women will have a later embryonic or fetal death. It is reasonable to advise patients to remain available to medical care until it can be determined whether the symptoms will persist or cease. Continued observation is indicated as long as bleeding and cramping are mild, the cervix remains closed, quantitative ß-hCG levels are increasing normally, and a normal embryo or fetus is evident on follow-up sonogram. If the bleeding and cramping progressively increase, the prognosis becomes worse. An unfavorable outcome is also associated with negative or falling ß-hCG values, sonographic evidence of an embryo or fetus decreasing in size (Fig. 4.4), a slow heart rate, and a uterus that is not increasing in size on pelvic examination. If careful clinical evaluation indicates that the conceptus is no longer viable, the treatment options are expectant management or evacuation of the uterus. In women with minimal intrauterine tissue by ultrasound, waiting for spontaneous passage of the products of conception is possible. The complication rate may be decreased by elective uterine curettage in patients with significant amounts of tissue (see “ Missed Miscarriage” later in the chapter).

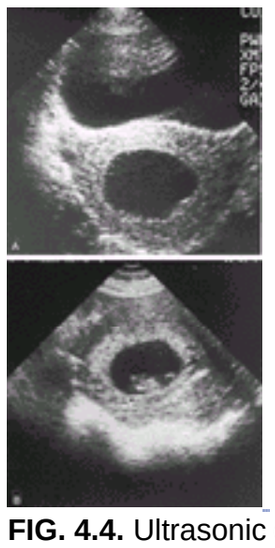

FIG. 4.4. Ultrasonic comparison of **(A)** an anembryonic pregnancy with no fetal tissue that is destined to abort with **(B)** a normal gestational sac with a transonic area, echogenic rim, and fetal pole.

Inevitable and Incomplete Miscarriage

Early pregnancy loss is a process rather than a single event. Previously classified as different entities, inevitable and incomplete miscarriages present a similar clinical picture and are treated in the same way. A miscarriage is inevitable when bleeding or gross rupture of the membranes is accompanied by pain and dilation of the cervix. The miscarriage is incomplete when the products of conception have partially passed from the uterine cavity, are protruding from the external os, or are in the vagina with persistent bleeding and cramping. Placental tissue is more likely to be retained when this occurs in the second trimester. Bleeding can be profuse and occasionally produces hypovolemia. A careful vaginal examination usually establishes the diagnosis. Rarely, one conceptus is aborted, and a normal retained twin proceeds to delivery at term. This unusual situation can be diagnosed by ultrasound at the time of first-trimester bleeding. There is otherwise no fetal survival in inevitable or incomplete miscarriages. Evacuation of the uterus is advisable to prevent maternal complications from further hemorrhage or infection.

In most cases, suction curettage can be performed promptly and safely in an outpatient setting using analgesia, a paracervical block, and an intravenous infusion of normal saline containing 10 to 20 U of oxytocin. Often, the cervix is dilated, and the products of conception can be removed from the cervical canal and lower uterine segment with ring forceps to facilitate uterine contractions and hemostasis. Suction curettage is performed using a plastic curette and vacuum pressure. As the curettage proceeds, tissue can be seen as it flows through the curette and suction tubing. The curette is rotated 360 degrees clockwise as it is withdrawn, and the procedure is repeated in a counterclockwise direction. When a grating sensation is noted and no more tissue is obtained, the endometrial cavity has been emptied.

Preparation is necessary to anticipate any problems such as allergic reactions to medication, uterine atony, uterine perforation, seizure, or cardiac arrest. In selected cases, a hemoglobin level should be obtained, and blood replacement may be necessary if hemorrhage occurs. If measures taken in the emergency room fail to promptly control bleeding, the patient should be transferred to the operating room for an examination under anesthesia and evacuation of the uterus. After curettage, the patient is observed for several hours. When stable, she is discharged and followed as an outpatient.

Medical management of incomplete miscarriage has been explored in well-designed trials. Misoprostol may be used instead of surgical evacuation of the uterus in clinically stable patients, though the need for uterine curettage in the misoprostol-treated patients is high (50%). In spite of this, misoprostol treatment of incomplete miscarriage is associated with lower rates of short- and long-term complications compared to surgical evacuation.

Rh-negative women with miscarriage should receive 50 g (in the first trimester) or the standard 300-g (in the second trimester) dose of Rh immune globulin to prevent Rh immunization. The tissue obtained should be examined to confirm the presence of products of conception and rule out the possibility of ectopic pregnancy.

Complete Miscarriage

Patients followed for a threatened miscarriage are instructed to save all tissue passed, so it can be inspected. When the entire products of conception have passed, pain and bleeding soon cease. If the diagnosis is certain, no further therapy is necessary. In questionable cases, ultrasound is useful to determine that the uterus is empty. In some circumstances, curettage may be necessary to be sure that the uterus is completely evacuated. Removal of remaining necrotic decidua decreases the incidence of bleeding and shortens the recovery time.

Missed Miscarriage

In this situation, expulsion of the conceptus does not occur despite a prolonged period after embryonic death. The reason that some dead embryos do not abort spontaneously is not clear. Typically, the patient's symptoms of pregnancy regress, the pregnancy test becomes negative, and no fetal heart motion is detected by ultrasound. Most patients do eventually abort spontaneously, and coagulation defects due to retention of a dead fetus are rare in the first half of pregnancy. However, expectant management is emotionally trying, and many women prefer to have the uterus evacuated. During the first trimester, this is done by suction curettage preceded by cervical preparation using misoprostol or insertion of laminaria if the cervix is closed. The procedure is often performed in a hospital setting with intravenous fluids and blood available in case significant bleeding occurs.

Evacuation of the uterus by medical means is also an acceptable approach in the first trimester. In one randomized, controlled trial, an 80% complete abortion rate was achieved using 800-µg of misoprostol (four 200-µg tablets) per vagina every four hours, and the need for dilation and curettage (D&C) was reduced to 28%. Most patients responded to the first dose of misoprostol. Combination regimens that include methotrexate or RU-486 with misoprostol appear even more promising, but have not yet been tested in missed abortion.

In the second trimester, the uterus can be emptied by dilation and evacuation (D&E) or induction of labor with intravaginal prostaglandin E_2 (PGE_2) or misoprostol. D&E is an extension of the traditional D&C and vacuum curettage. It is especially appropriate at 13 to 16 weeks gestation, although many proponents use this procedure through 20 weeks. The cervix is usually first prepared using misoprostol or passively dilated with laminaria to avoid trauma, and the fetus and placenta are mechanically removed with suction and instruments.

If induction of labor is chosen, vaginal PGE_2 is used, one 20-mg suppository is placed high in the posterior vaginal vault every 4 hours until the fetus and placenta are expelled. Between 2.5 and 5 mg of diphenoxylate given orally and 10 mg of prochlorperazine given intramuscularly can control diarrhea and nausea, and narcotics or epidural anesthesia can be used to control pain. In this situation, a retained placenta is relatively common and may require manual removal and uterine curettage. Misoprostol, 200-µg tablets placed high in the vagina every 4 hours, is equally effective. This regimen may cause less nausea, vomiting, diarrhea, and fever than PGE_2.

Septic Miscarriage

Septic abortion, once a leading cause of maternal mortality, has become a less frequent occurrence, primarily because changes in abortion laws have made pregnancy terminations by physicians available to women with unwanted pregnancies. However, any type of spontaneous miscarriage can also be complicated by infection. The infection is most commonly endometritis but can progress to parametritis and peritonitis. These patients present with fever, abdominal tenderness, and uterine pain. In severe cases, local infection progresses to septicemia and septic shock. The polymicrobial infection mirrors the endogenous vaginal flora and includes *Escherichia coli* and other aerobic, enteric, Gram-negative rods, group B-hemolytic streptococci, anaerobic streptococci, *Bacteroides* species, staphylococci, and microaerophilic bacteria.

The initial evaluation and management of septic abortion should include several steps:

- physical and pelvic examination
- complete blood cell count and determination of electrolyte, blood urea nitrogen, and creatinine levels
- type and screen or crossmatch of blood
- smears from cervix for Gram stain
- aerobic and anaerobic cultures of endocervix, blood, and available products of conception
- indwelling Foley catheter
- intravenous fluids (e.g., saline, Ringer lactate) through a large-bore angiocatheter
- administration of 0.5 mL of tetanus toxoid, given subcutaneously for immunized patients, or 250 U of tetanus immune globulin, administered deep within the muscle
- supine and upright radiographs of the abdomen to detect free air or foreign bodies.

Optimal therapy consists of evacuation of the uterus and aggressive use of parenteral antibiotics before, during, and after removal of necrotic tissue by curettage (Table 4.1). Prompt removal of the infected tissue is important and should be performed within a few hours after beginning intravenous antibiotics. Numerous antibiotic regimens have been recommended, but high-dose, broad-spectrum coverage as outlined in Table 4.1 is essential. Although most patients with septic abortions respond favorably to treatment, septic shock syndrome is a serious complication that requires aggressive management in an intensive care setting (see Chapter 25).

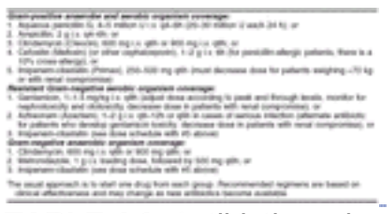

TABLE 4.1. *Antibiotic regimens for septic abortion*

RECURRENT MISCARRIAGE

Recurrent miscarriage (RM), traditionally defined as three or more consecutive first-trimester spontaneous losses, affects up to 1% of couples. Primary recurrent miscarriage is diagnosed in women who have never had a successful pregnancy, and secondary recurrent miscarriage in those whose repetitive losses follow a live birth. There is no specific classification for women who have multiple miscarriages interspersed with normal pregnancies. It is generally agreed that a workup for possible causes of RM is indicated in most patients after two or three consecutive miscarriages.

The management of couples with RM is controversial. This clinical entity has received much attention in the lay and medical literature during the past decade. A definite cause is established in no more than 50% of couples, and several alleged causes of RM are controversial. Despite publicity to the contrary, there is little evidence that poor nutrition, infections, unrecognized diabetes, toxic agents, or psychological trauma are significant etiologic factors. Some alleged experts and Internet sites inappropriately emphasize unproven hypotheses and results from poorly designed clinical studies. Seeking a solution, some patients and physicians may explore less well-accepted etiologies and empirical or alternative treatments. Moreover, new diagnostic tests for RM are continually being proposed to replace those that have been disproved and discarded. For example, antithyroid antibodies, elevated follicular-phase luteinizing hormone levels, circulating maternal embryotoxic factor, and abnormal lymphocyte subset ratios (elevated $CD56^{+}$ levels) have been touted within the last decade. It is beyond the scope of this chapter to critically analyze each new “treatment” or assay, but the mechanism of pregnancy loss and potential relationship to each of these remains largely theoretical. Until effective treatments are identified and proven by properly designed studies, these screening tests have little use in the routine evaluation of patients with RM.

Typically, investigation of anatomic, hormonal, genetic, and infectious factors has been recommended. Even these may be criticized because the derivation of their diagnostic use and treatments advocated are empirical and have come under scrutiny because they were never submitted to properly designed study. Importantly, evidence has mounted that the average women with RM has a fairly good prognosis for a successful next pregnancy without any specific treatment.

Known and Suspected Causes of Recurrent Miscarriage

Structural Uterine Defects Hysterosalpingography, magnetic resonance imaging, hysteroscopy, sonohysteroscopy, and laparoscopy can be used to diagnose septate uterus, other müllerian anomalies, uterine defects associated with diethylstilbestrol exposure, submucous myomas, and intrauterine synechiae. The prognosis for successful pregnancies in patients with müllerian anomalies is related to the type of malformation, with asymmetric fusion defects carrying the worst prognosis and septate, bicornuate, and didelphic uteri carrying increasingly better prognoses. In patients with RM, the prevalence of these anatomic defects is approximately 10% to 15%. The cause of pregnancy loss in women with uterine anomalies is uncertain. A diminished blood supply interfering with normal implantation and placentation and the reduced size of the uterine cavity are often cited as possible causes, but these reasons seem unlikely or insubstantial in the setting of the arcuate uterus. Abdominal metroplasty has been replaced in most cases by the hysteroscopic removal of uterine septa. This procedure can be accomplished in an outpatient setting and eliminates the need for cesarean delivery. Noncontrolled, retrospective studies suggest the subsequent live-birth rate is greater than 80%. Removal of synechiae and submucous myomas can also be performed hysteroscopically (see Chapter 47).

Endocrine Problems The luteal phase defect (LPD) has long been thought to be a cause of spontaneous abortion, but the evidence linking LPD to recurrent abortion is subject to criticism. It is traditionally thought that women with LPD have short menstrual cycles, postovulatory intervals less than 14 days, and secondary infertility. LPD was initially thought to be due to failure of the corpus luteum to make enough progesterone to establish a mature endometrial lining suitable for placentation. This theory has evolved to implicate poor follicular-phase oocyte development, which results in disordered estrogen secretion, inadequate ovarian steroidogenesis, and subsequent maldevelopment of endometrial receptors. In turn, these effects could result from excess luteinizing hormone or hyperandrogenic states. Some investigators claim that LPD accounts for over one fourth of cases of RM, but studies of this disorder have not included concurrently tested controls. Also, there is little agreement on the criteria necessary to make the diagnosis. Endometrial biopsy or luteal-phase serum progesterone levels are the most widely accepted diagnostic tests. Both are timed for the late luteal phase of the cycle. The endometrial biopsy is histologically dated, and a lag greater than 2 to 3 days is considered suspect. However, this should be confirmed by repeat biopsy, because delayed endometrial histology can occur sporadically in women with no reproductive problems. To further confuse the issue, normal women have endometrial histology suggestive of LPD in up to 50% of single menstrual cycles and 25% of sequential cycles. Though the association between LPD and RM remains speculative, many clinicians have treated women with RM with progesterone in their next pregnancy. One commonly advocated treatment is a 25-mg progesterone suppository inserted into the vagina twice a day (morning and night) beginning after ovulation and continuing until menses begin or through the first 8 to 10 weeks of pregnancy. Comparable doses of oral micronized progesterone have also been used. No properly designed studies have evaluated the role of progesterone treatment in women with RM with LPD. Older studies and meta-analyses are difficult to interpret because of marked differences in inclusion criteria and how LPD was diagnosed, the use of various progesterone compounds, and the small number of women studied. In a more recent randomized trial, a subgroup of women with polycystic ovary syndrome (PCOS) and three or more miscarriages were randomized to treatment with either progesterone or placebo pessaries. There was no difference in the pregnancy outcomes. Clomiphene and other ovulatory agents have been tried to improve follicular development and corpus luteum function, but the results have been variable. Human chorionic gonadotropin has been used in an attempt to stimulate the corpus luteum support of pregnancy in women with RM. One placebo-controlled, multicentered trial found no significant difference in the successful pregnancy rates (83% vs. 79%). In summary, the relationship between the LPD and recurrent pregnancy loss remains a subject of controversy. It has not been shown conclusively that progesterone treatment or corpus luteum support influences pregnancy outcome in women with recurrent pregnancy loss. PCOS has been found in one third or more of women with RM. However, the diagnosis of PCOS in women with RM does not predict a worse pregnancy outcome than in women with RM without PCOS. There is no known effective therapy for women with PCOS and RM.

Genetic Abnormalities Parental chromosomal anomalies are found in approximately 3% to 5% of couples with RM. Cytogenetic examination of both partners is helpful to predict recurrence and forms the basis for genetic counseling. Most abnormalities are balanced translocations, with two-thirds being reciprocal translocations and one-third robertsonian translocations. Couples with balanced translocations have spontaneous loss rates ranging from 50% for reciprocal translocations to 25% for robertsonian translocations. All couples with a parental chromosomal abnormality deserve counseling about genetic amniocentesis or chorionic villus sampling in any future pregnancy to exclude a serious fetal chromosomal abnormality. Parental chromosomal abnormalities do not usually preclude further attempts at pregnancy, because most couples eventually have normal offspring. For the rare homologous robertsonian translocation that prevents successful pregnancy, therapeutic possibilities include artificial donor insemination, in vitro fertilization with donor oocytes, and adoption. Chromosomal analysis of the products of conception is also clinically useful, particularly in the evaluation of the reason for failure of a treatment regimen. Molecular mutations that may be shown in the future to cause recurrent miscarriages include lethal, single-point mutations, possibly linked to *MHC* genes; mutations in genes that code for products critical for normal development; mutations in homeobox genes that control transcriptional regulation; mutations that lead to severe metabolic errors and embryonic death; and disorders of protooncogenes and oncogenes. One group has shown that certain polymorphisms of the *HLA-G* gene are associated with significantly higher rates of miscarriage among couples presenting with RM. Also, marked skewing of the normal 50:50 distribution of X chromosome inactivation in the mother, a condition termed *highly skewed X-chromosome inactivation*, may be associated with otherwise unexplained RM. Before testing is recommended, confirmation of these molecular genetic associations in different populations is required. For now, commercially available tests for these conditions are not widely available, and there are no proven treatment options.

Autoimmune Disorders

Antiphospholipid Syndrome Antiphospholipid syndrome (APS) has been recognized as a proven cause of pregnancy loss for over a decade. Approximately 5% to 15% of women with RM have lupus anticoagulant (LA), anticardiolipin (aCL), or both. These acquired antiphospholipid autoantibodies are induced by as yet unknown stimuli in the setting of aberrant immunoregulation. Low levels of immune globulin G or immune globulin M aCL are of questionable significance. Though women with APS may present with RM in the first trimester, fetal death in the second or early third trimesters may be more specific for the condition. Patients with high levels of aCL or a history of prior fetal death are at greatest risk of another fetal loss. The cause of fetal death appears to be a decidual vasculopathy that results in decidual infarction and insufficient blood flow to the placenta. Intervillous thrombosis has also been described. However, these lesions are nonspecific, and the degree of pathology is not always sufficient to explain the fetal death. The mechanisms by which aCL may cause decidual vasculopathy and fetal death are unknown. A number of pathophysiologic mechanisms have been proposed, including an imbalance of local prostacyclin and thromboxane production, enhanced platelet aggregation, decreased activation of protein C, increased tissue factor, and decreased trophoblast annexin V production or availability. Most recently, the complement system has been invoked as having a major role in antiphospholipid syndrome-related pregnancy loss. Maternally administered heparin is widely considered the treatment of choice for APS pregnancies, both to improve embryo-fetal outcome and protect the mother from thrombotic events (Table 4.2). Treatment is usually initiated in the early first trimester after ultrasonographic demonstration of a live embryo. The dose of heparin required for safe and effective treatment, however, is debated. Some experts use relatively low doses of heparin (e.g., 5000 U of standard heparin b.i.d.), particularly when treating women with recurrent preembryonic or embryonic losses. However, higher doses of heparin are recommended for patients with APS with prior thrombosis, and some experts urge full anticoagulation. The optimal dose of heparin is controversial for women whose APS is diagnosed because of prior fetal loss or neonatal death after delivery before 34 weeks gestation due to severe preeclampsia or placental insufficiency, but who do not have a history of thromboembolism. These women are at risk for thromboembolic disease, and it is our opinion that these cases should receive sufficient thromboprophylaxis. Low molecular-weight heparins (LMWHs) are widely used in Europe for the treatment of APS pregnancy, and there is little reason to suspect that the appropriate use of LMWHs differs from that of standard heparin with regard to efficacy. In most case series and trials, daily low-dose aspirin is included in the treatment regimen. One important caveat deserves mention—a small, placebo-controlled trial found that otherwise

healthy women with RM and low titers of antiphospholipid antibodies do not require treatment.

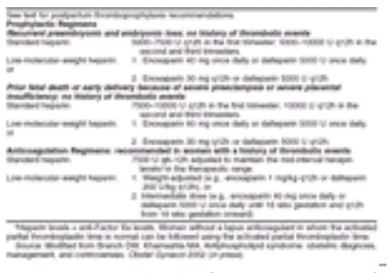

TABLE 4.2. *Subcutaneous heparin regimens used in the treatment of antiphospholipid syndrome during pregnancy*

Intravenous immune globulin has also been used during pregnancy, usually in conjunction with heparin and low-dose aspirin, especially in women with particularly poor past histories or recurrent pregnancy loss during heparin treatment. However, a randomized, controlled, pilot study of intravenous immune globulin treatment during pregnancy in unselected APS cases proved negative. Anticoagulant coverage of the postpartum period in women with APS and prior thrombosis is critical. We prefer switching the patient to warfarin thromboprophylaxis as soon as she is clinically stable from delivery. In most cases, an international normalized ratio of 3.0 is desirable, and postpartum coverage should extend for 6 to 8 weeks after delivery. Because of their risk for thrombosis, the same strategy is recommended in women without prior thrombosis but in whom APS is diagnosed because of prior fetal loss or neonatal death after delivery at or before 34 weeks gestation for severe preeclampsia or placental insufficiency. Both heparin and warfarin are safe for nursing mothers. The need for postpartum anticoagulation in women with primary APS diagnosed solely on the basis of recurrent preembryonic and embryonic losses is unclear.

Other Autoimmune Disorders Autoantibodies to thyroid antigens are associated with a modest increased rate of pregnancy loss if identified in early pregnancy or immediately before pregnancy. Some investigators have found a significant proportion of women with RM to have antithyroid antibodies; others have not. Even if antithyroid antibodies are associated with RM, no treatment options have proven beneficial. Approximately 15% of women with RM have detectable antinuclear antibodies (ANA). Subsequent pregnancy outcomes among women with a positive ANA test result are similar to those among women with a negative ANA test result. A randomized treatment trial of women with recurrent pregnancy loss and a positive autoantibody result, including ANA, found no benefit to treatment with prednisone and low-dose aspirin and treatment with placebo. Thus, currently available data do not support testing women with recurrent pregnancy loss for ANA.

Thrombophilic Disorders The relationship between inherited thrombophilic disorders and recurrent miscarriage has been the subject of intense study within the last several years. The most common inherited thrombophilic disorders are factor V Leiden and prothrombin G20210A mutation, found in approximately 8% and 3%, respectively, of Caucasian women in the United States. These mutations are associated with approximately 25% of isolated thrombotic events and approximately 50% of familial thrombosis. Other less common thrombophilias include deficiencies of the anticoagulants protein C, protein S, and antithrombin III. Hyperhomocysteinemia, most commonly due to the C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene, is also associated with venous thrombosis. Data regarding the association of these thrombophilic abnormalities and RM do not allow clear and consistent conclusions. The rather obvious fact that most women with common thrombophilic mutations, such as factor V Leiden, the prothrombin G20210A mutation, or the MTHFR C677T mutation, do *not* have RM further confounds the picture. One prospective study of next pregnancies in women with RM found a significantly lower successful pregnancy rate among those with the factor V Leiden mutation compared to those without (37.5% vs. 69.3%). Various studies are more consistent in finding an association between thrombophilias and second- or third-trimester fetal loss. The odds ratio for stillbirth is significantly higher in women with combined thrombophilic defects. Some women with RM have evidence of ongoing, perhaps chronic, thrombin generation or the formation of thrombosis-related microparticles. These studies underscore the potential importance of prothrombotic states to pregnancy loss, but more research is required to bring the current findings into the clinical realm. Despite the recent interest in this field, no treatment trials have been performed. Thus, which therapy, if any, is effective in promoting successful pregnancy among women with recurrent pregnancy loss and thrombophilia is uncertain.

Cervical Incompetence Incompetent cervix, also called premature cervical dilation, is an important cause of second-trimester pregnancy loss. It is characterized by gradual, painless dilation of the cervix with bulging and rupture of the membranes and subsequent expulsion of a fetus too immature to survive. Pregnancy loss from this cervical abnormality usually occurs in the second trimester and is thought to be an entirely different and distinct entity from a first-trimester miscarriage or premature labor in the third trimester. It results from different factors, presents a distinctive clinical picture, and requires different management. Moreover, miscarriage and premature labor are common, but mid-trimester premature cervical dilation is relatively rare. Unlike the rest of the uterus, the cervix is fundamentally a connective tissue structure. The cause of cervical incompetence is obscure, and various etiologic factors have been proposed. Previous surgery or trauma to the cervix, such as D&C, amputation, conization, cauterization, loop electrosurgical excision procedure (LEEP), or traumatic delivery, seem to be factors in some cases. In other instances, congenital cervical structural defects, uterine anomalies, or abnormal cervical development associated with in utero diethylstilbestrol exposure appear to play a role. Little agreement can be found regarding the diagnosis of cervical incompetence, except that it is one of exclusion that requires careful evaluation to rule out other potential causes of mid-trimester pregnancy loss. Other causes of very early delivery include abruptio placentae, chorioamnionitis, and uterine anomalies, but they usually present different clinical pictures. Whether or not the condition can be diagnosed during the nonpregnant state by methods designed to calibrate the diameter of the endocervical canal or during early pregnancy by sonographic findings is questionable. The absolute diagnosis of cervical incompetence can be made only by seeing the fetal membranes bulging through the partially dilated cervix of a patient in the second trimester of pregnancy who is not in labor. More typically, a presumptive diagnosis is made from the characteristic history of apparently silent dilation of the cervix followed by rupture of the membranes and a relatively painless, rapid labor with delivery of an immature infant. Also, the fetus is typically alive at the time of presentation to the hospital; delivery of a dead, macerated fetus makes the diagnosis of cervical competence questionable. Upon inspection in the nonpregnant state, the cervix may be shortened with a patulous os or may be deformed with lacerations that sometimes extend to the vaginal fornix. Although bed rest, various intravaginal devices, and pharmacologic agents have been used with some success, the generally accepted treatment for incompetent cervix is surgical. Various methods have been described, but the McDonald or Shirodkar procedures (Fig. 4.5) are most commonly employed prophylactically. These are techniques performed vaginally, usually under regional anesthesia, designed to reinforce the cervix close to the level of the internal os. If there is insufficient cervical tissue to allow placement of a cerclage vaginally, an abdominal approach is sometimes used. The reinforcement suture is usually placed toward the end of the first trimester after ultrasound documentation of a live fetus, after the risk of miscarriage has passed, and before the cervix starts to dilate.

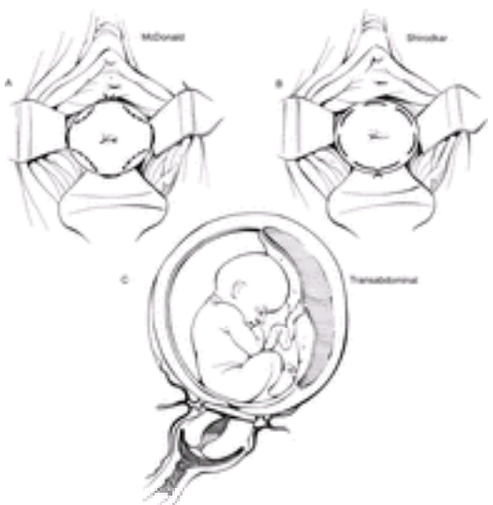

FIG. 4.5. Incompetent cervix can be treated by three procedures. **A:** In the McDonald cerclage procedure, a multiple-bite suture using large, monofilament nylon is placed around the cervix and tied securely to reduce the diameter of the cervical canal to a few millimeters. **B:** In the Shirodkar procedure, Merseline tape encircling the cervix is passed under the mucosa and anchored to the cervix anteriorly and posteriorly with interrupted sutures. **C:** With transabdominal cervicoisthmic cerclage, a Merseline band is placed in an avascular space medial to the uterine vessels at the level of the cervicouterine junction.

Placement of the cerclage in the second trimester after cervical change has occurred is sometimes necessary but appears less effective. The procedure should not be used if the diagnosis is in doubt, if membranes are ruptured, or if vaginal bleeding and cramping are part of the clinical picture. There is no evidence that postoperative antibiotics, progesterone, or tocolytic agents are useful adjuvants. If membranes rupture or labor ensues at any time, removal of the cerclage should be strongly considered to prevent chorioamnionitis, sepsis, cervical laceration, and rupture of the uterus. Otherwise, the suture is removed when fetal maturity is achieved, usually after 37 weeks gestation, which is often followed by the onset of labor and a relatively rapid delivery. If the patient desires further pregnancies, some physicians leave the cerclage in place and deliver by cesarean section. Often, the history is not typical, and it is difficult to determine whether or not premature cervical dilation will occur in a subsequent pregnancy. These patients are usually followed with frequent vaginal examinations and serial sonograms to diagnose potential cervical changes. Transvaginal ultrasound can be used to accurately assess cervical length and may be useful in deciding for or against cerclage in women with an unclear history. The effectiveness of cerclage has often been questioned, even in women with a classic clinical picture. Nevertheless, when patients are carefully selected, this type of management is 80% to 90% successful in preventing delivery of an immature fetus. There is little difference in the fetal survival rates between the McDonald and Shirodkar techniques. The procedure has also been used prophylactically for patients with previous preterm deliveries with less convincing evidence for cervical incompetence. Results from prospective randomized studies have led to conflicting conclusions.

Idiopathic Causes Because most cases of RM have no discernible cause, alloimmune factors have long been suspected. These have yet to be proven, largely because little is known about the mechanisms that prevent immunologic rejection of the conceptus in successful pregnancies (see Chapter 18). Early reports proposed that HLA compatibility between couples, the absence of maternal leukocytotoxic antibodies, or the absence of maternal blocking antibodies were related to RM. The

importance of these factors has not been substantiated, and these expensive tests are no longer clinically indicated. Contemporary research is focused on local decidual or trophoblast immunosuppressive factors such as cytokines, growth factors, hormones, enzymes, and endometrial proteins. Some of these immunoactive factors appear to be necessary for implantation and growth and development of the early placenta and embryo, and others may cause abortion, when expressed. There are, however, no practical clinical tests available for these factors and no proven treatment if they were found abnormal. Although no alloimmune mechanism has been unequivocally shown to cause RM in humans, several types of immunotherapy have been advocated. Originally, the attempt to improve maternal immunotolerance in recurrent aborters was based on evidence that pretransplant blood transfusions decreased rejection of organ allografts and that the rate of resorptions or abortions in animal models was reduced by prior immunization with spleen cells from a paternally related strain. The most popular regimen involves injections of the father's leukocytes. Though proponents persist, this treatment is questionable at best and harmful at worst. Most randomized trials have proven negative, and the largest and only multicenter randomized trial found that treated pregnancy outcomes were worse in the women who received leukocyte immunization. Based largely on this trial, the U.S. Food and Drug Administration has stated that the administration of this therapy for RM may only be done as part of a clinical investigation, and then only if there is an investigational new drug application in effect. Participating women should be counseled that immunization using viable leukocytes carries the risks of any blood transfusion, such as hepatitis, human immunodeficiency virus, and cytomegalovirus infections. Reactions have been uncommon but include soreness and redness at the injection site, cutaneous graft-versus-hostlike reaction, fever, maternal platelet and leukocyte alloimmunization, and blood group sensitization. Intravenous immune globulin has been proposed as an alternative therapy in patients with idiopathic RM. A number of randomized trials have been reported, and the results are conflicting. Nevertheless, this treatment seems to be no more successful than paternal cell immunization, and intravenous immune globulin is not recommended outside of a research protocol by either the American College of Obstetricians and Gynecologists or the American Society of Reproductive Medicine. It is imperative for physicians to recognize that the prognosis for idiopathic RM is by no means dismal. Numerous studies and several meta-analyses indicate that the average next pregnancy live-birth rate for placebo-treated women with idiopathic RM is 60% to 70%. Many couples see this modestly favorable prognosis in a somewhat positive light, and it compares favorably with the prognosis for conditions such as APS or parental karyotype abnormalities. Understanding this prognosis may allow the couple to choose against an expensive unproven treatment. One caveat—as expected, increasing maternal age and increasing number of miscarriages are negative variables.

Recommendations for Recurrent Miscarriage

The scheme for a reasonable and cost-effective evaluation of women with RM shown in Table 4.3 is based on current guidelines published by the American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynaecologists. A sympathetic attitude by the physician is crucial—establishment of trust and rapport and a sincere appreciation of the distress and grief experienced by these couples permit tactful and thorough discussions with patient and partner. It is reasonable to institute an evaluation after two consecutive miscarriages in anxious women or if the patient has few reproductive years remaining or has had an infertility problem. Couples interested in an investigational protocol are perhaps best referred to legitimate research centers.

History
Determine pattern and trimester of pregnancy losses and whether a live fetus was present; clues suggestive of autoimmune disease; unusual exposure to environmental toxins, drugs, infections; previous gynecologic disorders or surgery, including dilation and curettage; and previous diagnostic tests and treatments.
Physical
Abnormalities on pelvic examination, including findings suggesting abnormal cervix, diethylstilbestrol exposure, or uterine anomalies.
Tests
Lupus anticoagulant and anticardiolipin antibodies
Parental chromosome analyses (father and mother)
Evaluation of uterine cavity and shape by hysterosalpingogram, hysteroscopy, or other appropriate imaging studies
Chromosome analysis of products of conception
Other laboratory tests if suggested by history and physical examination

TABLE 4.3. *Proposed evaluation for recurrent miscarriage*

SUMMARY POINTS

- Miscarriage is the most common complication of pregnancy, and the most frequent etiology is a chromosomal abnormality of the conceptus.
- Ultrasound is helpful in determining whether or not the embryo is viable, and appropriate modern management may be either observation or evacuation of the uterus.
- Recurrent early pregnancy loss is sometimes associated with underlying maternal abnormalities that can be detected with standard tests. Physicians should be aware of unproven tests and controversial treatments in order to best counsel their patients.

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Chapter 5

Michael J. Heard and John E. Buster

Ectopic Pregnancy

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Incidence
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Diagnosis
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Ectopic Pregnancy and Assisted Reproductive Technology

Management of ectopic pregnancy is changing dramatically. Although ectopic pregnancy remains a leading cause of life-threatening first-trimester morbidity, informed clinical suspicion and modern diagnostic procedures now routinely lead to diagnosis and treatment before there are symptoms. Medical therapy with systemic methotrexate, an intervention targeted specifically toward proliferating trophoblasts, is now preferred to surgery as standard first-line therapy. Surgery remains the first choice for hemorrhage, medical failures, neglected cases, and cases where medical therapy is contraindicated. In the wake of these changes, the United States has seen a considerable drop in maternal morbidity and mortality from this disease.

Optimal dosing for methotrexate remains controversial. Rules for timing and technique for surgical intervention during medical failures are empirical. Early diagnosis and selection of optimal therapy are key to prevention of complications, preservation of fertility, control of costs, and elimination of mortality. Using an evidence-based approach to diagnosis and treatment for ectopic pregnancy, this chapter provides a comprehensive examination of the standard of care for this serious gynecologic disease.

INCIDENCE

The incidence of ectopic pregnancy in the United States is not known precisely. Recent attempts at the Centers for Disease Control and Prevention (CDC) to estimate the incidence of this disease have been thwarted, because many cases are treated medically in outpatient facilities and are not recorded in hospital registries. Where hospital records were used, a relentless increase in ectopic pregnancies from 4.5 per 1,000 in 1970 to 16.8 per 1,000 in 1989 to 19.7 per 1,000 (108,000 cases) in 1992 has been reported. The current incidence will probably prove much higher once the CDC is able to make estimates including outpatient records. Certain epidemiologic trends make this likely. First, there is a continued increase in risk factors (Table 5.1) in a society with unprecedented sexual liberties. Second, there is increased ascertainment of ectopics from use of more sensitive and specific diagnostic methods that detect many cases that, in the past, would have resolved spontaneously without diagnosis. Third, with the increasing use of assisted reproductive technology (ART) for treatment of infertility, there is an increase risk of ectopics which comprise up to 5% of pregnancies achieved by using ART. Not surprisingly, heterotopics also are being reported with increasing frequency in ART pregnancies. Between 1979 and 1986, 13% of maternal deaths were secondary to ectopic pregnancy; by 1992, this dropped to 9%. However, ectopic pregnancies continue to be the leading cause of maternal death in the first trimester accounting for 5% to 6% of all maternal deaths in the United States. Ninety percent of these deaths were due to hemorrhagic complications.

Factors identifying patients at increased risk for ectopic pregnancy. Patients at increased risk need aggressive monitoring of their pregnancies immediately after first missed menses.

Risk Factor	Odds Ratio[a]
High Risk	
Tubal surgery	21.0
Tubal ligation	9.3
Previous ectopic pregnancy	8.3
In utero exposure to DES	5.6
Use of IUD	4.2–45.0
Tubal pathology	3.8–21.0
Assisted reproduction	4.0
Morning-after pill	High
Moderate Risk	
Infertility	2.5–21.0
Previous genital infections	2.5–3.7
Multiple sexual partners	2.1
Salpingitis isthmica nodosa	1.5
Low Risk	
Previous pelvic infection	0.9–3.8
Cigarette smoking	2.3–2.5
Vaginal douching	1.1–3.1
First intercourse <18 yr	1.6

[a]Single values, common odds ratio from homogenous studies; point estimates, range of values from heterogenous studies.
DES, diethylstilbestrol; IUD, intrauterine device.

TABLE 5.1. *Risk factors associated with ectopic pregnancy*

PATHOGENESIS

Any event that impairs the ability of the tube to transport gametes or embryos will predispose to ectopic implantation. The clinical picture is determined by the site of ectopic implantation. The most common site of ectopic pregnancy is the fallopian tube, which accounts for 98.3% of all ectopic gestations. Implantation in the ampulla is observed in 79.6% of tubal ectopic pregnancies; 12.3% are in the isthmus, 6.2% are in the fimbrial end, and the remaining 1.9% occur in the interstitial (cornual) region. Ectopic nidation outside the fallopian tubes is rare; only 1.4% of ectopic pregnancies are abdominal pregnancies, 0.15% ovarian, and 0.15% cervical (Fig. 5.1).

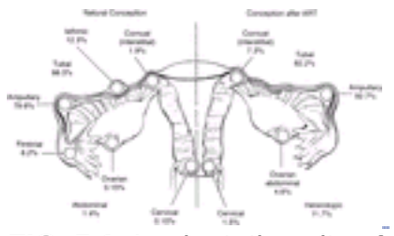

FIG. 5.1. Implantation sites for ectopic pregnancy following natural cycles and assisted reproductive technology.

In most tubal implantations, the proliferating trophoblasts invade the tubal wall. The degree of trophoblastic invasion of maternal tissues, the viability of the pregnancy, and the site of implantation determine the sequence of clinical events. As the trophoblasts proliferate, the growth may extend from the luminal mucosa, into the muscularis and lamina propria, into the serosa and, ultimately, full thickness even into large blood vessels in the broad ligament. With vascular invasion, bleeding takes place which distorts the tube, stretches the serosa, and causes pain. The embryo is abnormal and degenerates in about 80% of cases. Spontaneous tubal abortion occurs in about 50% of tubal ectopic pregnancies and is often clinically silent. Spontaneous tubal abortion with hemorrhage can occur with bleeding that is self-limited. Tubal rupture usually is associated with significant hemorrhage. This complication is most likely to occur in the isthmic part of the tube, which has limited distensibility. Chronic tubal rupture with extension into the broad ligament can produce a pelvic hematoma that can last for several weeks. Unruptured ectopic pregnancies can produce a chronic course, with persistently elevated ß-human chorionic gonadotropin (ß-hCG) levels that may last for weeks.

RISK FACTORS

Ectopic pregnancy most often is associated with risk factors leading to tubal epithelial damage, which alters gamete and embryo transport. Meta-analyses identify the risk factors listed in Table 5.1 as the most influential.

Tubal Damage and Infection

Documented tubal pathology carries a 3.5-fold common adjusted odds ratio for ectopic pregnancy. Patients with a previous ectopic pregnancy are 6 to 8 times more likely to experience another ectopic pregnancy, and 8% to 14% of patients experience more than one ectopic pregnancy. Patients with a history of tubal surgery have a 21-fold common adjusted odds ratio of ectopic pregnancy.

Tubal pathology frequently results from pelvic infections. Patients with a history of pelvic infections, including gonorrhea, serologically confirmed chlamydia, and nonspecific pelvic inflammatory disease, have a two-fold to four-fold higher risk of developing an ectopic pregnancy. The ectopic pregnancy rate is 4% in women with laparoscopically proven salpingitis, compared with 0.7% in women with normal tubes. In evaluating histologic specimens of ectopic pregnancy, microscopic evidence of inflammatory disease is present in 38% of cases. Recurrent episodes of pelvic infections increase the likelihood of tubal occlusions: 12.8% after one infection, 35.5% after two infections, and 75% in patients with three or more infections.

Salpingitis Isthmica Nodosa

Salpingitis isthmica nodosa is a disease defined by an anatomic thickening of the proximal portion of the fallopian tubes with multiple luminal diverticula. This pattern of tubal pathology increases the incidence of ectopic pregnancy by 52% in age- and race-matched controls.

Diethylstilbestrol

In utero exposure to diethylstilbestrol (DES) alters fallopian tubal morphology, resulting in absent or minimal fimbrial tissue, a small tubal os, and decreased length and caliber of the tube. Abnormal tubal anatomy accounts for the five-fold increase in the risk for ectopic pregnancy.

Cigarette Smoking

Patients who smoke cigarettes are at a slightly increased risk for ectopic pregnancy. It is difficult to conceptualize the link between ectopic pregnancy and cigarettes. Theories include impaired immunity in smokers predisposing them to pelvic infections, alterations in tubal motility, or a representation of certain lifestyles associated with increased risk of tubal injection.

Contraception

Intrauterine devices (IUDs) have been associated with ectopic pregnancy. A multicenter case-control study conducted by the World Health Organization in ten countries found an odds ratio of 6.4 for ectopic pregnancy in current IUD users compared with pregnant controls, whereas the odds ratio was only 0.5 when the comparison was made with nonpregnant controls. Similarly, in the Oxford Study of 17,032 contraceptive users, the proportion of unplanned pregnancies that were ectopic was higher in women using IUDs compared with women taking oral contraceptives. Thus, IUDs effectively prevent pregnancy, but if pregnancy occurs in a woman using an IUD, there is increased likelihood that the pregnancy will be ectopic.

Tubal ligation carries a similar risk for ectopic pregnancy to what is observed with current IUD use. A meta-analysis using case-control studies found the odds ratio for tubal sterilization to be 9.3 when compared with pregnant controls and 0.52 when compared with nonpregnant controls, a finding confirmed by two additional multicenter case-control trials. As with the IUD, tubal ligations effectively prevent pregnancy, but if pregnancy does occur, the suspicion for an ectopic pregnancy should be high.

Electrocoagulation procedures are associated with higher ectopic pregnancy risk than other forms of tubal sterilization, possibly resulting from tubal recanalization or uteroperitoneal fistula formation. Uteroperitoneal fistulas have been found in up to 75% of hysterectomy specimens from women with previous tubal ligations in which the tubes were cauterized flush with the uterus.

Oral contraceptives are associated with a reduced risk of ectopic pregnancy when compared with nonpregnant controls but with elevated risk when compared with pregnant controls. This protection is presumably due to the suppression of ovulation by oral contraceptives. It is therefore not surprising that patients who take emergency contraception, such as oral contraceptives after fertilization, are at substantial risk for an ectopic pregnancy. This has been attributed to altered tubal motility.

Barrier contraception (condoms, spermicides, and diaphragms) also reduces the odds ratio of ectopic pregnancy. An additional advantage may be attributed to the decreased risk of sexually transmitted diseases in women using barrier methods.

Evidence-based Recommendation

Women with a previous ectopic pregnancy, tubal surgery, tubal pathology, or in utero DES exposure are at high risk for ectopic pregnancy. Women who have experienced genital infections, infertility, or more than one sexual partner have a moderate risk of ectopic pregnancy. Previous pelvic or abdominal surgery, smoking,

vaginal douching, or an early age of first sexual intercourse have only a slightly increased risk of ectopic pregnancy.

Contraception, if used properly, is an effective way of reducing pregnancy, both intrauterine and extrauterine. If pregnancy occurs in women with an IUD, after tubal ligation, or following emergency contraception, suspicion for ectopic pregnancy should be high. (Strength of recommendation: A.)

SIGNS AND SYMPTOMS

Today, many ectopic pregnancies never produce symptoms; rather, they are timely diagnosed and treated because the patient is identified as high risk. Table 5.1 summarizes and weighs risk factors that should be examined in every woman who has just been identified as being pregnant. If the diagnosis is delayed, some patients may develop the classic triad of amenorrhea, irregular vaginal bleeding, and lower abdominal pain. Early diagnosis, unfortunately, is not always achievable. Sudden, severe, lower abdominal pain is the most common complaint in 90% to 100% of women with symptoms of an ectopic pregnancy. Pain radiating to the shoulder, syncope, and shock as a result of hemoperitoneum occur in up to 20% of patients.

The most common signs are detected upon abdominal examination. Abdominal tenderness is present in 90% of patients and rebound tenderness in 70%. The pelvic examination is usually nonspecific; cervical motion tenderness is present in up to two thirds of patients, while a tender adnexal mass is present in 50%.

DIAGNOSIS

Ectopic pregnancy can be diagnosed as early as 4.5 weeks gestation. Unfortunately, visualizing an ectopic pregnancy this early is frequently not possible. More importantly, traditional laparoscopic visualization (Fig. 5.2, Fig. 5.3, Fig. 5.5) is now rarely necessary. Routine diagnostic tests are serial measurements of ß-hCG, ultrasonography, serum progesterone levels, and uterine curettage.

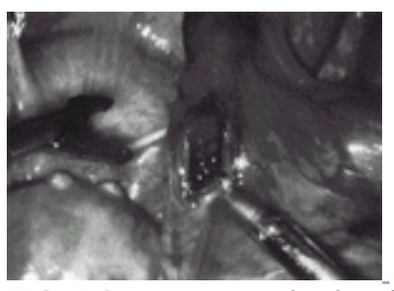

FIG. 5.2. Laparoscopic visualization of an isthmic ectopic pregnancy.

FIG. 5.3. Laparoscopic visualization of an ampullary ectopic pregnancy.

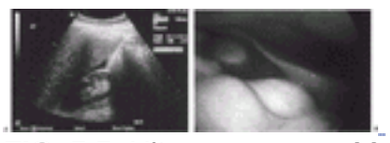

FIG. 5.5. Ultrasonogram of free fluid noted under the liver edge above the right kidney. Confirmed to be blood from a ruptured ectopic pregnancy at the time of surgery. (Courtesy of R. Mangal, M.D., Obstetrics/Gynecologic Associates, Houston, TX.)

Outpatient diagnosis of ectopic pregnancy using various algorithms has been shown to be safe and effective without need for hospitalization even when the diagnosis is equivocal. The clinical algorithm in Figure 5.4 is highly efficacious in diagnosing ectopic pregnancy.

FIG. 5.4. Diagnostic algorithm for ectopic pregnancy.

Serial ß-Human Chorionic Gonadotropin Determinations

ß-hCG determinations used today are based on the enzyme-linked immunosorbent assay (ELISA), detecting low ß-hCG concentrations in urine and serum, 20 mIU/mL down to 1 mIU/mL, respectively. The ß-hCG, produced by trophoblastic cells in normal pregnancy, rises at least 66% and up to two-fold every 2 days. This generally applies to ß-hCG values below 10,000 mIU/mL. Eight-five percent of abnormal pregnancies, whether intrauterine or ectopic, have impaired ß-hCG production with a prolonged doubling time. ß-hCG levels that plateau or fail to rise normally along with a low serum progesterone value should be considered nonviable. If a viable intrauterine gestation is not visible by transvaginal ultrasonography when the ß-hCG is above 2,000 mIU/mL (First International Reference Preparation [IRP]) and no fetal heartbeat can be visualized in the adnexa, uterine curettage can be performed. In this situation, treatment of a nonviable intrauterine pregnancy is performed or ectopic pregnancy is diagnosed when the ß-hCG levels do not fall. These ß-hCG thresholds are not universal, and each institution must identify its own values to avoid terminating normal intrauterine pregnancies.

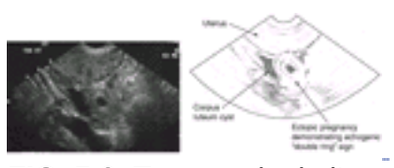

FIG. 5.6. Transvaginal ultrasonographic illustration of tubal ectopic gestation.

ß-hCG determinations are further employed for diagnosis after uterine curettage. If the ß-hCG fails to decline by 15% from a level drawn immediately before surgery, the pregnancy is presumed ectopic and treatment should be initiated.

Ultrasonography

Although the uterus and adnexa may be evaluated abdominally or vaginally, transvaginal ultrasonography reliably detects intrauterine gestations when the ß-hCG levels are between 1,000 and 2,000 mIU/mL (First IRP), as early as 1 week after missed menses. An intrauterine gestation should almost always be visualized when the ß-hCG level is greater than 2,000 mIU/mL.

Diagnosis of an ectopic pregnancy can be made with 100% specificity but with low sensitivity (15%–20%) if an extrauterine gestational sac containing a yolk sac or embryo is identified. A complex adnexal mass without an intrauterine pregnancy improves sensitivity to 21% to 84% at the expense of lower specificity (93.0%–99.5%). In reviewing the literature, the presence of any noncystic, extraovarian adnexal mass in the absence of an intrauterine gestation was diagnostic of an ectopic pregnancy with 98.9% specificity, 96.3% positive predictive value, 84.4% sensitivity, and a 94.8% negative predictive value. Despite the high resolution of transvaginal ultrasonography, an adnexal mass will not be found in 15% to 35% of patients with an ectopic pregnancy, particularly in early stages. Some sonographic images, such as the pseudogestational sac, may mislead even an experienced examiner to falsely diagnose a gestational sac.

Serial ß-hCG concentrations and transvaginal ultrasonography predict ectopic pregnancy with a positive predictive value of 95%. Diagnosis is made routinely by the absence of an intrauterine pregnancy (i.e., gestational sac) at a designated ß-hCG concentration. The vast majority of viable intrauterine pregnancies can be identified by ultrasonography when the ß-hCG is greater than 1,500 mIU/mL (First IRP). However, in those patients with an “indeterminate” ultrasonogram, one fourth have an ectopic pregnancy. Therefore, serial hCG and ultrasonography alone cannot diagnose all ectopic pregnancies.

Uterine Curettage

Uterine curettage is necessary when a transvaginal ultrasonogram and a rising or plateauing ß-hCG level below the cutoff value are not sufficient for diagnosis. A decrease in the ß-hCG level of 15% or more 8 to 12 hours after curettage is diagnostic of a complete abortion. If the ß-hCG titer plateaus or rises and the trophoblast was not removed by curettage, an ectopic pregnancy is likely.

Evidence-based Recommendation

Serial ß-hCG determinations, transvaginal ultrasonography, and uterine curettage allow for definitive diagnosis of ectopic pregnancy. A confirmatory laparoscopy is rarely necessary. (Strength of recommendation: A.)

TREATMENT FOR ECTOPIC PREGNANCY

Medical Management

Methotrexate therapy of ectopic pregnancy has been used successfully over the last two decades. A folic acid antagonist, methotrexate inhibits de novo synthesis of purines and pyrimidines, interfering with DNA synthesis and cell multiplication. Rapidly proliferating trophoblasts are particularly vulnerable to methotrexate and this differential sensitivity forms the basis of the therapy. When methotrexate is administered to pregnant women undergoing planned termination, a single dose of 50 mg/m^2 significantly blunts the hCG increment over the following 7 days and has been associated with a drop in circulating progesterone and 17a-hydroxyprogesterone concentrations prior to abortion. It appears that methotrexate directly impairs trophoblastic production of hCG with a secondary decrement of corpus luteum progestin secretion. Hemodynamically stable patients with unruptured ectopic pregnancy measuring less than or equal to 4 cm by ultrasonography are eligible for methotrexate therapy. Patients with larger masses or evidence of acute intraabdominal bleeding should undergo surgical treatment. The two commonly employed methotrexate treatment regimens are shown in Table 5.2.

Single-dose methotrexate protocol		
Day 1:	Baseline studies	
	Methotrexate	50 mg/m^2 i.m.
Day 4:	hCG titer	
Day 7:	hCG titer	
	CBC and platelet count	
	Liver and renal function tests	
Weekly:	hCG titer until negative	
Multiple-dose methotrexate protocol		
Treatment is discontinued when a decline is observed in two consecutive daily hCG titers, or after 4 doses of methotrexate.		
Day 1:	Baseline studies	
	Methotrexate	1.0 mg/kg i.m.
Day 2:	Citrovorum	0.1 mg/kg i.m.
Day 3:	Methotrexate	1.0 mg/kg i.m.
Day 4:	Citrovorum	0.1 mg/kg i.m.
	hCG titer	
Day 5:	Methotrexate	1.0 mg/kg i.m.
	hCG titer	
Day 6:	Citrovorum	0.1 mg/kg i.m.
	hCG titer	
Day 7:	Methotrexate	1.0 mg/kg i.m.
	hCG titer	
Day 8:	Citrovorum	0.1 mg/kg i.m.
	hCG titer	
	CBC and platelet count	
	Renal and liver function tests	
Weekly:	hCG titer until negative	

hCG, human chorionic gonadotropin; CBC, complete blood count.

TABLE 5.2. *Methotrexate protocols: single versus multiple*

Multiple-dose Methotrexate Multiple-dose methotrexate therapy is tailored to the patient's weight and ectopic pregnancy responsiveness. Outcomes of 12 studies comparing multiple-dose systemic methotrexate with laparoscopic salpingostomy are presented in Table 5.3. Between 1982 and 1997, this tabulation shows 325 cases of ectopic pregnancy treated with multiple-dose methotrexate. Of these cases, 93.8% were treated successfully with multiple-dose systemic methotrexate (no subsequent therapy was required), and 78.9% of the women tested had patent fallopian tubes; in addition, of the women desiring pregnancy, 57.9% had a subsequent intrauterine pregnancy and 7.4% developed a repeat ectopic pregnancy. These rates all compare favorably with conservative surgical management.

TABLE 5.3. *Outcome of different treatments for ectopic pregnancy*

There is one randomized clinical trial comparing laparoscopic salpingostomy with systemic multiple dose methotrexate. In it, 100 patients with laparoscopy-confirmed ectopic pregnancy were randomly treated with systemic methotrexate or laparoscopic salpingostomy. In the 51 patients treated with methotrexate, three (8%) required surgical intervention for active bleeding or tubal rupture. An additional course of methotrexate was required in two patients (5%) for persistent trophoblast, basal on ß-hCG secretion. Of the 44 patients in the salpingostomy group, two patients (5%) failed and required salpingectomies, and eight patients (22%) required treatment with methotrexate for persistent trophoblast. Tubal patency was present in 67% of the patients in the methotrexate group and in 61% in the salpingostomy group. This randomized study and previous meta-analysis have demonstrated the effectiveness of systemic methotrexate therapy as equal to laparoscopic salpingostomy.

Single-dose Methotrexate Single-dose methotrexate, although more convenient, is not as efficacious as multiple-dose methotrexate. The high success rates in the initial studies using single-dose methotrexate was most likely due to the inclusion of spontaneously aborting intrauterine pregnancies. Subsequent studies of single-dose methotrexate therapy involving 304 patients are presented in Table 5.3. Although overall success of treatment, measured as no surgical intervention, is 87.2%, 11.5% additional patients required more than one dose of methotrexate. Of the patients considered successfully treated (with one or more doses), tubal patency was found in 81.3% of the women evaluated. The subsequent intrauterine pregnancy rate was 61%, and for ectopic pregnancies 7.8%, in the patients desiring future fertility in the same group (those treated with either one or more doses of methotrexate). Based on the clinical evidence presently available, the routine use of methotrexate as a single-dose intramuscular regimen is probably not as effective as multiple dosage. However, single-dose therapy remains a standard according to publications of the American College of Obstetricians and Gynecologists. With this background, a recent meta-analysis of 26 studies evaluating methotrexate dosing for ectopic pregnancy by Barnhart et al. showed an odds ratio of 1.96 higher likelihood of rupture with use of single-dose methotrexate over multidose therapy. This failure rate was even higher when controlling for baseline ß-hCG values.

Safeguards and Counseling During methotrexate therapy, a patient should be examined by a single examiner only once. The physician and the patient must recognize that transient pain (“separating” or “tearing pain”) is common. Transient pelvic pain from resolution tubal bleeding of the ectopic pregnancy frequently occurs

3 to 7 days after the start of therapy, lasts 4 to 12 hours, and is presumably due to tubal abortion. Perhaps the most difficult aspect of methotrexate therapy is learning to distinguish the transient abdominal pain of successful therapy from that of a rupturing ectopic pregnancy. Isthmic ectopic pregnancies are probably at high risk for rupture, and there is simply no way to identify these in advance. A review of ectopic ruptures after methotrexate therapy revealed a high prevalence of isthmic (47%) ectopic pregnancies that was unexpected. These ectopic pregnancies have an early normal doubling time and rise in ß-hCG titers after methotrexate dosing. Physicians must therefore carefully observe for clinical indications that an operation is necessary (Table 5.4 and Table 5.5). Thus, surgical intervention is required when pain is worsening and persistent beyond 12 hours. Orthostatic hypotension or a falling hematocrit should lead to immediate surgery. Sometimes it is necessary to hospitalize the patient with pain for observation (usually about 24 hours). In addition, colicky abdominal pain is common during the first 2 or 3 days of methotrexate therapy, and the woman should avoid gas-producing foods, such as leeks and cabbage. Finally, the patient should avoid exposure to the sun, because photosensitivity can be a complication of methotrexate.

Indications for systemic methotrexate for uncomplicated ectopic pregnancy
Indications for Methotrexate:
◊ No rupture
◊ UTZ size ≤4 cm
◊ hCG ≤10,000 mIU/mL
◊ Positive fetal heartbeat: proceed with caution

UTZ, ultrasound; hCG, human chorionic gonadotropin.

TABLE 5.4. *Treatment with multiple-dose methotrexate*

Dealing with methotrexate failure
Operate when:
◊ Pain is severe and persistent
◊ Falling hematocrit
◊ Orthostatic hypotension

TABLE 5.5. *Methotrexate failure*

Methotrexate by Direct Injection In 1987, Feichtinger and Kemeter instilled 1 mL (10 mg) of methotrexate into an ectopic gestational sac under transvaginal ultrasonography, and resolution occurred within 2 weeks. Direct injection delivers concentrations of methotrexate to the site of implantation at higher concentrations than those achieved with systemic administration. Less systemic distribution of the drug should decrease the overall toxicity. However, this approach has the substantial disadvantage of requiring laparoscopic or ultrasound needle guidance. Outcomes in 21 studies involving direct injection of methotrexate with either laparoscopic or transvaginal ultrasound guidance are presented in Table 5.3. Between 1989 and 1997, 75.1% of 668 cases of ectopic pregnancy were treated successfully with methotrexate by direct injection, and some patients required more than one injection. Tubal patency and subsequent pregnancy rates were comparable to conservative laparoscopic surgery and systemic methotrexate: 80.2% of the women tested had patent oviducts and, of the women desiring pregnancy, 57.2% had a subsequent intrauterine pregnancy and 5.9% developed a recurrent ectopic pregnancy. Randomized, controlled trials have demonstrated successful treatment with methotrexate by direct injection in 86.2% of the patients. Again, successful therapy included some patients who received more than one injection. Tubal patency was present in 85.1% of the women evaluated, and intrauterine pregnancy occurred in 73.1% of the women desiring subsequent fertility. One of the earlier randomized, controlled trials was discontinued because three of seven patients assigned to laparoscopic injection of methotrexate required additional laparoscopic surgery. Even with the higher success rate in the randomized trials, this technique is more cumbersome than systemic methotrexate.
Side Effects High doses of methotrexate can cause bone marrow suppression, hepatotoxicity, stomatitis, pulmonary fibrosis, alopecia, and photosensitivity. These side effects are infrequent in the short treatment schedules used in ectopic pregnancy and can be attenuated by the administration of leucovorin (citrovorum factor). The side effects of methotrexate resolve within 3 to 4 days after the therapy is discontinued. Impaired liver function is the most common side effect. Other side effects include stomatitis, gastritis and enteritis, and bone marrow suppression. Local therapy by direct injection of methotrexate into the ectopic gestation resulted in fewer side effects, likely because of less systemic absorption. Even with local injection, impaired liver function tests, gastritis and enteritis, and bone marrow suppression can occur. Additional case reports exist in the literature. Cases of life-threatening neutropenia and febrile morbidity can occur after single or multidose intramuscular methotrexate, requiring hospitalization. Cases of transient pneumonitis from methotrexate therapy for ectopic pregnancy have been observed. Reversible alopecia (a loss of 33–50% of the scalp hair) on two separate occasions following single-dose therapy for an ectopic pregnancy has also been reported. Rarely, hematosalpinx and pelvic hematoceles have been noted as late sequelae of methotrexate following the normalization of ß-hCG levels. These patients have pelvic pain, abnormal bleeding, and a pelvic mass, requiring surgical intervention, 3 to 5 months after therapy. Methotrexate remains the first choice before surgical therapy.
Direct Injection of Cytotoxic Agents Prostaglandins, hyperosmolar glucose, potassium chloride, and saline by direct injection have been tried as therapeutic alternatives to methotrexate. The limited experience with prostaglandins and hypertonic glucose, poor success rates, and the need for laparoscopic or transvaginal aspiration makes these treatment alternatives unattractive.
Evidence-based Recommendation Multiple-dose systemic methotrexate is the medical treatment of first choice for ectopic pregnancy. (Strength of recommendation: A.)

Surgical Treatment

Since the first successful salpingectomy performed by Tait in 1884, ectopic pregnancies traditionally have been treated by salpingectomy during laparotomy. Historically, ectopic pregnancies were diagnosed at the time of emergency surgery, when concern for the patient's life superseded any concerns for her future fertility. It was not until 1953, when Stromme performed the first conservative procedure (salpingostomy) for ectopic pregnancy, that subsequent successful pregnancy outcomes were reported, confirming the potential for fertility preservation after salpingostomy. Subsequently, other conservative surgical procedures, such as manual fimbrial expression and segmental tubal resection with later reanastomosis, have been performed to preserve fertility. These surgical techniques have been modified for the laparoscope.

Ruptured Ectopic Pregnancy Early diagnosis and treatment of ectopic pregnancy avoids rupture in most cases. In the 1970s, 13.5% to 17.8% of patients with ectopic pregnancies arrived for treatment in hypovolemic shock, whereas in the early 1980s, only 4.4% of patients arrived in this condition. Today, either laparotomy or laparoscopy with salpingectomy is the first choice for rupture. Once contraindicated over concern of decreased venous return from intraperitoneal insufflation, laparoscopic salpingectomy is successful in patients in hypovolemic shock. Nearly all patients in hypovolemic shock require blood transfusions. In the hands of a skilled laparoscopist, with adequate cardiac monitoring and anesthesia, laparoscopic salpingectomy is an acceptable alternative to laparotomy. At present, it is the surgeon's choice of laparoscopy or laparotomy for ruptured ectopic pregnancy.
Stable Ectopic Pregnancy If methotrexate is contraindicated, laparoscopic salpingostomy is the first surgical choice. Salpingectomy can be performed either during laparotomy or laparoscopy using cautery or sutures (laparoscopic or endo-loops). Subsequent to salpingostomy, 53% of patients have intrauterine pregnancies, compared with 49.3% after salpingectomy. Recurrent ectopic pregnancy rates were slightly higher after conservative surgery, 14.8% compared with 9.9%. Laparoscopic salpingectomy is preferred over salpingostomy in cases of uncontrollable bleeding not resolving with conservative measures when extensive tubal damage is present, if the ectopic pregnancy is in the same tube, and if sterilization is desired. The recommended conservative surgical procedure for an ampullary ectopic pregnancy is linear salpingostomy, because the ectopic nidation typically is located between the endosalpinx and serosa rather than in the tubal lumen. A linear salpingostomy is created through a longitudinal incision by electrocautery, scissors, or laser over the bulging antimesenteric border of the fallopian tube. The products of conception are removed with forceps or gentle flushing or suction. After maintaining hemostasis, the incision is closed primarily or left to heal by secondary intention. Isthmic pregnancies routinely are treated with segmental excision, followed by intraoperative or delayed microsurgical anastomosis. The tubal lumen is narrower and the muscularis is thicker in the isthmus than in the ampulla, predisposing the isthmus to greater damage after salpingostomy and greater rates of proximal tubal obstruction. Manual fimbrial expression, also known as *milking*, should be used only when the trophoblastic tissue is already aborting spontaneously through the fimbriae. Laparoscopy has several advantages over laparotomy, including less blood loss, decreased need for analgesia, and improved postoperative recovery, as measured by shorter hospitalizations and length of time to resume normal activity. In addition, cost analysis has demonstrated significant savings in randomized trials. Laparoscopic salpingostomy and fimbrial expression have been evaluated in 32 studies and are presented in Table 5.1. Of the 1,614 patients treated between 1980 and 1997, treatment was successful in 93.4% (required no additional therapy). Of the patients evaluated for tubal patency using either hysterosalpingography or laparoscopy, 77.8% had patent tubes. Of the women desiring subsequent fertility, 56.6% had an intrauterine pregnancy and 13.4% developed another ectopic pregnancy. When evaluating subsequent fertility, intrauterine pregnancy rates are comparable for laparoscopy and laparotomy, as are rates of recurrent ectopic pregnancy.

PERSISTENT ECTOPIC PREGNANCY FOLLOWING SALPINGOSTOMY

Persistent ectopic pregnancy is diagnosed by a plateauing or rising ß-hCG concentration following conservative surgical therapy. Although the number of reported cases is small, women with persistent ectopic pregnancies are treated successfully using single-dose systemic methotrexate.

The increased rate of persistent ectopic pregnancies has been a criticism of conservative laparoscopic therapy when compared with laparotomy. A decision analysis that compared prophylactic methotrexate with linear salpingostomy against no methotrexate in a group of 1,000 women concluded that prophylactic methotrexate at the time of surgery was preferable if certain conditions are met as follows: (a) the incidence of persistent ectopic pregnancy is greater than 9% with observation alone after salpingostomy, (b) the incidence of persistence is less than 5% when prophylactic methotrexate is given, (c) the probability of ectopic pregnancy rupture is greater than 7.3% with a persistent ectopic pregnancy, and (d) the complication rate associated with prophylactic methotrexate is less than 18%. Because the great majority of

clinical circumstances meet these recommendations, prophylactic methotrexate administration is recommended.

Evidence-based Recommendation

Due to lower morbidity and equal efficacy, laparoscopic surgery is preferable to laparotomy in the treatment of bleeding or complicated ectopic pregnancy. Salpingectomy by laparotomy is reserved for ectopic ruptures with a hemodynamically unstable patient. (Strength of recommendation: A.)

ECTOPIC PREGNANCY AND ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

Incidence

The risk of ectopic pregnancy is increased in patients undergoing an ART procedure. This increased risk has been attributed to the cause of infertility for which most patients seek treatment, that is, tubal factor infertility. Information on ectopic pregnancies resulting from ART comes from data obtained from institutions in the United States and Canada reporting to the Society for Assisted Reproductive Technology. The rate of pregnancies that resulted in ectopic pregnancies after in vitro fertilization (IVF) in 1999 was 3%. This included outcome of ART cycles using fresh, nondonor eggs or embryos in approximately 53,000 embryo transfers. This lower percentage likely reflected the trend toward performing salpingectomies when hydrosalpinges are present to improve the success of ART.

Location

As in naturally occurring ectopic pregnancies, the fallopian tube is the most common site for ectopic pregnancies following IVF. Data obtained from three case-control studies reveal that 82.2% of ectopic pregnancies were tubal. When tubal location was specified, 92.7% were ampullary and 7.3% interstitial. Extratubal ectopic nidations were as follows: 4.6% ovarian or abdominal, 1.5% cervical, and 11.7% heterotopic pregnancies (see Fig. 5.1).

Tubal Pathology

The most important predisposing factor for ectopic pregnancy in patients undergoing IVF is tubal pathology. Ectopic pregnancies are 4 times higher in patients with tubal factor infertility compared with patients with normal tubes. Hydrosalpinges are associated more commonly with ectopic pregnancy than other types of tubal pathology. Prior tubal reconstructive surgery (salpingostomy) increases the risk of ectopic pregnancy by 10% above that in patients with tubal factor infertility without prior surgery.

Thus, it is not surprising that patients with previous pelvic inflammatory disease have a six-fold increase in ectopic pregnancy after IVF. However, a history of prior ectopic pregnancy does not seem as important a risk factor in IVF cycles as in natural cycles.

Salpingectomy, particularly with hydrosalpinx, has been shown to decrease risks of ectopic pregnancy while increasing pregnancy rates after IVF. Meta-analysis has demonstrated that the presence of hydrosalpinges decreases the chance for viable pregnancy by approximately 50% when compared with patients with tubal disease but without hydrosalpinges.

The implantation rate was also noted to be 50% lower with a higher chance of miscarriage and ectopic gestation. The ultimate conclusion is that when a hydrosalpinx is present there is a decreased pregnancy rate with resultant decreased delivery rate following IVF.

In addition, patients who undergo salpingectomy or proximal tubal occlusion prior to oocyte retrieval and transfer are at decreased risk for pelvic infection as well as future ectopic pregnancy.

Ovulation Induction

Hormone alterations during ovulation induction theoretically alter tubal function. In animal models, estrogen administration results in functional tubal blockage and embryo arrest in the fallopian tube. In humans, steroid hormones alter tubal function and contractility, thus affecting tubal peristalsis. There remains controversy as to whether ovulation-inducing agents, including clomiphene citrate, increase ectopic pregnancy rates.

Embryo Transfer

Knutzen et al. injected 50 µL of radiopaque fluid in mock embryo transfers and found that the material entered the tubes either partially or totally in 44% of subjects, suggesting misplacement of embryos into the fallopian tubes leads to ectopic pregnancy. Embryo catheter placement was implicated also in the increased risk of ectopic pregnancies, which occurred more frequently in patients who underwent deep fundal transfer versus midcavity placement. Although transfer techniques may increase the chances of embryos reaching the fallopian tubes, ectopic pregnancies may result from tubal pathology preventing the embryos from moving back into the uterus.

Heterotopic Pregnancy

Heterotopic pregnancies occur in 1% to 3% of pregnancies following an ART procedure and usually are diagnosed incidentally on routine follow-up ultrasonographic studies. This increased prevalence of heterotopic pregnancies following ART may be related to ovarian hyperstimulation and multiple ovum development. Of 111 reported heterotopic pregnancies following ART, 88.3% were tubal, 6.3% cornual, 2.7% abdominal, 1.8% cervical, and 0.9% ovarian.

Evidence-based Recommendation

Heterotopic and extratubal ectopic pregnancies are more frequent following ART than with natural cycles. Salpingectomy or proximal tubal occlusion of a preexisting hydrosalpinx prior to IVF helps prevent tubal ectopic pregnancies while increasing pregnancy rates following ART. (Strength of recommendation: B.)

EXPECTANT MANAGEMENT

Ectopic pregnancies may resolve spontaneously. In a cavalier experiment in 1955, Lund hospitalized 119 women with ectopic pregnancy for observation. All were at least 6 weeks gestation. Some required multiple blood transfusions, and many were hemodynamically unstable. However, 68 resolved without surgery. Twelve additional studies reported in the literature since Lund's study found similar results (Table 5.3). Of the ectopic pregnancies, 67.2% resolved without surgery. Thus, both conservative medical and surgical therapy overtreats at least 50% of women with ectopic pregnancy. Falling ß-hCG levels under 1,000 mIU/mL have been followed with conservative expectant management. Although patients with an equivocal diagnosis of ectopic pregnancy may be treated in this fashion, there are no data to support expectant management in clinical practice.

Evidence-based Recommendation

Expectant management of ectopic pregnancy may be considered an appropriate conservative therapy for some patients with low initial (1,000 mIU/mL) and falling hCG levels.

COST ANALYSIS

In 1990, total costs for ectopic pregnancies were estimated to be $1.1 billion. Direct costs, expenditures for health care, accounted for 77% of the total costs, and the remainder were incurred as a result of lost wages or household responsibilities not performed due to illness (indirect costs). Direct costs from hospital charges were estimated at $6,079 per case, with hospital accommodations (mean length of stay, 3.47 days) and operating room charges accounting for the majority of the hospital expense, 36% and 40%, respectively. An additional $3,254 for professional fees increased inpatient charges to $9,333, and $149 for postoperative follow-up visits increased the total direct cost to $9,482 per case. Indirect costs for a 28-day disability were estimated at $250.5 million, 67% as a result of lost wages and the remainder from lost household duties.

Laparoscopic surgery was less expensive than laparotomy. Surgical management generally has been directed toward laparoscopy. The cost of laparoscopic conservative surgery or salpingectomy was estimated at $2,125 and $1,872, respectively. Costs for conservative treatment or salpingectomy via laparotomy were

estimated to be higher, $3,420 and $3,490, respectively. Systemic methotrexate therapy is even more cost efficient.

Charges for patients successfully treated with methotrexate average $1,563 (range, $1,169 to $2,300). Patients requiring laparotomy, due to hemodynamic instability, incur a higher average charge of $8,001 (range, $3,171 to $22,082). The average length of stay following laparotomy was 5.2 days.

A study, undertaken to compare the costs of systemic methotrexate with surgery, concluded that there would be a reduction in overall costs if patients were treated without confirmatory laparoscopy when hCG levels were below 3,000 mIU/mL; otherwise, there was not a substantial cost saving over surgery. Because a confirmatory laparoscopy no longer is required for diagnosis, the lower cost for medical therapy is more realistic. Compared with the cost of a laparoscopic salpingostomy, methotrexate results in a 20% decrease in the cost of treatment.

Evidence-based Recommendation

Systemic methotrexate for unruptured ectopic pregnancy is less expensive than surgery, and direct costs are decreased substantially with methotrexate therapy. In addition to its cost effectiveness, systemic methotrexate does not subject patients to surgery and the complications associated with it. This cost benefit, however, diminishes with higher hCG titers and even disappears with levels greater than 3,000 mIU/mL, because of treatment failures and increased complications. (Strength of recommendation: B.)

RARE TYPES OF ECTOPIC PREGNANCY

Abdominal Pregnancy

The incidence of abdominal pregnancy is estimated at 1 in 8,000 births and represents 1.4% of all ectopic pregnancies. The prognosis is poor, with an estimated maternal mortality rate of 5.1 per 1,000 cases. The risk of dying from an abdominal pregnancy is 7.7 times higher than from other forms of ectopic pregnancy. The high rate of morbidity and mortality from abdominal pregnancy often results from a delay in diagnosis.

Abdominal pregnancies can be categorized as primary or secondary. These ectopic pregnancies may become apparent throughout gestation, from the first trimester to fetal viability. Symptoms may vary from those considered normal for pregnancy to severe abdominal pain, intraabdominal hemorrhage, and hemodynamic instability. Primary abdominal pregnancies are rare and are thought to occur as a result of primary peritoneal implantation. They usually abort early in the first trimester due to hemorrhagic disruption of the implantation site and hemoperitoneum. Secondary abdominal pregnancies occur with reimplantation after a partial tubal abortion or intraligamentary extension following tubal rupture. Historical criteria to distinguish between primary and secondary abdominal pregnancies are moot, because treatment is directed by the clinical picture.

Ultrasonography is the diagnostic tool of choice and usually can identify the empty uterus along with the extrauteral products of conception. If the fetus is near viability, hospitalization is recommended. If time permits, bowel preparation, administration of prophylactic antibiotics, and adequate blood replacement should be made available prior to an operative delivery. Unless the placenta is implanted on major vessels or vital structures, it should be removed. Although complications may occur, including sepsis, abscess formation, secondary hemorrhage, intestinal obstruction, wound dehiscence, amniotic fluid cyst formation, hypofibrinogenemia, and preeclampsia, the placenta can be left in place to prevent further hemorrhage at the time of surgery. In contrast to the typical tubal ectopic pregnancy, methotrexate is unlikely to accelerate retained placental absorption, because the trophoblastic cells are no longer actively dividing.

Ovarian Pregnancy

Ovarian pregnancy, the most common form of abdominal pregnancy, is rare, accounting for less than 3% of all ectopic gestations. Clinical findings are similar to those of tubal ectopic gestations: abdominal pain, amenorrhea, and abnormal vaginal bleeding. In addition, hemodynamic instability as a result of rupture occurs in 30% of patients.

Women with ovarian pregnancies are usually young and multiparous, but the factors leading to ovarian pregnancies are not clear.

The diagnosis usually is made by the pathologist, because many ovarian pregnancies are mistaken for a ruptured corpus luteum or other ovarian tumors. Only 28% of cases were diagnosed correctly at time of laparotomy. The recommended treatment is cystectomy, wedge resection, or oophorectomy during laparotomy, although laparoscopic removal has been successful.

Cornual Pregnancy

Cornual or interstitial pregnancy accounts for 4.7% of ectopic gestations and carries a 2.2% maternal mortality. Almost all cases are diagnosed after the patient is symptomatic. The most frequent symptoms are menstrual aberration, abdominal pain, abnormal vaginal bleeding, and shock, resulting from the brisk hemorrhage associated with uterine rupture. Due to myometrial distensibility, rupture is usually delayed, occurring at 9 to 12 weeks gestation.

A unique risk factor for interstitial pregnancy is previous salpingectomy, present in about 25% of patients.

Only a high index of suspicion and repeated ultrasonographic examination with Doppler flow studies allows early diagnosis. With a timely early diagnosis, alternatives to the traditional cornual resection during laparotomy have been performed successfully. These include laparoscopic cornual resection, systemic methotrexate administration, local injection of methotrexate, potassium chloride injection, and removal by hysteroscopy. Regardless of the initial treatment attempted, if uncontrolled hemorrhage occurs, immediate hysterectomy is warranted.

Cervical Pregnancy

The incidence of cervical pregnancy ranges from 1 in 2,500 to 1 in 12,422 pregnancies. The most common predisposing factor is a prior dilation and curettage, present in 68.6% of patients. Interestingly, 31% of these were performed for termination of pregnancy. Other predisposing factors implicated in cervical pregnancies are previous cesarean delivery and IVF.

The most common initial symptom of cervical pregnancy is painless vaginal bleeding. These ectopics usually are diagnosed incidentally during routine ultrasonography or at the time of surgery for a suspected abortion in progress. In reported cases, 91% of patients sought treatment for vaginal bleeding, and 29.2% had massive bleeding. Not surprisingly, abdominal pain occurred with vaginal bleeding in only 25.8% of cases. The cervix is usually enlarged, globular, or distended. On occasion, it appears cyanotic, hyperemic, and soft in consistency. Sonography and magnetic resonance imaging have improved diagnosis of cervical pregnancy. Up to 81.8% of patients have been diagnosed correctly with ultrasonographic identification of the gestational sac in the cervix below a closed internal cervical os, with trophoblastic invasion into the endocervical tissue.

When the patient is hemodynamically stable, conservative therapy commonly is employed. There are no large studies, only several case series. These have shown that use of methotrexate and uterine artery embolization are safe and effective for treatment in the stable patient with a cervical pregnancy. Systemic and local treatment with various agents carries an overall success rate of 81.3%. Unfortunately, massive hemorrhage may occur despite conservative measures, and hysterectomy is warranted.

Heterotopic Pregnancy

Heterotopic pregnancy is the coexistence of an intrauterine and ectopic gestation. In 1948, the spontaneous heterotopic pregnancy rate was calculated as 1 in 30,000 pregnancies, based on an ectopic pregnancy incidence of 0.37% and dizygous twinning rate of 0.8%. In the 1980s, the calculation rose to 1 in 10,000 due to an increased ectopic pregnancy rate. Today, heterotopic pregnancies occur in 1 in 3,889 to 1 in 6,778 pregnancies. In a review of 66 heterotopic pregnancies by Reece et al., 93.9% were tubal and 6.1% ovarian.

Simultaneous existence of intra- and extrauterine pregnancies poses several diagnostic pitfalls. Heterotopic pregnancies are diagnosed in most cases after clinical signs and symptoms develop, and 50% of patients are admitted for emergency surgery following rupture. The delay in diagnosis is secondary to the finding of an intrauterine pregnancy, with the assumption that any symptoms will be self-limited.

Similar to tubal ectopic pregnancies, the most common complaint is lower abdominal pain. Routine ultrasonography detects only about 50% of tubal heterotopic

pregnancies, and the remainder are diagnosed during laparoscopy or laparotomy when patients become symptomatic. Serial levels of the ß subunit of hCG are not helpful due to the effect of the intrauterine pregnancy.

If patients are hemodynamically unstable, exploratory laparotomy is warranted. If the diagnosis is suspected or the patient is symptomatic but hemodynamically stable, laparoscopy can be performed. Expectant management is not recommended, because ß-hCG levels cannot be monitored adequately. Systemic methotrexate is contraindicated if a viable intrauterine pregnancy is present and desired. Local injection of methotrexate with potassium chloride has been noted successful in a small case series.

SUMMARY POINTS

- In most circumstances, ectopic pregnancy can be diagnosed before symptoms develop and treated definitively with few complications.
- Quantitative ß-hCG testing, ultrasonography, and curettage allow early diagnosis of ectopic pregnancy and use of medical therapy as the initial therapy option.
- Conservative surgical therapy and medical therapy for ectopic pregnancy are comparable in terms of success rates and subsequent fertility. Medical therapy is the preferred choice because of the freedom from surgical complications and lower cost.
- Surgery is the treatment of choice for hemorrhage, medical failures, neglected cases, and when medical therapy is contraindicated.
- Multiple-dose methotrexate is preferable to single-dose methotrexate, direct injection, or tubal cannulation and is the first choice for unruptured, uncomplicated ectopic pregnancy.
- Laparoscopic salpingostomy or salpingectomy is favored for cases of intraabdominal hemorrhage, medical failure, neglected cases, and complex cases when medical therapy is contraindicated.
- Prophylactic postoperative systemic methotrexate (a single dose) can prevent virtually all cases of persistent ectopic pregnancy following salpingostomy.
- Salpingectomy prior to IVF decreases ectopic pregnancy incidence while increasing pregnancy rates in select patients with preexisting tubal disease.

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Chapter 6

Kenneth Ward

Genetics and Prenatal Diagnosis

PATTERNS OF INHERITANCE
Single Gene Disorders
Polygenic, Multifactorial Disorders
Cytogenetic Disorders
Parent of Origin Effects
THE MOLECULAR GENETICS REVOLUTION
Deoxyribonucleic Acid
The Genome Project
GENETIC EVALUATION
Genetic History and Physical Examination
Genetic Counseling
Pregnancy Termination
Laboratory Screening
PRENATAL DIAGNOSIS
Maternal Serum Screening
Fetal Imaging
Fetal Sampling for Prenatal Diagnosis
Prenatal Treatment and Gene Therapy
GENETICS IN GYNECOLOGIC DISORDERS
TRENDS
SUMMARY POINTS

REFERENCES

Genetic screening has become an important component of prenatal care. Recent discoveries have expanded the indications for cytogenetic or molecular genetic tests performed on chorionic villi, amniocytes, and fetal blood. Soon first-trimester DNA-based prenatal diagnosis will become possible for thousands of additional conditions. New technologies such as flow cytometry, fluorescent in situ hybridization, and DNA amplification with the polymerase chain reaction (PCR) enable testing of a single cell for chromosomal or Mendelian problems. This approach already has allowed preimplantation testing of embryos and minimally invasive diagnosis using the small population of fetal cells in the maternal circulation. Over the next decade, gene therapy will be applied prenatally for the treatment of inborn errors and postnatally for the treatment of genetic diseases. This will provide additional impetus for genetic evaluation.

Genetic principles are central to understanding the pathophysiology of many of the conditions for which obstetrician-gynecologists provide care (Table 6.1). More than 20 million Americans have a diagnosed genetic disease. One percent of all newborns have a recognizable Mendelian disorder, 0.5% have a chromosomal syndrome, and many more have a polygenic, multifactorial disorder. Most pregnancy losses and most congenital anomalies have genetic causes. Genes also play an important role in common gynecologic disorders such as leiomyomata, endometriosis, gynecologic cancers, and infertility. Genetic variants are responsible for tendencies to have multiple gestations, preeclampsia, gestational diabetes, and other pregnancy complications. Susceptibilities to infectious or teratogenic agents are determined genetically. Our rapidly expanded knowledge of the human genome will revolutionize obstetric and gynecologic practice.

One in twenty newborns has a detectable genetic defect at birth.
Over 20 million Americans have a diagnosed genetic disease.
Life-years lost to genetic diseases are estimated at 6.5 times greater than years lost to heart disease—the nation's number one killer.
Thirty percent of pediatric hospital admissions and 10% of adult admissions are for disorders that are wholly or partly genetic.
All cancers have somatic or inherited genetic changes.

TABLE 6.1. *The burden of genetic disease*

Recognizing that a condition is genetic enables us to find the gene responsible for the illness, which can lead to improved means of classification, diagnosis, prevention, and treatment. Correlation of the phenotype with the genotype often provides specific predictive insights. Because any DNA test can be performed prenatally, discovery of the gene that causes a particular disease can give at-risk couples the necessary information to prepare for having an affected child, to consider prenatal therapy if available, or to choose to end the pregnancy.

Patients often have genetic illnesses that will affect pregnancy or their gynecologic care, illnesses that may remain undiagnosed unless physicians are thorough in their evaluation of unusual signs or symptoms. For example, a new obstetric patient has a wasted facial appearance, generalized weakness, and difficulty releasing her grip when shaking the physician's hand. Hopefully, this patient has already been evaluated and correctly diagnosed. If not, it is the obstetrician's responsibility to refer a patient with unusual signs and symptoms for evaluation. In this case, the patient has the classic signs of myotonic dystrophy, an autosomal dominant disorder. Formerly, myotonic dystrophy was a difficult diagnosis to establish in some patients, but the diagnosis can be made easily using DNA analysis of her blood. The physician and this woman need to know that she is at significant risk for developing polyhydramnios, which could result in preterm labor; her fetus may have positional deformities and is at risk for a severe, often fatal, neonatal form of myotonia; her labor is likely to be prolonged, and she may be unable to push during the second stage. If she requires cesarean section, she may have undiagnosed cardiac problems that place her at higher risk for anesthesia. If failure to recognize these risks results in a bad outcome, a lawsuit claiming negligence might be brought.

PATTERNS OF INHERITANCE

Single Gene Disorders

The observation that “like begets like” has been stated throughout recorded history, but current theories describing how genetic traits and illnesses are inherited are just over 100 years old. In the late 1800s, Mendel described how individual genetic traits were passed on from generation to generation. Single gene disorders (i.e., mendelian disorders) are conditions caused by a mutation at a single site in the DNA and inherited in the proportions predicted by Mendel's laws. These disorders can be dominant conditions in which the phenotype is expressed even when only one chromosome of a pair has a defect, or recessive conditions which are expressed only if the defect exists on both chromosomes. Classically, these different modes of inheritance are revealed by pedigree analysis (Fig. 6.1 and Fig. 6.2).

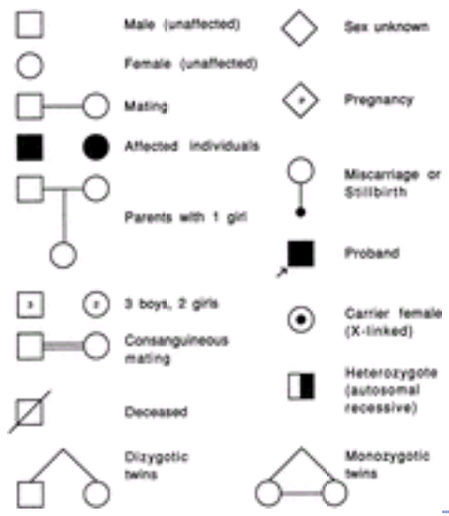

FIG. 6.1. Symbols used to draw a pedigree.

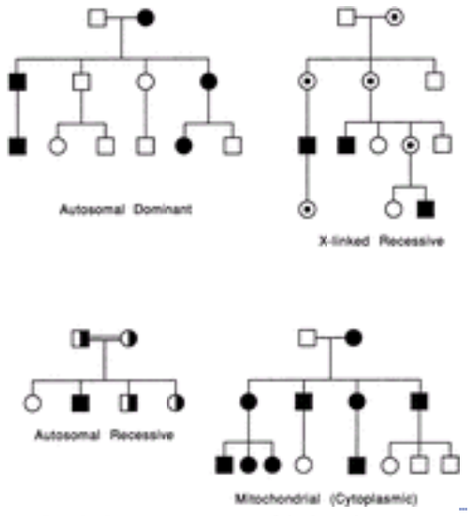

FIG. 6.2. Patterns of inheritance.

As we learn more about the tremendous variation that occurs at every locus, the distinctions between dominant and recessive conditions have become blurred. Dominance and recessiveness are attributes of the phenotype, not attributes of the gene or allele. They are empirical terms, and they depend on the sensitivity of the method used to describe the phenotype. The researchers must specify particular phenotypic features when describing inheritance. For instance, sickle cell anemia is a recessive disease only if the full-blown disease is considered, but it is a codominant condition if the hemoglobin is being analyzed by electrophoresis. The ABO blood group is an example of a trait in which both codominant and recessive inheritance is seen. The retinoblastoma gene is a recessive tumor suppressor gene at the cellular level, but abnormalities in the gene are responsible for the autosomal dominant tendency to develop retinoblastomas and osteosarcomas.

In autosomal dominant conditions, the disease is expressed in persons who are heterozygous for the disease-causing mutation. McKusick's catalog of mendelian disorders describes more than 3,000 dominant conditions. Marfan syndrome, myotonic dystrophy, neurofibromatosis, achondroplasia, and Huntington disease are examples of autosomal dominant disorders. The probability of an affected person transmitting the abnormal gene to the children is 50% with each pregnancy. Typically, autosomal dominant conditions have less than 100% penetrance, and fewer than 50% of the offspring show signs of the disorder. Male and female offspring usually are affected with equal frequency and severity. The trait passes through one parental line only, and father-to-son transmission can occur. For highly penetrant, autosomal dominant conditions, the gene is expressed in each generation (i.e., vertical transmission). New mutations are relatively common and, on average, paternal age is advanced when isolated, sporadic, or new mutation cases appear. Autosomal dominant phenotypes often involve isolated or multiple *structural* defects. They can be extremely variable and the onset of clinical features is often age dependent. Dominant disorders tend to be less severe than recessive diseases, but they are usually lethal in the rare persons who are homozygous for a dominant disease.

Autosomal recessive conditions are expressed only in persons in whom both versions (i.e., alleles) of the involved gene are abnormal. More than 1,500 autosomal recessive conditions have been described. Cystic fibrosis (CF), sickle cell anemia, Tay-Sachs disease, and phenylketonuria are examples of autosomal recessive disorders. Male and female offspring are affected with equal frequency and severity. Each parent is a heterozygous carrier, and abnormal genes are inherited from both parents. Each offspring of two carrier parents has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected. If the recessive phenotype is extremely rare, consanguinity usually is found in the pedigree. Affected persons rarely have affected children; autosomal recessive inheritance shows a “horizontal” pattern in a pedigree, with typically only a single generation of siblings affected. Affected persons who mate with unaffected persons who are not carriers have only unaffected, carrier offspring. Most autosomal recessive phenotypes are biochemical or enzymatic in nature, and they tend to be less variable and more severe than dominant conditions.

X-linked inheritance occurs when a trait is carried on the X chromosome. Boys are hemizygous for X chromosome genes, but girls can be homozygous or heterozygous. Of the 300 X-linked recessive diseases that are recognized, the hemophilias and Duchenne muscular dystrophy are the best known. Characteristics of X-linked recessive inheritance include a higher incidence of the disorder in male than in female offspring. The mutant gene or disease never is transmitted directly from father to son, and all the daughters of an affected man are carriers. The trait is transmitted through carrier females, and affected males in the same kindred are related to one another through the females. X-linked dominant diseases are much rarer; examples include Alport syndrome, vitamin D-resistant rickets, and incontinentia pigmenti. They appear twice as often in female as in male offspring. All daughters of an affected man have the disorder, but no sons are affected. Heterozygous affected women transmit the mutant allele at a rate of 50% to progeny of both sexes. If the affected woman is homozygous, all of her children will be affected.

Y-linked or holandric inheritance occurs when a trait is carried on the Y chromosome. Only male offspring are affected, and there is only male-to-male transmission. No known disease genes are inherited in this fashion, but genes for gender determination, tooth size, and height occur on the Y chromosome.

Mitochondrial inheritance is a more recently described mode of inheritance, causing traits and disorders that are inherited through the mitochondrial chromosome. Unique patterns are seen in affected families. Mitochondria are inherited exclusively with the cytoplasm of the egg; a woman who carries a disease will pass the disease to 100% of her offspring. Male carriers will pass the disorder to none of their offspring. Leber optic atrophy and certain rare myopathies are inherited in this fashion.

Polygenic, Multifactorial Disorders

Multifactorial or polygenic inheritance is the most common form of inheritance. Even in the classic mendelian disorders described above, there can be tremendous quantitative and qualitative differences in the phenotype among persons who have the same allele or the same genetic mutation. This variability can be evident as nonpenetrance of certain features (or the entire phenotype) and as differences in the severity of features, the frequency of cyclic or episodic events, or the age of onset of the first clinical sign of the disorder. Genetic variability can be caused by the underlying genetic background of the affected person, including gender influences and limitations. The phenotype may be influenced further by maternal factors such as cytoplasmic inheritance, the intrauterine environment, or imprinting. X-linked disorders can be altered by variations in X inactivation or lionization. Each genotype undergoes subtle changes through somatic mutation, gene amplification, or transpositions and positional effects over time. Exogenous factors such as the environment, teratogens, medical intervention, and chance also influence variability.

Most congenital anomalies reflect multifactorial inheritance (Table 6.2). A common error some obstetricians make is to counsel a patient that rare conditions will not occur repetitively in her family. If the birth defect in question has a strong genetic component or if there is an identifiable environmental or teratogenic component which would recur in subsequent pregnancy, the risks may remain high for that patient (Table 6.3). The rates may be even higher if a mendelian or chromosomal condition has gone unrecognized in the affected child. Before counseling patients about the recurrence risk of any birth defect, it is pertinent to review which syndromes are associated with that birth defect and ask whether any member of the family has those syndromes. When this requires skill or knowledge beyond the usual expertise of an obstetrician-gynecologist, referral to a medical geneticist is appropriate.

Anomaly is a structural feature that departs from the normal.
Syndrome is a recognizable pattern of structural defects, often with a predictable natural history that can be identified on several patients, thus allowing diagnosis and classification.
Sequence is a pattern of defects that results from a single event early in pregnancy.
Association is a grouping of anomalies that frequently occur together but are not actual syndromes.
Malformation is a morphologic defect resulting from abnormal development.
Disruption is morphologic defect resulting from extrinsic breakdown or interference with normal development.
Deformation is an abnormal form, shape, or position caused by mechanical forces.

TABLE 6.2. *Types of birth defects*

TABLE 6.3. *Empiric recurrence risks for common congenital anomalies*

Multifactorial inheritance usually works according to a threshold model. Several factors must collaborate to cause a bodily function to go awry, and only after these factors reach some critical point is the phenotypic effect seen. Many different factors can affect the observed recurrence risk. The intrinsic heritability “or geneticness” of the condition is frequently the most important factor. This usually is determined by examining whether monozygotic twins are concordant for a particular condition relative to dizygotic twins. For instance, neonatal seizures show a very high heritability rate, with 85% to 90% concordance in monozygotic twins verses 10% to 15% concordance in dizygotic twins. The population incidence of the condition is another important variable. The recurrence risk is higher for common disorders or within populations with a high incidence of the disorder. In disorders with a relatively high heritability, the recurrence risk of the disorder approximates the square root of the population incidence. There can be marked variation in the population frequency of different disorders and different ethnic groups. For instance, cleft lip occurs commonly in Native Americans, but African Americans have a nine-fold lower incidence of cleft lip than the general population.

If the incidence of a congenital anomaly shows a sex bias, the recurrence risk is higher in the offspring (and other relatives) if the parent is of the less frequently affected sex. For example, pyloric stenosis affects 5 times as many male as female offspring, and empirical data show that there is a 25% chance of producing an affected child if the mother had pyloric stenosis at birth and only a 4% risk if the father is the affected parent. Similarly, the recurrence risk is higher when the gender of the affected child is the less frequently affected. Again, the risk of having another child with pyloric stenosis is 3.2% if the first-affected sibling is a boy and 6.5% if the affected sibling is a girl. Hirschsprung disease, clubfoot, and cleft lip are examples of anomalies which are more common in male infants. Cleft palate, anencephaly, hip dysplasia, and scoliosis are more common in female infants.

The number of affected individuals in a kindred can affect the recurrence risk. The greater the number of family members who have already been affected with a multifactorial condition, the more likely it is that the genetic background is favorable for expression of this condition. After a couple has one affected child with cleft lip and palate, there is a 4% empirical recurrence risk. After two affected children, the risk rises to 10%. Consanguinity also increases the risk of recurrence because of the greater likelihood of deleterious genes being shared, but a more distant relationship from an affected person decreases the risk of recurrence.

The severity of the disorder often predicts the recurrence risk. An illustration of this is found in Hirschsprung disease. The recurrence risk is proportional to the length of the aganglionic segment of the colon. Neural tube defects are the most notable exception to this rule, because the recurrence risk for any neural tube defect appears to be the same whether the first-affected child had anencephaly or a small spina bifida lesion.

Cytogenetic Disorders

Cytogenetic disorders are changes in the genome visible under a light microscope. These gross lesions involve the loss or duplication of a large number of genes; multiple malformations and dysfunctions usually are observed clinically. Diagnostic clues for a cytogenetic disorder can range from subtle dysmorphic features to major structural malformations, particularly craniofacial, skeletal, cardiac, and genitourinary malformations. No individual anomaly is pathognomonic for a particular chromosomal syndrome, rather it is the pattern that can be distinctive. There is tremendous overlap between patterns and because nonchromosomal syndromes can mimic chromosomal abnormalities, obtaining a karyotype is always necessary to confirm the diagnosis. Cytogenetic disorders usually are associated with some degree of mental retardation and growth deficiency. Most have an increased rate of perinatal loss and premature mortality of live-born neonates. The rate of chromosome abnormalities is at least 40% to 60% in first-trimester abortuses, and the rates of abnormalities also are elevated in fetal deaths and preterm and post-term deliveries (Table 6.4 and Table 6.5). About 1 in 160 babies is born with a genetic defect detectable by ordinary cytogenetic means (Table 6.6).

Gestational age in weeks	With chromosomal abnormalities (%)
<8	72.1
8–11	53.5
12–15	47.9
16–19	23.8
20–23	11.9
24–27	13.2
Stillbirths	6.0
Neonatal deaths	5.5

Source: Angell RR, Sandison A, Bain AD. Chromosome variation in perinatal mortality: a survey of 500 cases. *J Med Genet* 1984;21:39–44, with permission.

TABLE 6.4. *Incidence of chromosomal aberrations in pregnancy losses at various gestational ages*

Type	Frequency (%)
Trisomy 14	3.7
Trisomy 15	4.2
Trisomy 16	16.4
Trisomy 18	3.0
Trisomy 21	4.7
Trisomy 22	5.7
Other trisomies	14.3
45,X	18.0
Triploid	17.0
Tetraploid	6.0
Unbalanced translocations	3.0
Other	4.0

Source: Carr DH, Gedeon M. Population cytogenics of human abortuses. In: Hook EB, Porter IH, eds. *Population cytogenics*. New York: Academic Press, 1977:1–9, with permission.

TABLE 6.5. *Types of chromosomal abnormalities in spontaneous abortuses*

Sex chromosome abnormalities in males	Male births
XYY	1/1,000
XXY	1/1,000
Other	1/3,000
Sex chromosome abnormalities in females	**Female births**
45,X	1/10,000
XXX	1/1,000
Other	1/3,000
Autosomal aberrations in babies	**Births**
+D (trisomy 13)	1/20,000
+E (trisomy 18)	1/8,000
+G (nearly all trisomy 21)	1/800
Other trisomies	1/50,000
Rearrangements	**Births**
Balanced	1/500
Unbalanced	1/2,000
Total chromosomal aberrations	**1/160 births**

Source: Hook EB, Hamerton JL. In: Hook EB, Porter IH, eds. *Population cytogenetics: studies in humans.* New York: Academic Press, 1977, with permission.

TABLE 6.6. *Incidence of chromosomal aberrations seen in newborn surveys*

Cytogenetic studies have been used clinically for approximately 40 years. In the late 1950s, it was determined that humans have 46 chromosomes and that many of the recognized birth defect syndromes, such as Down syndrome, Turner syndrome, and Klinefelter syndrome, have abnormalities of chromosome number or structure. Normally, the nucleus of most human cells contains two sets of chromosomes, with one set contributed by each parent. Each set has 22 autosomes and either an X or a Y sex chromosome (Fig. 6.3).

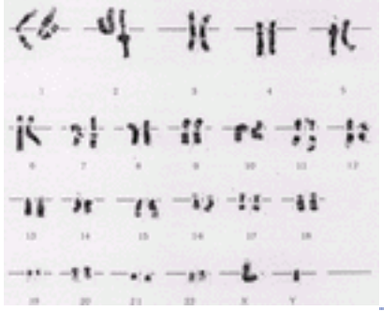

FIG. 6.3. Normal human karyotype (46,XY).

Metaphase chromosome preparations can be prepared from any cell undergoing mitosis. Typically, in order to obtain adequate numbers of cells, mitosis is induced artificially using a mitogenic chemical such as phytohemagglutinin. The cells are then incubated in a dilute solution of an agent that poisons the mitotic spindle. The chromosomes are swollen using a hypotonic salt solution, fixed on a slide, and dried for staining. The stained chromosomes can be observed by light microscopy.

The dyes used to stain chromosome preparations reveal patterns of light and dark bands that reflect regional variations in the molecular composition of each chromosome. Giemsa is the most commonly used dye. Q-banding is a fluorescence technique that gives results similar to the G-banding (i.e., Giemsa banding), while R-banding (i.e., reverse banding) gives a pattern opposite to that with G- or Q-banding. T-banding specifically stains the telemetric regions of chromosomes, which can help to screen for missing regions at the ends of the chromosomes, and C-banding primarily stains the centromeric region of the chromosomes.

Differences in the size of the chromosomes, the banding pattern, and the centromere position allow the 24 chromosomes to be differentiated from each other in an analysis called a karyotype. The most common features looked for on a karyotype include aneuploidy (i.e., abnormal number of chromosomes) or structural chromosome abnormalities such as deletions, inversions, insertions, or translocations (Table 6.7) (Fig. 6.4).

p	Short ("petite") arm of a chromosome
q	Long arm of a chromosome
del	Deletion of a chromosomal segment
der	Derivative chromosome resulting from a structural rearrangement
dup	Duplication of a chromosome segment
i	Isochromosome
ins	Insertion of a chromosomal segment into another chromosome
inv	Inversion of a chromosomal segment
r	Ring chromosome
rob	Robertsonian translocation
t	Translocation
ter	Terminal segment of chromosome (pter, terminal short arm; qter, terminal long arm)
/	Diagonal hash-line indicates mosaicism (46,XX/45,X indicates a mosaic patient with cell lines containing 46 chromosomes and 45 chromosomes respectively, i.e., mosaic Turner syndrome)
+ or –	When appears before a chromosome indicates the addition or loss of that whole chromosome (i.e., +21 indicated trisomy 21, Down syndrome); when appears after a chromosome, indicates the addition or loss of a part of a chromosome (i.e., 8q- indicates the loss of part of the long arm of chromosome 8)

TABLE 6.7. *Chromosomal nomenclature*

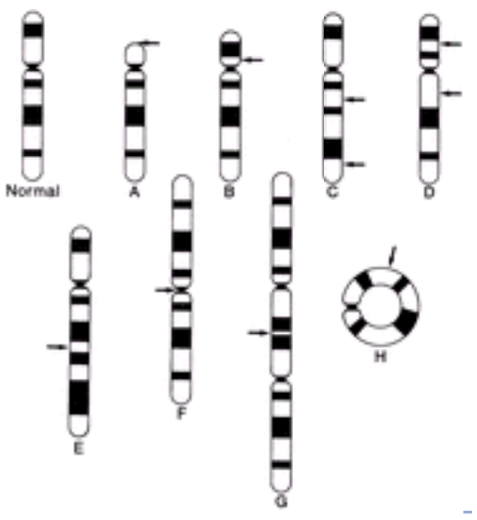

FIG. 6.4. Types of chromosomal abnormalities. A, terminal deletion; B, interstitial deletion; C, paracentric inversion; D, pericentric inversion; E, translocation (additional material from a different chromosome); F, isochromosome; G, dicentric chromosome; H, ring chromosome. The *arrows* indicate the sites of chromosomal breaks where rearrangement occurs.

Because the technology to study cytogenetic disorders is well established, there is greater clinical experience with this than with other types of genetic testing. There are several well-defined indications for obtaining a fetal karyotype analysis (Table 6.8). Pregnant women who are 35 years or older routinely are offered a fetal karyotype analysis, because trisomy tends to occur more commonly with advancing maternal age (Table 6.9). Other indications for obtaining a fetal karyotype include having a previous child with an abnormal karyotype, parental chromosomal rearrangements, unexplained intrauterine growth retardation, and an abnormally low level of maternal serum a-fetoprotein. In addition, many fetal anomalies associated with karyotypic abnormalities can now be visualized using high-resolution ultrasonography (Table 6.10). A fetal structural abnormality detected by ultrasonography is another frequent indication for obtaining a fetal karyotype.

Advanced maternal age
Previous child with an abnormal karyotype
Parental chromosome rearrangements
Fetal structural abnormality on ultrasonography
Unexplained intrauterine growth retardation
Abnormally low MSAFP

MSAFP, maternal serum α-fetoprotein.

TABLE 6.8. *Indications for a fetal karyotype*

	Trisomy 21		Any abnormality	
Age	Live birth	Amnio	Live birth	Amnio
20	1/1,734	1/1,231	1/526	—
25	1/1,250	1/887	1/476	—
30	1/965	1/685	1/385	—
31	1/915	1/650	1/385	—
32	1/794	1/563	1/322	—
33	1/639	1/452	1/286	—
34	1/496	1/352	1/238	—
35	1/386	1/274	1/192	1/83
36	1/300	1/213	1/156	1/76
37	1/234	1/166	1/127	1/67
38	1/182	1/129	1/102	1/58
39	1/141	1/100	1/83	1/49
40	1/100	1/78	1/66	1/40
41	1/86	1/61	1/53	1/32
42	1/66	1/47	1/42	1/26
43	1/52	1/37	1/33	1/21
44	1/40	1/29	1/26	1/19
45	1/31	1/22	1/21	1/15
46	1/24	1/17	1/16	1/12
47	1/19	1/13	1/13	1/20
48	1/15	1/10	1/10	1/18
49	1/11	1/8	1/8	1/16

Source: Hook EB Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA* 1983;249:2034–2038, with permission.

TABLE 6.9. *The risk of karyotypic abnormalities related to maternal age at delivery*

Finding	% Abnormal karyotype[a]
Holoprosencephaly	40–60
Dandy-Walker malformation, cerebellar hypoplasia	
Isolated hydrocephalus	5–10
Spina bifida	1–5
Agenesis of the corpus callosum	
Choroid plexus cysts—large or associated with other abnormalities	1–2
Facial abnormalities	
Cystic hygroma	>60
Nuchal thickening	
Cardiac malformations	20–35
Duodenal atresia	30
Omphalocele	10
Hydrothorax	
Diaphragmatic hernia	
Genitourinary anomalies	4–10
Obstructive uropathy	
Renal cystic dysplasia with other abnormalities	
Clubfoot with other abnormalities	
Severe intrauterine growth retardation	
Polyhydramnios or oligohydramnios and other abnormalities	
Single umbilical artery with other anomalies	
Multiple placental cysts	
Nonimmune hydrops	10–20

[a]Numbers are provided only when there is a large enough experience and general consensus in the literature.

TABLE 6.10. *Risk of a chromosomal abnormality with selected sonographic findings*

A variety of genetic defects, including the common trisomies and many chromosomal translocations, can be detected by routine karyotype analysis. Recent modifications, including chromosome painting that allows a particular chromosome to be identified directly, or fluorescent in situ hybridization (FISH) that allows specific sites along the chromosome to be identified, have greatly extended the capabilities of the cytogenetics laboratory. However, there are molecular and single gene rearrangements that cannot be observed by light microscopy and require molecular genetic technology for evaluation.

FISH is a cytogenetic technique in which a specific DNA probe with a fluorescent label is bound to homologous DNA in a clinical sample. FISH can be performed either on a metaphase chromosome spread to detect microdeletions and microduplications, and during interphase to detect a larger chromosomal region in a nondividing cell. Interphase FISH can be performed on cultured cells, tissue sections, and on cytologic smears. FISH has been used to detect common aneuploidies, such as trisomy 21, trisomy 18, trisomy 13, and the sex chromosome aneuploidies, in prenatal diagnosis.

Because uncultured amniocytes can be used, the FISH technique can offer more rapid detection of chromosome aneuploidies. In one of the first large studies, FISH was performed as an adjunct to conventional cytogenetics in 4,500 patients. Region-specific DNA probes to chromosomes 13, 18, 21,X, and Y were used to determine ploidy by analysis of signal number in hybridized nuclei. A sample was considered to be euploid when all autosomal probes generated two hybridization signals and when a normal sex chromosome pattern was observed in greater than or equal to 80% of hybridized nuclei. A sample was considered to be aneuploid when 70% or more of hybridized nuclei displayed the same abnormal hybridization pattern for a specific probe. The accuracy of all *informative* FISH results, euploid and aneuploid, was 99.8%, and the specificity was 99.9%.

Current prenatal FISH protocols are not designed to detect all chromosome abnormalities and should be used only as an adjunctive test to cytogenetics. FISH can provide rapid and accurate clinical information in pregnancies when fetal abnormalities have been observed by ultrasonography.

Future improvements are likely. FISH protocols, which would allow the simultaneous and unequivocal discernment of all human chromosomes, are under development. Each chromosome is labeled in a unique way using several different colors. A “spectral karyotype” can be generated, which allows visualization of a unique, defined emission spectra for each human chromosome. Computerized analysis may allow automatic and rapid analysis, with resolution approaching routine G-banding.

Parent of Origin Effects

Genomic imprinting refers to the differential expression of genes based on the parent of origin of the gene. Imprinting usually is mediated by differential methylation of the alleles involved. Most experimental evidence regarding imprinting comes from animal studies, but some naturally occurring human analogs exist. The paternal genetic contribution appears to be essential for the development and function of the placenta and extraembryonic tissues, but the maternal contribution is required for embryonic development. Ovarian teratoma, the most common benign pelvic tumor in women of reproductive age, is characterized by a diploid karyotype, in which both haploid sets of chromosomes are maternal in origin. Complete hydatidiform moles, which show failure of normal embryonic and fetal development, are usually diploid with two paternal haploid chromosome sets and no maternally derived chromosomes.

The differential function of parental chromosomal contributions in development is also evident when studying human triploidy. In an android conception (i.e., two paternal, one maternal chromosome set), the fetus is severely growth retarded, with a disproportionately large head and syndactyly of digits of the hand. The placenta is usually very large and hydropic. Survival into the second trimester or occasionally into the third trimester is possible but usually requires the presence of mosaicism with a diploid cell line. When the chromosomal constitution is gynoid (i.e., two maternal, one paternal set), the conceptus is underdeveloped and the placenta is small and cystic; such pregnancies rarely continue beyond the first trimester.

In some persons with an apparently normal karyotype, both versions of a pair of homologous chromosomes were inherited from one parent, a phenomenon called uniparental disomy. This can give rise to abnormalities if genomic imprinting causes regions of both chromosomes to be inactivated or overexpressed.

THE MOLECULAR GENETICS REVOLUTION

In the mid 1950s, there were only two “facts” known about the human genome. It was thought that humans had 48 chromosomes and that X-chromosome inactivation in humans occurred by the same mechanism as had been observed in fruit flies. Both of these observations have been proven to be in error. In the past few decades,

there has been an explosion of knowledge about the human genome, largely attributed to advances in molecular biology.

Deoxyribonucleic Acid

Genes are the instructions required for building structural proteins and enzymes and peptide hormones, and the complete set of genetic instructions for any organism is called its genome (Table 6.11). The human genome has 46 chromosomes, including 22 pairs of autosomes and two sex chromosomes. The genome is made up of three billion base pairs, somewhere between 40,000 and 100,000 genes. The functions of approximately 10,000 human genes have been characterized, and in 2003 the first draft of the human genome sequence will be completed.

46 chromosomes including
22 pairs of autosomes
2 sex chromosomes
40–70,000 genes
2,900,000,000 base pairs

TABLE 6.11. *The human genome*

In 1944, Avery and colleagues demonstrated that DNA is the chemical that carries genetic instructions. Roughly equal parts of DNA and its supporting proteins make up the 46 chromosomes. If the strands of DNA in the nucleus of a single cell could be unwound and spliced together, the resulting DNA molecule would stretch more than 1.5 meters long, but it would be only 20 trillionths of a centimeter wide.

The genetic code is spelled out with the four nitrogenous bases: adenine, thiamine, cytosine, and guanine (Fig. 6.5). The purine and pyrimidine bases are arranged in a ladderlike, double helix arrangement that is very stable (i.e., theoretic dissociation constant = 10 - 23). During cell division, DNA is duplicated with extremely high fidelity by synthesis of a new strand of one side of the molecular ladder.

DNA	CAG—CGG—GGT
RNA	GUC—GCC—CCA
Protein	Valine—Alanine—Proline

FIG. 6.5. Genetic code. The DNA code consists of four characters and is read three characters at a time. It is translated into an RNA message, which instructs cells in how to assemble proteins from amino acid building blocks.

The human genome consists of at least 40,000 genes, but the genes comprise only one tenth of the encoded information. Most of the genome is of unknown function, but it probably codes for the proper spacing, alignment, and punctuation of the genetic instructions. About 99.8% of the DNA sequence is identical from one person to the next. Stated another way, there are many minor differences between any two persons; on average, there is a variation of one nucleotide for every 200 to 500 base pairs. When these sequence differences occur within genes, they can lead to genetic diseases or genetic variation. Most of the minor differences have no observable effect because they occur in the noncoding regions of the genome, regions of DNA that do not contain genes. These otherwise unimportant differences have been the basis of the current explosion of genetic knowledge, because much of our ability to study genes or diagnose genetic illness exploits differences (i.e., DNA sequence polymorphisms) in these regions to track or find neighboring genes.

The DNA sequence is read by cellular enzymes three bases at a time, and each triplet directs the positioning of a particular amino acid within the structure of a protein (see Fig. 6.5). The protein coding instructions are transmitted to the cellular machinery through messenger RNA, a transient, intermediary molecule that is similar to a single strand of DNA (Fig. 6.6). The RNA strand is transcribed from the DNA template in the nucleus and has an opposite or complementary genetic sequence. Messenger RNA moves from the nucleus into the cytoplasm, where the protein manufacturing organelles build a protein. Analysis of messenger RNA molecules is extremely useful in the laboratory for detecting genes.

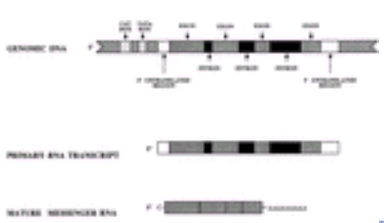

FIG. 6.6. Anatomy of a gene. Regulatory regions are present in the 5' region. Introns are spliced out of the final messenger RNA.

Several advances in molecular biology have enabled the molecular genetics revolution to take place. The first was the discovery of restriction enzymes, which are bacterial proteins that can cut DNA molecules at specific sites by recognizing the DNA sequence at those sites. Over 400 restriction enzymes have been discovered, many are commercially available, and about 25 are used commonly. Restriction fragment length polymorphisms (RFLPs) occur because of minor sequence changes (usually single base substitutions) that abolish or create a recognition site, altering the length of a digestion fragment. Restriction sites occur frequently, and several restriction sites can occur in the vicinity of any given gene. When these RFLPs are polymorphic, they become useful markers for linkage studies, diagnostic testing, and paternity testing (Fig. 6.7). RFLPs and other DNA polymorphisms provide the landmarks for genetic maps.

FIG. 6.7. Linkage study using restriction fragment length polymorphisms. Each lane represents the genotype of one family member. *M*, mother; *F*, father; *D*, daughter; *S*, son. In this example, the disease allele is associated with the upper band passed from the mother to the son.

Scientists have gained a greater understanding of how to manipulate the physical conditions, such as pH, salt concentration, and temperature, of in vitro DNA reactions. These skills—combined with the use of restrictions enzymes—allowed the development of recombinant DNA or new combinations of DNA engineered in the laboratory. Recombinant DNA technology has made possible the development of gene probes (pieces of DNA usually radioactively labeled) that recognize and bind specifically to a homologous sequence in another sample of DNA. These technologies also underlie cloning—the copying of DNA segments in lower animals and the

manufacturing of human proteins using bacteria or cell cultures.

Various blotting technologies are used commonly to study DNA. With blotting, biologically relevant molecules undergo electrophoresis and are transferred to a stable membrane for repeated experiments. Blots are called Southern blots if DNA is being analyzed, Northern blots if RNA is being analyzed, and Western blots if proteins are being analyzed.

DNA testing is clinically applicable to many disorders and can be performed in one of several ways (Table 6.12). When the molecular basis of a disease is known, direct mutation testing can provide a yes or no answer on any DNA sample. For instance, in CF, hundreds of mutations have been discovered. A battery of mutations can be tested for using various methods such as dot blots, which are simple to interpret (Fig. 6.8).

TABLE 6.12. *Common conditions for which DNA testing is available*

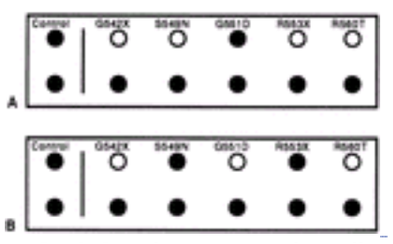

FIG. 6.8. Direct mutation diagram. Direct detection of cystic fibrosis mutations using reverse dot blots. In this example, five mutations in exon 11 of the cystic fibrosis gene (G542X, S549N, G551D, R553X, R560T), are tested for using a simple YES/NO assay. Exon 11 is amplified using the polymerase chain reaction. The product of the reaction is labeled to allow its detection and is placed on a membrane. The membrane has been prepared with oligonucleotide probes, which detect either the normal or the abnormal sequence. **A:** results from a known cystic fibrosis carrier. **B:** results from a child with cystic fibrosis.

Similarly, fragile X syndrome is usually the result of an expansion of a triplet sequence within the gene. Normal persons usually have only 5 to 50 copies of this triplet repeat, but affected patients have hundreds or thousands of copies of the triplet repeat. Similar triplet expansions cause myotonic dystrophy, Huntington disease, and Kennedy disease. The region containing the triplet can be amplified using the PCR, which produces millions of copies of the small region of DNA from the X chromosome that contains the fragile X repeat. Specificity is achieved by directing the reaction using two complementary primers on either side of the region of interest. Once amplified, the size of the product can be measured to evaluate the number of triplets, determining whether the mutation exists (Fig. 6.9).

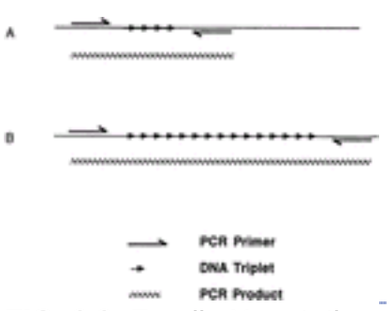

FIG. 6.9. Fragile X mutation detection. In patient A, a shorter polymerase chain reaction product corresponds with a smaller number of triplet repeats. Patient B exhibits an expanded number of repeats. Affected patients typically have hundreds or even thousands of copies of the triplet.

For families with unusual mutations or with diseases for which the molecular basis is unknown, linkage testing can be performed. Linkage tests compare DNA polymorphisms close to the disease-causing gene in family members known to have or carry the disease with those of unaffected and at-risk family members. Indirect assessments can be made about whether at-risk persons have the disease allele. The accuracy of these predictions depends on correct diagnosis and relationships of the family members, and the genetic distance between the polymorphism tested and the disease allele. For some families, linkage testing an be uninformative (Fig. 6.10).

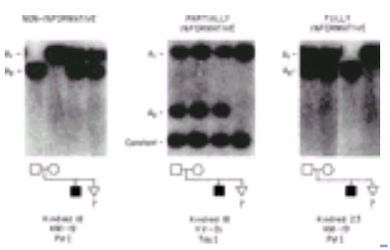

FIG. 6.10. Informativeness of linkage testing for cystic fibrosis. Marker KM-19 in kindred 18 is “not informative”-the disease alleles can not be distinguished in the parents.

The Genome Project

The Human Genome Project promises to be the single most important project in biology; genetics and genomics are now the central sciences of medicine. An understanding of the relationship between genetic variation and disease risk will alter the future prevention and treatment of common illnesses.

The full human sequence will be completed in 2003, but a very accurate draft is available now for over 95% of the genome. Disease gene identifications that formerly required years of chromosome walking and jumping, cloning, physical mapping, sequencing, and sequence assembly can now be completed in weeks. Industrialized sequencing technologies using capillary electrophoresis, micro arrays, and others developed for the genome project are now widely used for genotyping and sequencing.

We also now have a tremendous catalog of individual sequence variation in humans. Tens of thousands of micro-satellite markers are available for linkage analysis and hundreds of thousands of SNPs (single nucleotide polymorphisms) for genetic association studies. The tools are now well developed for doing these functional studies to find which variations and mutations cause individuals to be at risk for numerous medically important, genetically complex human diseases. The genome project has delivered improved cDNA resources, better predictive software, and additional knowledge about the non-protein coding regions of the genome. Remarkable technologies are commercially available for comprehensive analysis of gene expression in single cells, tissues, or whole organisms.

Advances in gene knockout technology, antisense technology, gene transfer, and gene transfection allow greater in vitro insights using appropriate model systems, including both cell culture and whole organisms. The complete sequence of the *Escherichia coli*, yeast, nematode, fruit fly, and mouse genomes provide important evolutionary clues to gene function and extend the range of experiments possible.

At the same time there have been parallel improvements in the technology for global protein analysis. Gene expression is played out at the protein level—elegant techniques are now available to examine spatial and temporal patterns of protein expression, protein-ligand interactions, and protein modifications.

Finally, the genome project occurred at the same time as the information technology revolution. Tremendous bioinformatics and computational software is now available for gene discovery, expression profiling, understanding gene-environment interactions, and so on. Suffice it to say, better tools are now available for making advances in women's health care than ever before in human history.

At least 3% of the annual budget of the project is going to the Ethical, Legal, and Social Issues section of the enterprise. This amount of early attention to societal impact is unprecedented for a science and technology project. Grant-funded programs have examined privacy issues, genetic discrimination in insurance and employment, and the role of coercion. Genetic discoveries may challenge long-held beliefs about equality, predetermination, and free will as we learn about genes that have a major role in personality, creativity, intelligence, and mental illness. The safety, efficacy, and utility of new gene tests should be evaluated, especially before treatment is available.

GENETIC EVALUATION

Genetic History and Physical Examination

Important details are being learned about many rare disorders which practitioners may see only once in their careers. In the past, many practitioners have had a “laissez-faire” attitude about genetic disorders, because “you can't do anything about your genes.” However, it is important to detect genetic conditions so that the patient can have adequate counseling about the condition and the risk to offspring. For severe conditions, patients often are interested in prenatal diagnosis, so they can consider pregnancy termination or prepare for the birth of an affected child. Our new predictive powers have led to an expanded medicolegal duty to warn patients of risks of which they may not have been aware. Failure to provide accurate and timely reproductive counseling has resulted in a host of lawsuits. Genetic diagnosis becomes even more critical as more treatment options become available for the child with a severe genetic disease.

In light of these expanding obligations to screen, what is expected of the general obstetrician-gynecologist? As with any medical diagnosis, the history is the most important part of the genetic evaluation. Important aspects of a genetic history, such as the patient's age, menstrual history, and obstetric history, are queried routinely as part of any routine obstetric or gynecologic history. In addition, it is important to ask about the patient and her partner's ethnicity (Table 6.13). The family history should extend to third-degree relatives (i.e., cousins). A minimal familial history can usually be elicited using the following questions:

TABLE 6.13. *Single gene disorders with an ethnic predilection*

- Do you have a family history of diabetes, hypertension, cancer, or twins?
- Are there any diseases that seem to run in your family?
- Is there a history of genetic disease like cystic fibrosis, hemophilia, or muscular dystrophy?
- Is there anyone with mental retardation or any kind of birth defect?
- Have any of your sisters, cousins, or other relatives had problems with their pregnancies?
- Are your parents alive? Are they healthy?
- As far as you know, are you and your husband or partner related by blood?
- Do you know your ethnic background? (Do you know where your relatives are originally from?)
- Is there any reason you are especially concerned that you might have trouble with your pregnancy or that your baby may be born with a birth defect or other medical problem?

It takes only a few minutes to ask these questions of a new patient. The final, open-ended question is often the most revealing. Alternatively, many practitioners find it helpful to ask similar questions using a patient-completed questionnaire. I use a form similar to the one suggested by the American College of Obstetricians and Gynecologists (ACOG) (Fig. 6.11). It is designed so that only “yes” responses need to be dealt with further. Including a form such as this one in the patient's chart clearly documents that a genetic history was obtained for medicolegal purposes. More than one fifth of healthy obstetric patients affirmatively answer at least one important question on the form.

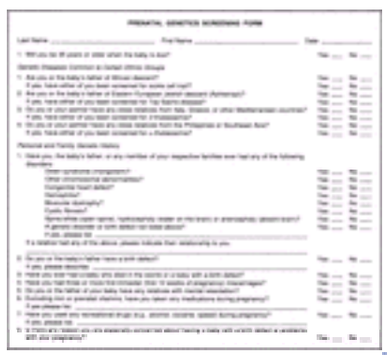

FIG. 6.11. Genetic screening questionnaires.

The physician should suspect genetic factors if a patient has an unusual problem and other people in her family have the same disorder. Similarly, if a patient reports a positive family history, it is important to decide whether the patient unknowingly has the same disease. When a patient reports an unfamiliar genetic condition or a rare illness, the physician should seek information about the genetics of this condition. Is she at risk of passing the condition to her offspring? Is prenatal diagnosis available? Is prenatal treatment available? For instance, consider a patient whose first child died of methylmalonic aciduria. In a subsequent pregnancy, her obstetrician noted this history on his prenatal record but did not inform the patient that there was a one-in-four risk that her current fetus could be affected. The obstetrician was unaware that prenatal diagnosis is available and, more importantly, that a simple treatment (i.e., giving the mother supplemental vitamin B_{12}) could prevent much of the morbidity of this particular form of methylmalonic aciduria. The child was born severely damaged and died at 2 years of age. The patient was very angry that she was not informed about prenatal therapy, and a lawsuit was initiated. Obstetricians cannot be expected to be expert in every rare enzymopathy, but this case illustrates how important it is to seek out additional information about rare conditions through a literature search or by consultation with a genetics center. Fortunately, helpful computerized databases are available on the internet such as OMIM (Online Mendelian Inheritance in Man) and Gene Tests (a directory of DNA diagnostic laboratories).

The general physical examination may reveal dysmorphic features or a distinctive physical finding that frequently is associated with genetic problems. For instance, a dislocated lens found on funduscopic examination of the eye is a distinctive feature consistent with Marfan syndrome or homocystinuria. If the patient has no history of severe ocular trauma, she probably has one of these conditions. Obstetricians cannot be as good at detecting such clues as an expert medical geneticist, because “the eye cannot see what the mind does not know.”

Genetic Counseling

Genetic counseling is a communication process which deals with the occurrence or risk of occurrence of a genetic disorder in a family. As our abilities to learn about the fetus have increased, more couples have an indication for prenatal diagnosis or a need to discuss reproductive options. Although every obstetrician has a role in providing genetic counseling, many practitioners find that genetic counselors—persons with advanced degrees and who are specially trained in the educational, psychological, and administrative aspects of medical genetics—are helpful consultants. Genetic counselors are experienced in obtaining and interpreting a thorough family history; often counselors are involved in the establishment or confirmation of a diagnosis. When presented with a prenatal diagnosis, they can obtain and interpret the history of a current pregnancy, explaining fetal risks and discussing the options available. Genetic counselors can provide the detailed counseling that is necessary regarding fetal chromosomal abnormalities of consanguinity, recurrence risks of multifactorial disorders, fetal abnormalities identified by ultrasonography, or infertility and habitual abortion. They are trained extensively about genetic screening for diseases that are common in various ethnic groups. Genetic counselors play a central role in the discussions regarding the option of aborting a genetically abnormal fetus. This type of counseling is traditionally informational and nondirective.

Pregnancy Termination

Pregnancy termination for genetic reasons can be particularly heart wrenching for a couple because the pregnancy usually is a desired pregnancy. Patients should be encouraged to involve their doctors, genetic counselors, clergy, other support persons, and family in these difficult decisions.

It is the physician's responsibility to explain the fetal diagnosis and prognosis. If a woman decides to have a pregnancy termination, the physician should explain the termination procedure, options if there are any, and the relative risks of the different procedures. The cost of the procedure is discussed and whether the procedure is covered by public funding or insurance. The physician should explain the benefits of diagnostic examination of the fetus by DNA, metabolic, or chromosomal analysis or by dysmorphologic examination. The disposition of the fetal remains should be discussed. The possibility that a fetus may live for a short period after induced labor termination is discussed. With late second-trimester or third-trimester inductions, it is often appropriate to encourage patients to see or hold the baby, and to name their baby. Patients are advised that lactation may occur after the delivery, and they are told about the options available to reduce lactation. With late terminations, the option of having a memorial service or in some way commemorating the baby's existence should be discussed. Physicians and counselors help couples decide what information to tell other children and family members, friends, and acquaintances.

It is important to reinforce that the genetic defect is not caused by the patient. The woman who is carrying the pregnancy and undergoes the termination may grieve in different ways than may the father of the baby. Referral to local support groups and counselors is often appreciated. Six to eight weeks after the procedure, a follow-up visit should be scheduled to summarize the diagnostic findings, review recurrence risks, and discuss prenatal diagnosis or therapy options for future pregnancies.

Laboratory Screening

Laboratory studies play an important role in the diagnosis of genetic disorders. A genetic illness is sometimes first discovered as an incidental finding on blood studies or an ultrasonographic examination. For instance, a low mean corpuscular volume on an automated complete blood count suggests thalassemia. In some instances, a positive family history prompts laboratory studies that clarify a patient's risk. Some programs have evolved to screen entire populations for genetic conditions using laboratory assays. Just as we currently perform a history and physical examination or a cholesterol screen to identify disease risk, soon there will be a DNA screen to detect mutations in dozens of important genes involved in cancer, cardiovascular disorders, and metabolic disease.

Population screening is appropriate when a defined subset of the population is at risk, and an accurate and inexpensive heterozygote test is available (Table 6.14). It is optimal if prenatal diagnosis is available, as well (e.g., sickle cell anemia, Tay–Sachs disease, thalassemia). The goals of screening programs are early diagnosis to allow better treatment of affected persons and identification of at-risk matings between persons who are heterozygotes or carriers of recessive disease. Neonatal screening programs for phenylketonuria, galactosemia, and hypothyroidism are carried out in most states. Successful carrier screening for Tay–Sachs disease has been achieved in several Jewish populations. The cost effectiveness of the screening program is often a primary concern in deciding whether to proceed with population screening. Equally important issues include the ability to manage minor variants which do not require action, stigmatization of carriers, and responsibility for decisions not to screen.

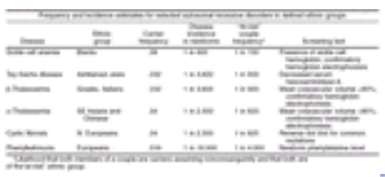

TABLE 6.14. *Population screening*

PRENATAL DIAGNOSIS

Limited but important information about the fetus can be gained using the traditional diagnostic techniques of history, auscultation, and palpation. It is important to consider the onset of fetal movement and the assumption of the vertex position as developmental milestones that the fetus does or does not achieve. Experienced examiners can assess fetal size, size or dates discordance, fetal positioning, and fetal heart rate abnormalities.

Maternal Serum Screening

Screening for fetal genetic conditions can be achieved by testing maternal serum. The first such program involved the use of maternal serum a-fetoprotein (MSAFP) levels to test for neural tube defects, an etiologically heterogenous group of conditions characterized by failure of embryonic closure of the neural tube. A cause for a neural tube defect can be identified in only 5% to 20% of cases, and most cases are thought to be polygenic or multifactorial. Between 90% and 95% of all infants with neural tube defects are born to women with no history of a child with neural tube defect.

There is substantial evidence for genetic predispositions to neural tube defects, including racial and ethnic variations in incidence, the increased incidence when a couple is consanguineous, gender bias, and increased monozygotic twin concordance. There is also strong evidence for environmental factors including maternal folate deficiency, previous spontaneous abortion or stillbirth, and the seasonal incidence. Mendelian disorders associated with neural tube defects include Meckel syndrome, in which affected individuals have a posterior encephalocele. Chromosomal syndromes, such as trisomy 18, trisomy 13, and triploidy, and sporadic syndromes such as OEIS complex (i.e., *o*mphalocele, *e*xtrophy, *i*mperforate anus, *s*pinal defect) can result in neural tube defects. Other well-described environmental causes of neural tube defects include amniotic band disruption sequence, maternal diabetes, maternal use of valproic acid, and hyperthermia. Forty-five percent of fetuses with neural tube defects have anencephaly, 45% have spina bifida, 5% have an encephalocele, and the remaining 5% have iniencephaly or exencephaly.

The incidence of neural tube defects is high (approximately 1%) in Ireland, Wales, Alexandria, and the Punjab. The rate is between 1 in 1,000 and 2,000 in the United States. Across the United States, the incidence is higher in the east than in the west, and highest in the Appalachian region. In the United States, if a person has previously had one child with neural tube defect, the recurrence risk is 2% to 3%. If there have been two affected children, it is 6.4%, and with three affected children, it may be as high as 25%. For patients at high risk for neural tube defect, prenatal diagnosis can be performed by targeted ultrasonography and an amniocentesis for amniotic fluid a-fetoprotein and acetylcholinesterase at approximately 16 weeks of gestation. The peak concentration of a-fetoprotein in the amniotic fluid occurs between 12 and 14 weeks, the widest margin between abnormal and normal distributions at approximately 16 to 18 weeks. A cutoff of 2.5 multiples of the median again yields a 98% detection rate, with a 0.8% false-positive rate. Acetylcholinesterase level determinations in amniotic fluid do not depend on gestational age. Amniotic fluid a-fetoprotein and acetylcholinesterase levels are normal in the 5% to 10% of cases of neural tube defects that are closed. Other open fetal defects, such as omphalocele and gastroschisis, can cause a rise in amniotic fluid a-fetoprotein.

MSAFP screening was introduced for assessing fetuses of women with no known risk factors for neural tube defects in the 1980s. Like all screening tests, the predictive value of the test depends on the population prevalence and particular cutoff used for setting the limits of normal and abnormal. In the United States, a cutoff of 2.5 multiples of the median frequently is used, meaning that 5% of those tested will have positive results. With this cutoff, more than 95% of anencephalic fetuses, 80% of fetuses with open spina bifida, and approximately 5% of fetuses with closed spina bifida are detected, for an overall detection rate of approximately 64%. MSAFP screening is most accurate from week 16 to 18. MSAFP starts to increase at approximately 13 weeks and peaks at 32 weeks gestation. An inaccurate gestational age determination is the most common reason for an abnormal MSAFP result.

It is important to correct MSAFP values for maternal weight, race, diabetes, and multiple gestation. There is a negative correlation between maternal weight and MSAFP. Blacks have approximately 1.1 times the MSAFP level of Caucasians, and Asians have an intermediate level between blacks and Caucasians. In insulin-dependent diabetics, the MSAFP level is approximately 60% of nondiabetic controls, and it is inversely correlated with the hemoglobin A_{1C} levels. Between 1% and 2% of infants of diabetic mothers have babies with neural tube defects. In multiple gestation, the median twin MSAFP level from 16 to 20 weeks is about 2.5 multiples of the median for a singleton pregnancy.

Low MSAFP levels have been associated with Down syndrome. One fifth to one third of these fetuses' mothers exhibit low MSAFP levels, with a median MSAFP of 0.7. Additional assays, such as unconjugated estriol, can provide more information about risk. Estradiol levels are low in cases of trisomy 21, very low in trisomy 18, and normal with spina bifida. Human chorionic gonadotropin levels are high in trisomy 21, very low in trisomy 18, and low in anencephaly.

For some couples, MSAFP screening raises anxiety, because the results are available around the time they feel that miscarriage is not going to occur and after the pregnant woman already feels fetal movement. When counseling patients about MSAFP screening, it is important to stress that it is a screening rather than a diagnostic test. The physician should explain the possible reasons for a high or low result, discuss the evaluation that would be recommended in that case, and stress that most babies of mothers with an abnormal screening result are normal. Frequently, discussions about a-fetoprotein screening bring out other issues the couple are worried about with respect to birth defects. This discussion is also an opportunity to educate the couple about the background incidence of birth defects.

The search is on for new biochemical markers which would improve the sensitivity and specificity of maternal serum screening. Retrospective studies suggest that maternal serum levels of dimeric inhibin A may be highly predictive. When the fetus is affected by Down syndrome, the maternal serum inhibin A concentrations are 2.1 times the median value in controls. Serum concentrations of inhibin A in Down syndrome pregnancies do not rise above normal until the end of the first trimester. The levels were not significantly different in the women with fetuses affected by trisomy 18.

Small retrospective studies also have examined the feasibility of first-trimester screening for Down syndrome. Earlier screening for Down syndrome would allow more time for intervention in the event of a positive test result. For women who choose pregnancy termination, the procedure can be carried out at a time when it is medically, psychologically, and perhaps morally less problematic. On the other hand, earlier tests will find many Down syndrome fetuses that would have aborted spontaneously. The follow-up diagnostic tests carry a greater risk of miscarriage (of normal pregnancies) at these earlier gestational ages. Serum a-fetoprotein screening for neural tube defects (NTDs) is impossible during the first trimester.

Initial studies show that maternal serum free ß-human chorionic gonadotropin and pregnancy-associated plasma protein A are useful markers. The “free-ß” chorionic gonadotropin levels are approximately one half the median, and pregnancy-associated plasma protein A levels are twice the median control levels in Down syndrome pregnancies. Urinary markers are being evaluated also. Large, prospective studies are needed to further assess first-trimester screening. Eventually, sorting fetal cells from maternal blood may prove to be the most sensitive and specific screening test.

Fetal Imaging

For many years, the fetus could be seen before birth only by using x-ray films. Radiographic examinations have limited prenatal indications because of concerns about fetal radiation exposure and because the information obtained by radiographs is limited to inspection of the calcified structures. Today, fetal radiography is used mostly for the differential diagnosis of skeletal dysplasias in the third trimester. In the past, attempts to gain information about the fetal soft tissues involved injecting into the amniotic fluid a water-soluble dye to outline the fetal gastrointestinal tract or a fat-soluble dye to outline the fetal skin. Modern high-resolution ultrasonography has revolutionized fetal imaging, giving clinicians a noninvasive way to get information about the internal and external features of the fetus.

Newer imaging methods serve as a useful adjunct to ultrasonographic examination for the prenatal diagnosis of certain conditions. Computed tomography (CT) uses low doses of radiation and computerized processing to obtain cross-sectional images. Magnetic resonance imaging (MRI) is based on detection of moving hydrogen atoms when tissues are subjected to a strong magnetic field. Both methods are expensive, but they are noninvasive and do not exhibit the shadowing phenomena seen with ultrasonography. CT and MRI are most useful for suspected central nervous system anomalies, particularly if ultrasonographic imaging is limited by reverberation artifacts caused by the fetal skull. They also are useful for cases of oligohydramnios; decreased amniotic fluid makes ultrasonographic imaging difficult, but the condition holds the fetus still for CT or MRI.

Fetal movement is a major limiting factor with CT and MRI, but the newer ultrafast scanners can produce an image within fractions of a second. Prenatal studies do not necessarily require maternal sedation or fetal paralysis with an intrauterine, intramuscular injection of a muscle relaxant such as curare. Fast CT scans have slightly lower resolution but an even lower dose of radiation compared with conventional CT. Another advantage of CT is the ability to use contrast agents. For instance, CT amniography can differentiate cyst adenomatoid malformation of the lung and diaphragmatic hernia by demonstrating the location of fetal stomach and small bowel. MRI allows differentiation in tissue densities and is exceptionally useful for differentiating white and gray matter in the central nervous system, fat, and flowing blood. MRI computers can construct images in any plane desired. Although there are no known biologic hazards with MRI, there are also no clear indications for use of MRI in the first trimester. Because the teratogenic risk is unknown, MRI use should be limited to the second and third trimesters.

Direct visualization of the fetus is indicated only in certain clinical situations and can be performed using a small-bore, fiberoptic endoscope. The trocar for the most commonly used fetoscope is 2.2 mm in diameter; the scope, itself, is 1.7 mm in diameter. The narrow field of view and the short focal length give a limited view of a small portion of the fetus. Fetoscopy may reemerge as an important adjunct to amniocentesis and fetal blood sampling as narrower scopes are developed. Scopes small enough to fit through the shaft of a 20-gauge needle have been developed, but it is not yet possible to get enough light inside the uterus to allow visualization with such a narrow scope. Embryoscopy has been used during the first trimester to visualize the embryo or early fetus through the membranes. This is accomplished by passing the endoscope through the cervix and up against the membranes. Neither fetoscopy nor embryoscopy may be possible in many cases because of the placental position or cloudy amniotic fluid.

Fetal Sampling for Prenatal Diagnosis

Amniocentesis Amniocentesis was introduced to the United States in the 1960s, and it is the most extensively used fetal sampling technique. Genetic amniocentesis is performed routinely at approximately 15 weeks of gestation when the amniotic fluid volume is approximately 200 mL. At this gestational age, ultrasonographic examination cannot detail all of the fetal anatomy, but it can reliably ascertain dates or rule out multiple gestations. Typically, 20 mL of fluid is removed with a 20- to 22-gauge needle using a transabdominal approach with ultrasound guidance (Fig. 6.12). Biochemical testing can be performed on the fluid as indicated. Amniotic fluid a-fetoprotein levels are obtained routinely to screen for open fetal defects, and fetal cells can be grown for karyotype determination or for DNA assays. DNA assays that use the PCR to amplify small amounts of DNA allow direct analysis of amniotic fluid. Roughly one third of the amniocenteses must be performed transplacentally. In most operators' experience, this has not been associated with substantially increased risk if care is taken to avoid major fetal vessels. The transplacental approach is associated with a slightly higher incidence of Rh sensitization. With either approach, it is imperative that Rh-negative women who may be carrying an Rh-positive fetus receive RhoGAM.

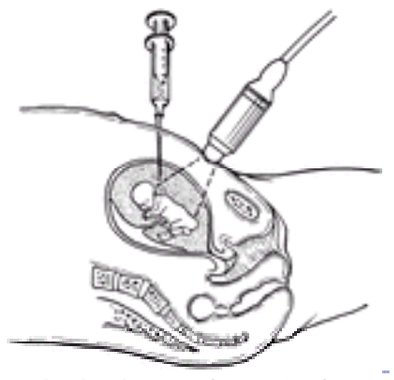

FIG. 6.12. Amniocentesis.

With multiple gestations, it is usually possible to sample each of the gestations. Indigo carmine dye can be placed in the sac after the amniocentesis is completed to prevent tapping the same sac twice. Biochemical assays of amniotic fluid are somewhat harder to interpret in multiple gestations, because many biologic molecules can diffuse from one sac into the other. Few women describe amniocentesis as terribly painful. Those who do frequently experience a uterine contraction at the time the needle is inserted. It is not unusual to have some cramping or a bruised feeling at the site after the procedure. Vaginal spotting or amniotic fluid leakage occurs in 1% to 2% of cases. After a routine amniocentesis, the fluid usually stops leaking within 2 to 3 days. Even when the amniotic fluid volume becomes markedly decreased, miscarriage is not inevitable, because the membranes usually seal and the amniotic fluid can reaccumulate within a week, allowing the pregnancy to progress normally. As ultrasonographic equipment has improved, the maternal risk incurred with amniocentesis has decreased. Symptomatic amnionitis occurs in fewer than 1 of 1,000

patients. Serious maternal bowel or vascular injuries are extremely rare. The procedure-related rate of fetal loss after amniocentesis generally is quoted as 0.5% (1 in 200), but many centers are reporting lower rates.

Chorionic Villus Sampling Chorionic villus sampling (CVS) is a diagnostic technique that was introduced to the United States in the mid-1980s. With this technique, a small sample of the chorionic villi is taken for examination of chromosomal status, biochemical assays, or DNA tests. Assays depending on analysis of amniotic fluid such as a-fetoprotein cannot be performed on a chorionic villus sample. CVS usually is accomplished by the transcervical or transabdominal route. Occasionally a transvaginal CVS is performed with the uterus extremely retroflexed. A transcervical CVS usually is performed between 9 and 12 weeks of gestation, at which time a plastic catheter, approximately 1.5 mm in diameter, is passed through the cervix and then directed toward the placental mass under continuous ultrasound guidance (Fig. 6.13). Between 10 and 20 mg of villi are aspirated through this catheter by negative pressure using a syringe. Transabdominal CVS is performed using an 18- to 20-gauge spinal needle passed into the thickest portion of the placenta that is readily assessable (Fig. 6.14). Villi are aspirated into a syringe. This procedure can be performed throughout gestation.

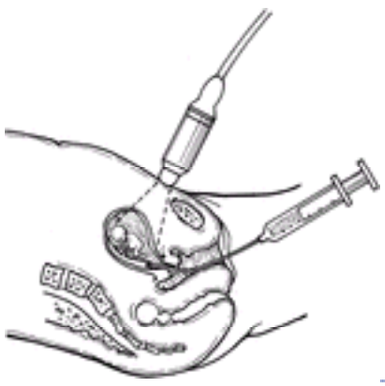

FIG. 6.13. Transvaginal chorionic villus sampling.

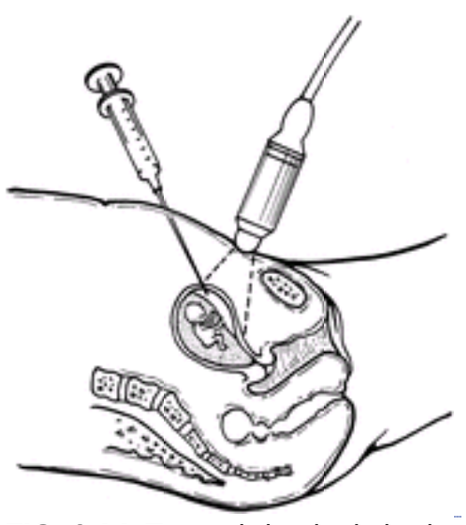

FIG. 6.14. Transabdominal chorionic villus sampling.

Transabdominal CVS is considered easier to learn and safer, but patient acceptance appears to be lower. Theoretically, transcervical CVS would have a greater risk of infection, although this has not been borne out by large surveys. In most series, a larger sample is obtained with transcervical CVS, but more passes are required to obtain this sample. Transcervical procedures require more uterine manipulation, and bleeding or leakage of fluid is more common during and after the procedure. Most laboratories report a greater level of maternal cell contamination with transcervical CVS, although this is rarely a clinically important issue. Those performing CVS should be facile with both techniques, because patient anatomy frequently dictates which is the optimal technique. CVS compares favorably with amniocentesis with regard to safety. Two large National Institutes of Health cooperative trials found a procedure-related loss rate of approximately 0.8%. In approximately 2% of first-trimester chorionic villus samples, a discrepancy is found between the cytogenetic analysis of the placenta and that of the fetus. Frequently, a second invasive procedure, usually amniocentesis or fetal blood sampling, is required to determine whether the fetus is affected. This phenomenon is called confined placental mosaicism. Pregnancies in which confined placental mosaicism is found by CVS may be at risk for spontaneous abortion, perinatal loss, or intrauterine growth retardation. The reported rates of loss have ranged from 3.6% to 16.7%. In chromosomally abnormal conceptuses, a mosaic normal cell line in the placenta may be the factor that allows prolonged survival of aneuploid fetuses. Kalousek studied 14 placentas from live-born or from terminated pregnancies with trisomy 13 or 18, and found the placentas were all mosaic for, or contained only, diploid cells. There have been several reports of increased incidents of limb anomalies when fetuses have undergone very early CVS using the transabdominal approach. These reports are of concern, because the affected children have a relatively distinctive pattern of malformation, and it is biologically plausible that their anomalies may be related to CVS. The absolute number of fetuses with this problem is small, but the publicity regarding these findings has caused many women to avoid CVS. The Centers for Disease Control performed a multistate case-control study to assess and quantify the risk for specific limb deficiencies associated with CVS. Between 1988 and 1992, 131 infants with nonsyndromic limb deficiency, born to mothers 34 years of age or older, were reported in seven population-based birth defect surveillance programs. Control subjects were 131 infants with other birth defects. They found that exposure to CVS was associated with a six-fold increase in risk for transverse digital deficiency (odds ratio = 6.4; 95% confidence interval, 1.1 to 38.6). The data showed a significant trend toward increased risk with earlier gestational exposure. The CDC estimates that the absolute risk for transverse digital deficiency in infants after CVS is approximately 1 per 3,000. Most feel that the actual risk is significantly lower and that there is minimal to no risk when CVS is performed after 70 days of gestation. Further studies are needed to determine whether the problem is specific to CVS or whether the same risk affects other invasive first-trimester diagnostic manipulations.

Fetal Blood Sampling and Fetal Biopsy Originally, fetal blood was sampled by inserting a needle into the placenta; the blood obtained was usually a mixture of fetal and maternal blood, which limited its usefulness. In 1977, fetoscopy came into use, allowing a needle to be placed in a cord vessel under direct sonographic visualization. Pure fetal samples could be obtained, but fetoscopy requires special equipment and expertise, and the procedure-related loss rate was between 3% and 7%. With improvement in ultrasonographic imaging during the mid-1980s, cordocentesis can be performed in a manner similar to amniocentesis (Fig. 6.15).

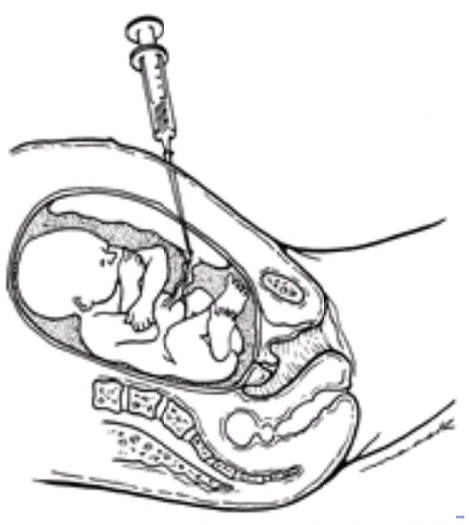

FIG. 6.15. Cordocentesis (fetal blood sampling).

A transplacental route usually is preferred, and a spinal needle is advanced under ultrasound guidance into a vessel with cord insertion into the placenta. Cordocentesis usually is not performed until after 17 weeks gestation. Depending on the indication, procedure-related loss rates of as low as 1% have been reported with no observed increase in the rate of preterm delivery. Typically, no maternal sedation or antibiotics are required. In most cases, a fetal sample can be obtained on the first attempt, usually in less than 10 minutes, and any substance measurable in adult blood can be assayed in fetal blood. Most cordocenteses are performed to obtain a fetal karyotype because of fetal anomalies or to determine the fetal hematocrit to assess isoimmunization or severe fetal anemia. Fetal platelet counts, acid-base status, antibody levels, and blood chemistries can be assayed as indicated. Hematologic values are checked routinely (particularly the mean corpuscular volume which is higher in fetus than mother) to be certain that the blood obtained is fetal. A Kleihauer test can be performed to check for maternal blood contamination. A variety of other tissues, particularly fetal skin, liver, and muscle, have been sampled prenatally to diagnose a genetic disorder using either electron microscopy or biochemical analysis. Such biopsies are necessary if a genetic abnormality is expressed only in certain tissues and the causative gene is unknown. Now that the molecular basis of many of these disorders is known, simpler DNA assays using villi, amniocytes, or blood usually obviate the need for tissue biopsy. Initially, fetal

biopsies were performed using fetoscopy, but they now are performed under ultrasound guidance. Typically, local anesthesia, maternal sedation (with or without fetal paralysis), and prophylactic antibiotics are used for tissue biopsy procedures. As with any invasive procedure, RhoGAM is necessary for the nonsensitized Rh-negative mother who may be carrying an Rh-positive fetus.

Early Amniocentesis Early amniocentesis is similar to amniocentesis at the “traditional” gestational age, except that the procedure is performed at 10 to 12 weeks of gestation. Early amniocentesis was proposed as an alternative first-trimester prenatal diagnostic technique, but a large Canadian prospective study demonstrated an unacceptable rate of procedure-related malformations in the exposed pregnancies.

Preimplantation Diagnosis Various methods of diagnosis before a pregnancy is formally established are becoming available in the 1990s. Someday these extremely early diagnoses may be necessary to allow initiation of genetic therapy treatments. For many couples, preimplantation diagnosis provides an alternative to selective pregnancy termination, allowing them to avoid the moral issues and the psychological trauma that accompanies termination of a wanted pregnancy. For most genetic conditions, carriers have both normal and abnormal gametes, and chance determines whether an abnormal gamete is incorporated into the conceptus. Aided by the rapid progress in assisted reproductive technologies and molecular diagnostic techniques, it has become possible to test gametes in vitro and select healthy gametes for fertilization. Sperm sorting has been accomplished using molecular probes tagged with laser-activated dyes and using separation techniques such as flow cytometry, but current approaches usually cause unacceptable damage to the sperm. Greater success has been possible in genotyping oocytes, which are larger and more resistant to damage. Oocyte diagnosis takes advantage of the unique properties of female meiosis; unlike sperm, oocytes conveniently discard their unused genetic material in the form of polar bodies. For a heterozygous woman, the discarded genetic material can be tested to see whether it contains the abnormal allele. If it does, then the oocyte must contain the normal allele. Conversely, if the polar body tests positive for the normal allele, the oocyte must contain the abnormal allele. Only the normal oocytes are then fertilized. Contamination with cumulus cells adherent to the exterior surface of the zona pellucida can lead to errors. Polar body biopsy can be performed only in conjunction with in vitro fertilization. The first polar body has no essential function and contains no embryonic material; it is small and relatively easy to remove using micromanipulation techniques (Fig. 6.16). Theoretically, DNA testing results can be obtained before fertilization, leaving a long period for confirmatory studies before implantation. Aneuploidy screening can be incorporated as well, at least for maternal meiosis I nondisjunction. The main disadvantages are that polar body biopsy is an indirect assay of the oocyte and that it can be used only for maternal carriers. In addition, the further away from the centromere the gene is located, the more likely recombination is to occur, making polar body biopsy results indeterminate. Polar bodies that are heterozygous need to be discarded or the oocytes biopsied again to remove the second polar body.

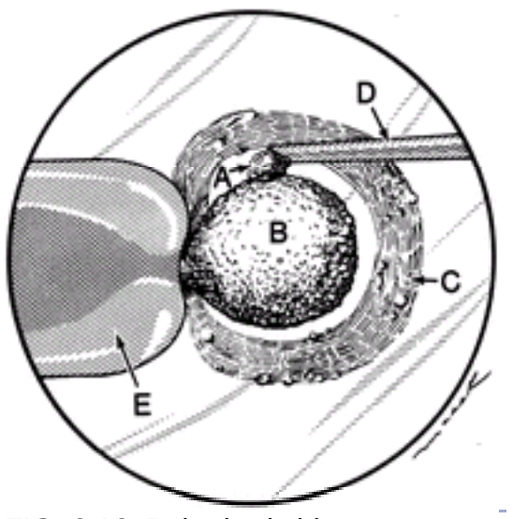

FIG. 6.16. Polar body biopsy.

Initial success has been greater with “selective implantation” protocols in which the diagnosis is made during the first week after fertilization but before implantation. Preimplantation embryos can be grown in vitro and biopsies obtained after the first few cleavage divisions. There is much experience with this technique in animal research, and embryo splitting at this stage has been used extensively for diagnosis in the cattle and sheep industry. The eight-cell preembryo is probably at the ideal stage for biopsy. Cells are still independent and totipotent, they have not developed gap junctions which will make them adherent, and damage is tolerated relatively well. By this stage, some of the embryonic genes have begun to function, and it may become possible to perform some biochemical microassays. This technique is limited by the difficulty in removing blastomeres, which are larger than polar bodies, and the short time to work with the sample before the chance of successful implantation begins to lessen. It has proved difficult to freeze spare embryos after biopsies and, as with other preimplantation techniques, there is the possibility of sperm or cumulus cell contamination. Attempts have also been made to perform testing 5 days after fertilization, when the preembryo has reached the blastocyst stage. The blastocyst consists of roughly 120 cells that are mostly trophoblastic tissue, but the inner cell mass that eventually becomes the embryo is clearly visible. Only the best laboratories have had any success culturing human preembryos to this developmental stage in vitro. As an alternative, investigators have tried to lavage naturally conceived blastocysts from the uterus during the 2 to 3 days when the conceptus is normally free-floating in the endometrial cavity before implantation. Unfortunately, it has proved exceedingly difficult to obtain multiple blastocysts by lavage after superovulation. Various methods of sampling blastocyst cells have shown success in animal models including bisection, aspiration of the cavity, and excision of cells herniating through the zona pellucida. The latter is achieved after mechanical disruption of the zona to cause premature herniation or after spontaneous hatching. The advantages of blastocyst biopsy include the relative differentiation of the cells, greater cell number, better transfer efficiency, and self-selection of the healthiest embryos. Lavage of naturally conceived blastocysts offers a potentially “low-tech” approach to preimplantation diagnosis. Perhaps contrary to expectations, disruption of zona pellucida may enhance hatching. Technical limitations include the small number of blastocysts available and their limited incubation time. The cells are very adherent to each other, increasing the risk of damage to the inner cell mass. As with CVS mosaicism, there is the possibility that the trophectoderm does not reflect the fetal karyotype or biochemical status.

Fetal Cells in Maternal Circulation The newest fetal sampling technique that shows promise involves separating fetal cells that occur naturally in the maternal circulation. Nucleated erythrocytes, fetal leukocytes, and syncytiotrophoblast cells are found in the maternal circulation during most pregnancies, from as early as 6 weeks gestation. It is possible to use a separation technique such as flow cytometry to establish an enriched population of fetal cells and then assay these cells for fetal mutations using a technique such as DNA amplification. Certain cell types have a long life span in the maternal circulation, allowing persistence of cells from prior pregnancies, and confusing results are possible. “Vanished” abnormal co-twins can lead to diagnostic errors. Ultimately, this method may provide a noninvasive, reliable screen for aneuploidy that is inexpensive enough to use in low-risk populations.

Cystic Fibrosis Screening The *CFTR* gene was discovered in 1989, and more than 1,000 mutations which can lead to CF have been identified. Couples who both carry the CF gene would have a 1 in 4 chance of delivering a child with CF. Cystic fibrosis causes pulmonary and gastrointestinal disease of varying severity. Most patients with CF have substantial illness and shortened life span and require lifelong medical care. Screening is now widely available for the most frequent CF mutations. Recently ACOG advised that DNA screening for CF should be made available to *all* couples seeking preconception or prenatal care. The ACOG/American College of Medical Genetics publication entitled *Cystic Fibrosis Carrier Testing: the Decision is Yours* can be helpful for this purpose. Because Caucasians have a higher rate of CF (particularly European or Ashkenazi Jewish), obstetric care providers are advised to offer screening specifically to these couples and to record in the medical record the couple's decision on whether to be screened (Table 6.15.).

Caucasians	1 in 29
Hispanic Americans	1 in 46
African Americans	1 in 65
Asian Americans	1 in 90

TABLE 6.15. *Cystic Fibrosis: carrier rates in the United States*

Prenatal Treatment and Gene Therapy

As we begin to understand the molecular mechanisms by which genes cause disease, we will have the opportunity to design and apply preventive, health maintaining measures. Some genetic conditions can be treated by giving patients the protein they are missing or by stimulating a function that is not performing properly (e.g., growth hormone deficiency, diabetes).

More sophisticated gene therapies are being tested. Finding the CF gene enabled the disease to be “cured” in the test tube and improved in animal models. Scientists may be able to design proteins or antisense RNAs that can be used as a drug to block the effect of abnormal genes or kill cancer cells. Modified viruses may be used to insert corrected genetic instructions. Prenatal gene therapy with stem cell transplantation has been attempted for severe combined immunodeficiency with some preliminary success.

Many genetic conditions need to be treated prenatally. Although in utero treatment is experimental, prenatal treatment of disorders with vitamin-dependent or responsive cofactors has been successful. For instance, prenatal treatment of the vitamin B_{12}-responsive form of methylmalonic acidemia by administration of 10 mg per day of vitamin B_{12} has improved the biochemical defect. Similarly, infants with biotin-responsive multiple carboxylase deficiency have been aided by maternal biotin supplementation. In these rare disorders, prenatal treatment can mean the difference between life and death for affected infants. Dietary restriction of galactose in mothers who are at risk of delivering a galactosemic infant, and dietary restriction of phenylalanine in mothers who themselves have phenylketonuria, are helpful means of preventing the devastating effects of these metabolic conditions. Gene therapy and prenatal tissue transplantation are likely to rapidly expand the therapeutic

options for treating and preventing metabolic disease.

GENETICS IN GYNECOLOGIC DISORDERS

Genes play an important role in the pathogenesis of many common gynecologic disorders. Molecular genetic investigations of persons with gonadal dysgenesis and pseudohermaphroditism have defined many aspects of human sexual differentiation. Because it is the smallest chromosome, the Y chromosome became the first human chromosome to be mapped completely.

Genetic testing for susceptibility to ovarian cancer is rapidly becoming part of routine practice. Most cancer is clonal in origin, meaning it arises from a single aberrant cell. Cytogenetic or molecular alterations are observed uniformly in malignant cells. Although some of these changes appear to be random events occurring in rapidly dividing cells, other specific genetic changes play an etiologic role in development of certain cancers. Particular mutations may be either germinal (i.e., inherited) or somatic (i.e., acquired). Either can be seen in familial cancer clusters: germinal because of segregation within the family of a cancer-causing mutation and somatic because of shared environmental exposures to carcinogens. Mendelian transmission of cancer predisposition usually is observed as multifocal and early-onset disease. Typically, cancer-predisposing mutations are found to overexpress protooncogenes that normally drive important cell functions or to inactivate tumor suppressor genes that normally exert a protective effect.

Genetic testing for BRCA1 and BRCA2 mutations is now recommended to most women with invasive ovarian cancer. Approximately 10% of patients with ovarian cancer will have a positive test result, including 4% of women without a family history of ovarian cancer. Women with the BRCA mutation have better ovarian cancer survival rates than women without the mutation, possibly due to enhanced susceptibility to chemotherapy. A variety of strategies for prevention of ovarian cancer in relatives at risk, including chemoprevention and prophylactic oophorectomy, have shown some efficacy.

Common gynecologic diseases such as endometriosis and polycystic ovary syndrome are familial, and genes involved in these conditions are likely to be discovered over the next few years. Age at menopause, susceptibility to hot flushes and osteoporosis, susceptibility to pelvic relaxation, and susceptibility to chronic vaginitis are likely to have genetic components, as well. Disease gene discoveries related to these conditions may suggest novel diagnostic and therapeutic approaches.

TRENDS

The genome project promises to provide us with the most important information in human biology. Technologies developed for the genome project and the genomic sequence, itself, will provide the basis for much of biomedical research in the next century. The possibilities for understanding normal development, disease predisposition, and cancer are staggering. The ability to obtain an accurate prenatal diagnosis will expand exponentially over the next few decades. Gene therapy is becoming a reality faster than anyone thought possible. The challenge is for the obstetrician-gynecologist to stay abreast of all these developments and to educate patients about developments that can influence their care.

SUMMARY POINTS

- Most obstetric and gynecologic diseases show a polygenic, multifactorial pattern of inheritance. One in twenty newborns has a diagnosable genetic disorder.
- A thorough family history is currently the most important part of a genetic evaluation, but laboratory screening of the general population is becoming available for an increasing number of genetic conditions.
- Accurate prenatal diagnosis is now possible for hundreds of genetic conditions through ultrasonographic and genetic testing.
- The Human Genome Project is providing new information each month, making it difficult for care providers to keep abreast of all the new developments, especially for rarer diseases. Reference to current on-line data and liberal referral to genetic counselors and geneticists is necessary when encountering rare conditions.
- Over the next decade, genetic testing will continue to become less invasive, and there will be greater opportunities to prevent the morbidity of genetic disease through prenatal and presymptomatic treatments.

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Chapter 7

Jerome Yankowitz

Drugs in Pregnancy

PRINCIPLES OF TERATOLOGY
ANTIBIOTICS AND OTHER ANTIINFECTIVE AGENTS
Antibiotics
UPPER RESPIRATORY TRACT COMPLAINTS
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Decongestants
Cough Suppressants
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PRINCIPLES OF TERATOLOGY

Anything a pregnant woman ingests or is exposed to could affect her fetus. This is problematic for the health care provider who must treat a wide variety of illnesses during pregnancy. In fact, over 60% of American women receive a prescription for at least one medication during pregnancy. This figure is about 99% for women in France and over 70% for Hungarian women. The most common conditions for which medications are prescribed include gastrointestinal, dermatologic, psychological, and psychiatric disorders and pain.

Generally, whatever medication would be given to a nonpregnant women is the appropriate choice in pregnancy. Awareness of the few exceptions and how to choose from available options requires a knowledge of teratology and alterations in drug metabolism related to pregnancy. Teratology is the study of abnormal development or the production of defects in the fetus. Birth defects affect 2% to 3% of all neonates. With longer follow-up, at least 5% of individuals are found to be affected by a birth defect. Exogenous causes of birth defects, including drugs or chemical exposures, account for almost 10% of birth defects. Thus, at least 0.2% to 0.3% of pregnancies are affected by teratogenesis.

The Food and Drug Administration (FDA) introduced a drug classification system in 1979 to discourage nonessential use of medication during pregnancy. Drugs are classified as either A, B, C, D, or X, with the latter being the most teratogenic. There has been growing perception that the FDA classification has led to excessive maternal anxiety and unnecessary pregnancy termination. The FDA is evaluating a revised labeling system for drugs and biologic agents that will include a description of the drugs based on clinical management, summary of risk assessment, and discussion of data.

How much drug the fetus will be exposed to is determined by a complex interaction of many factors, including how the agent is absorbed, the volume of distribution, metabolism, and excretion. Absorption is via the gastrointestinal tract, skin, lungs, or after parenteral administration. Pregnancy alters absorption in a variety of ways, including prolongation of gastric emptying time by the increased progesterone. The volume of distribution is generally increased during pregnancy. Estrogen and progesterone alter hepatic enzyme activity with varying effects on drug metabolism and clearance, depending on the precise pathway. Renal excretion is generally increased during pregnancy. Other factors affect precisely how much drug crosses the placenta. Passage of drugs across the placenta is influenced by several factors. Lipid-soluble substances readily cross the placenta, and water-soluble substances pass less well. Those with greater molecular weight also cross the placenta less easily. The degree to which a drug is bound to plasma protein influences the amount of drug that is free to cross. Virtually all drugs cross the placenta to some degree, with the exception of large organic ions such as heparin and insulin. Active placental transfer must be considered, also.

Other concepts related to teratology include specificity, timing, dosage, maternal physiology, embryology, and genetics. Specificity indicates that a substance may be teratogenic in some species but not others. For example, thalidomide produces phocomelia in primates but not rodents. Often, animal data of safety or teratogenic effect is not necessarily applicable to humans. Timing is also critical. When administered between 35 and 37 days gestation, thalidomide produces ear malformations, but between 41 and 44 days, amelia or phocomelia. Dosage is also important. In most cases, administration of a low dose will result in no effect while malformations occur at intermediate doses and death at higher doses. Death may cause organ-specific teratogenic action to go unnoticed. The route of administration, possibly secondary to absorption, is also important. Small doses over several days may have an effect different than the same total dose given at once. Sequential dosing, as opposed to a bolus, may induce an enzyme to metabolize the substance that potentially causes less damage. Constant exposure may destroy cells that would have catabolized the drug if administered in periodic doses. As noted above for thalidomide, timing of exposure relative to embryologic events is important. Teratogen exposure in the first 2 to 3 weeks after conception is generally thought to have no effect or to result in spontaneous loss (all-or-nothing phenomenon). The period of susceptibility to teratogenic agents is during the period of organogenesis, which occurs primarily at 3 to 8 weeks postconception (35-70 days after the last menstrual period or LMP) or to 10 weeks from the LMP. After this period, embryonic development is characterized primarily by increasing organ size (10-12 weeks); thus, the principal effect of exposure will be growth restriction or effects on the nervous system and gonadal tissue. These systems continue to develop throughout pregnancy. During organogenesis each organ system will have different critical periods of sensitivity. A teratogen can act by causing cell death, altering tissue growth (hyperplasia, hypoplasia, or asynchronous growth), or interfering with cellular differentiation or other basic morphogenic processes.

The genetic make-up of the mother and fetus can affect individual susceptibility to a drug. Fetuses with low levels of the enzyme epoxide hydrolase may be more likely to manifest the fetal hydantoin syndrome than those with normal levels of epoxide hydrolase. Combinations of agents may produce different degrees of malformation or growth restriction than if given individually. Fetuses whose mothers are on combination antiepileptic agents are at the highest risk for malformations, including neural tube defects and facial dysmorphic features.

Most drug therapy does not require cessation of nursing because the amount excreted into breast milk is small enough to be pharmacologically insignificant.

ANTIBIOTICS AND OTHER ANTIINFECTIVE AGENTS

Antibiotics are used widely during pregnancy to treat a variety of disorders including upper respiratory tract infections, urinary tract infections, and others (Table 7.1). Pregnant patients are particularly susceptible to vaginal yeast infections. This is one reason that antibiotics should be used only when clearly indicated. Therapy with antifungal agents may be necessary after the course of antibiotic therapy.

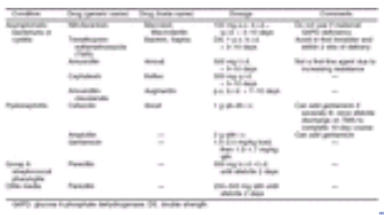

TABLE 7.1. *Antibiotics used for common infections in pregnancy*

Antibiotics

Penicillins Penicillin derivatives, including amoxicillin and ampicillin, have a wide margin of safety and lack toxicity for both the woman and her fetus. Penicillin is a ß-lactam that inhibits bacterial cell wall synthesis and can be administered orally, intramuscularly, and intravenously. It is the drug of choice for the treatment of a wide variety of bacterial infections including group A streptococcal pharyngitis, otitis media, and mild *Streptococcus pneumoniae* pneumonia. Penicillin is the drug of choice to treat syphilis. Pregnant women with allergy to penicillin should be desensitized to receive their full course when being treated for a syphilis infection. Ampicillin and amoxicillin are good choices for enterococcal urinary tract infections, but many other pathogens are resistant, so they should be used selectively.
Amoxicillin-clavulanate (Augmentin) combines the ß-lactam with a ß-lactamase inhibitor that expands the spectrum of activity. This combination can be used for sinusitis and urinary tract infections. The extended spectrum penicillins are also safe, but they are much more expensive and generally not used as first-line agents for most disorders during pregnancy. The cephalosporins are safe and used for urinary tract infections, including pyelonephritis, and for gonorrhea. The penicillins can be used safely during breast-feeding.
Clindamycin Clindamycin is a macrolide and acts on the bacterial ribosome preventing transcription. It can be used to treat bacterial vaginosis, although metronidazole is the first-line medication. It generally is reserved for anaerobic infections that are not sensitive to other agents. Up to 10% of patients will develop pseudomembranous colitis. Clindamycin is safe during breast-feeding.
Metronidazole Metronidazole inhibits bacterial protein synthesis. It is used to treat trichomonas and bacterial vaginosis. This agent was found to be positive in the Ames test but has not been proven to be carcinogenic in humans, nor has it been shown to produce birth defects. Although some authorities suggest deferring use past the first trimester, there are no data supporting this suggestion. This medication is safe in breast-feeding, although the American Academy of Pediatrics recommends interrupting breast-feeding for 12 to 24 hours following a 2-gram dose.
Aminoglycosides Aminoglycosides inhibit bacterial protein synthesis. They can be used to treat pyelonephritis but should be used only when serious gram-negative infection is suspected. Maternal administration has been associated with ototoxicity in the fetus leading to hearing loss. Breast-feeding is safe, because little drug passes to the neonate via the breast milk.
Trimethoprim-sulfamethoxazole This combination (Bactrim or Septra) inhibits folic acid metabolism and is very active against many organisms that cause urinary tract infections. No definite teratogenic effects have been described, but in 2,296 Michigan Medicaid recipients, first-trimester trimethoprim exposure was associated with a slightly increased risk of birth defects, particularly cardiovascular, and in a retrospective study, the odds ratio was 2.3. Given this and the mechanism of action via the folate pathway, avoidance in the first trimester is prudent. It displaces bilirubin from its protein binding sites in the neonate, potentially contributing to an increased risk of hyperbilirubinemia or kernicterus in newborns. Therefore, it should not be used close to delivery. This theoretic effect has not been substantiated in clinical trials. Trimethoprim-sulfamethoxazole has been used to treat otitis, sinusitis, *Shigella* colitis, and *Pneumocystis carinii* infections, in addition to both asymptomatic bacteriuria and acute cystitis. Use of this medication is safe during breast-feeding.
Nitrofurantoin Nitrofurantoin inhibits bacterial protein and cell wall synthesis. It is eliminated by excretion, and this bactericidal activity makes it highly effective in treating uncomplicated lower urinary tract infections. It can induce hemolytic anemia in patients with glucose 6-phosphate dehydrogenase deficiency and, because the newborn's red blood cells are deficient in reduced glutathione, the label carries a warning against use of the drug at term. However, hemolytic anemia in the newborn after exposure before birth has not been reported. This medication is compatible with breast-feeding.
Erythromycin Erythromycin and azithromycin inhibit bacterial protein synthesis. They often are used as an alternative to the penicillins and are first-line treatment for mycoplasma and chlamydia infections. These medications also are useful in treating community-acquired pneumonia or severe bronchitis. Use of both erythromycin and azithromycin are compatible with breast-feeding.
Antiviral Agents The emergence of the human immunodeficiency virus and acquired immunodeficiency syndrome has resulted in development of many antiviral agents. Previously, herpes was one of the few viral infections for which pregnant women might be exposed to treatment (Table 7.2).

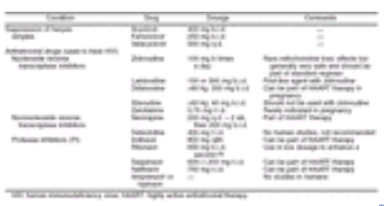

TABLE 7.2. *Antiviral agents in pregnancy*

Acyclovir and Valacyclovir Acyclovir (Zovirax) has resulted in no fetal abnormalities in 601 exposures reported. The Centers for Disease Control and Prevention recommends that pregnant women with disseminated infection (e.g., herpes, hepatitis, or varicella pneumonia) be treated with acyclovir. No human studies during pregnancy have been carried out with famciclovir.
Human Immunodeficiency Virus Treatment A variety of agents may be used to treat patients with human immunodeficiency virus infection. The medications generally fall into three categories, the nucleoside reverse transcriptase inhibitors (nRTIs), the nonnucleoside analog reverse transcriptase inhibitors (NNRTIs), and the protease inhibitors (PIs). Zidovudine is the most widely studied nRTI, and no adverse effects have been seen over 4 years of follow-up. In the same class of medications, didanosine, stavudine, and lamivudine also seem to be safe. Nevirapine, an NNRTI, has had no reported adverse effects. The PI class has not been as extensively studied.

UPPER RESPIRATORY TRACT COMPLAINTS

The common cold is the most frequent acute illness, and most are self-diagnosed and treated. Medicine used to treat symptoms associated with the common cold are among the most commonly used drugs in pregnancy. Most patients complain of fatigue, malaise, rhinorrhea, nasal congestion, cough, and sore throat. The cold can be caused by a variety of viruses, rhinoviruses, coronaviruses, respiratory syncytial virus, adenovirus, parainfluenza and influenza viruses, and others. Therefore, in the absence of a complicating superinfection with bacteria, antibiotic treatment is not appropriate.

The most common treatments are used to alleviate the symptoms listed above and include antihistamines, decongestants, and cough remedies.

Antihistamines

Most antihistamines are safe during pregnancy. Brompheniramine (Bromfed) was associated with an increased relative risk of malformations in the Collaborative Perinatal Project but not the Boston Collaborative Drug Surveillance Program. Other safe antihistamines include chlorpheniramine, clemastine, diphenhydramine, and doxylamine.

There are newer antihistamines with little or no data in pregnancy and are best used as second-line therapy. These include astemizole (Hismanal), cetirizine (Zyrtec), loratadine (Claritin), and fexofenadine (Allegra).

Decongestants

The most common oral decongestants are all sympathomimetic agents and include pseudoephedrine, phenylephrine, and phenylpropanolamine. There have been some reports of an association with gastroschisis and first-trimester maternal exposure to pseudoephedrine. In the first trimester, an alternative would be to try use of topical preparations, including the nasal decongestants oxymetazoline (Afrin) and phenylephrine (Neo-Synephrine).

Cough Suppressants

Codeine and dextromethorphan are the most common cough suppressants. Neither has been associated with a teratogenic effect.

Most cold treatments including the antihistamines, decongestants, and cough suppressants are safe during breast-feeding.

ASTHMA TREATMENT

Although the cold is the most common acute illness during pregnancy, asthma is the most common chronic respiratory condition. About 5% of pregnancies are complicated by asthma, and it may cause increases in preterm birth, low birth weight, and other complications. Whether aggressive and active management reduces these risks to the background level is a controversial issue. Asthma is characterized by airway inflammation and hyperreactivity.

Treatment of the asthmatic should start with reduction of environmental factors that worsen the disease. All patients should receive the influenza vaccination yearly. Allergens should be avoided, as should both active and passive exposures to cigarette smoke. For patients who do not respond optimally to these environmental alterations, a variety of pharmacologic treatments are available (Table 7.3).

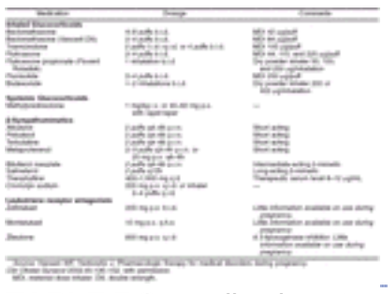

TABLE 7.3. *Medications to treat asthma*

ß-Sympathomimetic Agents

The short-acting ß-sympathomimetic agents are the first-line treatment for acute asthma exacerbations. Albuterol inhalers (Proventil, Ventolin) are commonly used. Terbutaline and metaproterenol inhalers are acceptable alternatives. No teratogenic risks have been ascribed to these medications and all are compatible with breast-feeding. For longer term treatment salmeterol, a long-acting ß-sympathomimetic agent, is available and safe.

All of the ß-sympathomimetic agents can cause tachycardia and other cardiovascular effects. These are usually mild and self-limited.

Glucocorticoids

Inhaled glucocorticoids are also first-line therapy. They act by reducing inflammation. Agents include beclomethasone, fluticasone, and others. No teratogenicity for inhaled steroids has been seen, and they are compatible with lactation.

Systemic glucocorticoids also can be used for acute exacerbations but may increase the risk for cleft lip and palate up to five-fold.

Theophylline

Theophylline was at one time a first-line agent for treatment of asthma, but with the emergence of the ß-agonists and inhaled glucocorticoids, its role has been reduced markedly. This agent can be administered intravenously for acute asthma or orally for chronic suppression. The narrow therapeutic window has contributed to this medication falling out of favor. Used for many years, theophylline has shown no evidence of teratogenicity, and it can be used during breast-feeding.

Cromolyn Sodium

Cromolyn sodium is used for long-term therapy in patients with atopy, functioning as a mast cell stabilizer. Administered by inhaler, there are no known teratogenic or lactation concerns.

Leukotriene Receptor Antagonists and Lipoxygenase Inhibitors

The leukotriene receptor antagonists (zafirlukast, montelukast) and the 5-lipoxygenase inhibitors affect the inflammatory pathways. These agents are new, and human data are few to none. Given sparse data, if these agents can be avoided during pregnancy and lactation, other drugs should be used.

GASTROINTESTINAL DISORDERS

Gastrointestinal problems are extremely common in pregnancy and include nausea, vomiting, hyperemesis gravidarum, gastroesophageal reflux, intrahepatic cholestasis of pregnancy, and inflammatory bowel disease. The clinical picture of several serious disorders may be altered or overlooked during pregnancy and include appendicitis, cholecystitis, pancreatitis, hepatitis, and carcinoma of the gastrointestinal tract.

Nausea and vomiting, or morning sickness, occurs in as many as 90% of pregnancies. Nonpharmacologic treatment can include acupressure at the Neiguan point (2 inches proximal to the wrist crease between the tendons of the flexor carpi radialis and palmaris longus muscles), which may be of benefit. Ingestion of ginger appears to reduce nausea and vomiting in pregnancy. Pyridoxine, vitamin B_6, also appears to reduce symptoms. Pharmacologic treatment can include use of antihistamines, antidopaminergics, and other agents (Table 7.4).

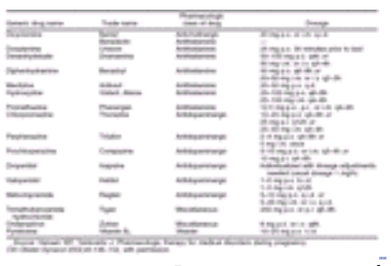

TABLE 7.4. *Drugs commonly used for management of nausea, vomiting, and hyperemesis gravidarum*

Antihistamines

Doxylamine (Unisom) is an antihistamine that was a component of Bendectin (doxylamine and pyridoxine). An effective treatment for the nausea and vomiting of pregnancy, Bendectin was withdrawn from the American market in 1983 because of unproved allegations that it increased the risk of malformations. Doxylamine can be combined with pyridoxine, reconstituting the two active ingredients of Bendectin. Other commonly used antihistamines include dimenhydrinate (Dramamine); diphenhydramine (Benadryl); hydroxyzine (Vistaril, Atarax), which has both antianxiety and antihistamine properties; and promethazine (Phenergan), which has a central cholinergic blocking activity.

Antidopaminergic Agents

Several antidopaminergic agents have been used in pregnancy and are probably safe. The list includes prochlorperazine (Compazine), metoclopramide (Reglan), chlorpromazine (Thorazine), perphenazine (Trilafon), droperidol (Inapsine), and haloperidol (Haldol). There tend to me more maternal side effects with these medications than with the antihistaminic agents. There are also some conflicting data about possible minimal increased risks of birth defects with the latter members of

the group. I tend to suggest use of the prochlorperazine or metoclopramide as first-choice agents in this class. These agents are probably safe in breast-feeding, but some require observing the neonate for sedation.

Other Agents

Trimethobenzamide (Tigan), which provides nausea inhibition at the chemoreceptor level, and ondansetron (Zofran) have been used, but there is less experience with these agents, and certainly the latter is much more expensive with no greater efficacy than standard antihistamines.

Reflux or heartburn is a common complaint during pregnancy, particularly in later gestation. Up to 80% of women may have some symptoms of reflux or heartburn. As with hyperemesis, starting with the least invasive environmental or lifestyle changes is prudent. Advice includes elevation of the head of the bed while sleeping, wearing loose clothing, eating frequent small meals that are low in fat, and cessation of smoking. Antacids would then be the first-line therapy (Table 7.5) and are not known to be associated with any fetal risk. The next class of agents is the histamine receptor antagonists, which can have a reduced bioavailability following antacid use. Therefore, the antacids and the histamine receptor antagonists should be given at least 1 hour apart. The histamine antagonists include cimetidine (Tagamet), famotidine (Pepcid), ranitidine (Zantac), and nizatidine (Axid). There are limited data concerning nizatidine, so the first three would be initial choices. All are compatible with breast-feeding. Promotility drugs can be used and include metoclopramide (described above) and cisapride (Propulsid), about which little has been reported. Sucralfate (Carafate) inhibits pepsin activity and may improve symptoms. The proton pump inhibitors are relatively new agents and, therefore, I would not recommend them. Misoprostol, a prostaglandin E_1 analog, is contraindicated in pregnancy.

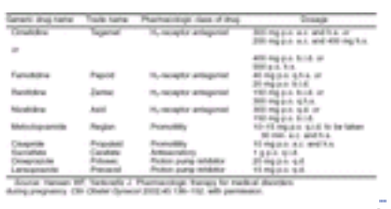

TABLE 7.5. *Drugs commonly used for gastroesophageal reflux in pregnancy*

Intrahepatic cholestasis of pregnancy causes itching of the extremities, trunk, palms, and soles. The pruritus can worsen at night and become severe. In the past, cholestyramine (Questran) was the treatment of choice. Cholestyramine is a nonabsorbable anion exchange resin that binds bile acids, which are elevated in cholestasis. There is now some evidence that ursodeoxycholic acid (UDCA, ursodiol), a minor, naturally occurring hydrophilic bile salt, both reduces maternal pruritus and improves biochemical abnormalities without obvious adverse effects on the newborn. Evidence is accumulating from controlled clinical trials that UDCA is safe. When intrahepatic cholestasis is diagnosed, UDCA coupled with close maternal fetal surveillance is indicated due to potential increases in spontaneous preterm delivery, fetal distress with meconium staining of amniotic fluid, and fetal death.

Inflammatory bowel disease in the form of ulcerative colitis and Crohn disease occur commonly during the reproductive years. Sulfasalazine (Azulfidine) is used for the treatment of both ulcerative colitis and Crohn disease. It is composed of 5-aminosalicylic acid and sulfapyridine. It is poorly absorbed from the gastrointestinal tract and is therefore safe in pregnancy. There is a potential for side effects if used during breast-feeding, so the American Academy of Pediatrics cautions women about use of sulfasalazine during lactation. Mesalamine (Asacol) also can be used during pregnancy and may have fewer maternal side effects than the sulfasalazine. Azathioprine is an immunosuppressant and appears safe to use during pregnancy.

ANALGESIC USE

Analgesics, both by prescription and over-the-counter purchase, are among the most commonly used medicines in pregnancy. This class of drugs basically falls into two categories, the nonsteroidal antiinflammatory agents and the opioid family.

Nonsteroidal Antiinflammatory Drugs

Aspirin is one of the nonsteroidal antiinflammatory drugs (NSAIDs) and acts by irreversible inhibition of enzymes in the prostaglandin synthesis pathway. Caution certainly should be advised in use of aspirin beyond the lowest daily dosages, because this drug readily crosses the placenta. First-trimester use has been associated with an increased risk of gastroschisis. Although dosages at or below 100 mg per day have been studied to determine whether there is a reduction in preeclampsia or intrauterine growth restriction without complications, higher dosages have been associated with increased risk of placental abruption. The World Health Organization Working Group on Human Lactation and the American Academy of Pediatrics Committee on Drugs both raise concern about maternal use of aspirin while breast-feeding.

Indomethacin and ibuprofen are commonly used NSAIDs that cause competitive and reversible inhibition of prostaglandin synthesis. These NSAIDs can cause constriction of the fetal ductus arteriosus as gestational age progresses and, therefore, their use is not suggested after about 32 weeks gestation. They have not been shown to cause malformations, but use beyond the first trimester can cause oligo- or anhydramnios secondary to direct renal effects. Both indomethacin and ibuprofen are considered compatible with breast-feeding.

Acetaminophen is widely used in pregnancy. It crosses the placenta but is considered safe in the usual dosages. It can be used routinely in all trimesters to relieve pain and lower fevers. It is usually the analgesic of choice for a wide variety of aches, pains, and headaches. It is compatible with breast-feeding.

Opioid Analgesics

Many narcotic preparations are available and are used during pregnancy. They all cross the placenta but have not been associated with malformations when used in usual dosages. Use close to delivery can result in neonatal depression. The common narcotics, codeine, meperidine, and oxycodone, are all compatible with breast-feeding.

PSYCHIATRIC DISORDERS

Major depression (15% incidence) and schizophrenia (8%-10% incidence) are very common during the reproductive years. As with any medication, there are concerns about teratogenesis, neonatal withdrawal, or long-term neurobehavioral effects, but these issues must be balanced by the risks to the mother and fetus or infant of withdrawing the necessary medication (Table 7.6).

Medication	Dosage
Amitriptyline	25–50 mg q.h.s.
Chlorpromazine	100 mg q.d. or b.i.d.
Desipramine	25–50 mg q.h.s.
Fluoxetine	10–20 mg q.h.s.
Haloperidol	5–10 mg/d
Imipramine	25–50 mg q.h.s.
Lithium	0.6–2.1 g/d in 3 divided doses
Nortriptyline	10–25 mg q.h.s.

Source: Hansen WF, Yankowitz J. Pharmacologic therapy for medical disorders during pregnancy. *Clin Obstet Gynecol* 2002;45:136–152, with permission.

TABLE 7.6. *Starting dosages for psychotropic medications in pregnancy*

The tricyclic agents have been widely used to treat depression and also anxiety, obsessive compulsive disorders, migraines, and other problems. None of the tricyclics has been associated with malformations. If needed, it would be prudent to use the agents with the most accumulated experience, including nortriptyline, desipramine, amitriptyline, and imipramine. There is no evidence to date of clear adverse neonatal effects during breast-feeding, but the American Academy of Pediatrics considers the effects of amitriptyline and imipramine unknown but of concern for the nursing infant.

The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine and the newer agents, fluvoxamine, paroxetine, and sertraline. Extensive experience with

fluoxetine shows no clear increased risk of malformations. There is much less experience with the newer agents, but none of the data indicates a teratogenic effect. The effects on the infant of the group of drugs that includes fluoxetine are unknown but may be of concern in relation to breast-feeding. The patient should weigh the strength of her desire to breast feed and the benefits of breast-feeding against the potential effects of continued SSRI use.

Other agents are prescribed for depression. Monoamine oxidase inhibitors have not been studied sufficiently to draw a conclusion about their safety. The psychostimulants may cause problems following in utero exposure and are best avoided. St. John's wort, an extract of the plant *Hypericum perforatum*, has been touted for antidepressant properties, but recent studies have not proven efficacy, so this medication should also be avoided.

The mood stabilizers, specifically lithium, valproic acid, and carbamazepine, have all been identified as teratogens. The data on lithium causing malformations have weakened with additional studies. Initial reports found a 5% to 10% risk of malformations with a markedly increased risk of Ebstein anomaly. More recent reports show little, if any, increased risk of malformation and have failed to confirm the specific association with Ebstein anomaly. For the patient with a first-trimester exposure to lithium, targeted ultrasonography in the second trimester is warranted. Lithium also has been associated with hydramnios, possibly secondary to fetal diabetes insipidus. Although there is little data, the American Academy of Pediatrics considers lithium to be contraindicated during lactation.

Valproic acid and carbamazepine are both associated with an increased risk of neural tube defects, so second-trimester serum screening for a-fetoprotein and targeted ultrasonography are warranted. Yet many of the neural tube defects are closed and difficult to detect.

The antianxiety agents generally fall into the benzodiazepine family. There have been reports of an increased risk of cleft lip after exposure not substantiated in other reports. Although the odds ratio may have been increased, the absolute rate of clefting would still be low given a rate of only 0.06% in the normal population. The American Academy of Pediatrics states that the effects on the neonate during lactation are unknown but may be of concern.

The antipsychotic agents include the butyrophenones (including haloperidol) and phenothiazines. No clear teratogenic effect has been seen with either group. Haloperidol is classified as having an unknown but possibly concerning effect if used during lactation.

VITAMIN AND MINERAL USE

Prenatal use of multivitamins, often with additional iron, is commonly advocated by many health care providers for pregnant women. There is clear evidence that the folate component reduces the first occurrence and recurrence rate of neural tube defects. Other studies point to possible reduction in cardiac and urinary tract abnormalities. For the woman who eats a balanced diet, most of the recommended daily allowances should be obtained except for folate and iron. However, there are multiple at-risk populations that may not attain the goals, including those patients with eating disorders, vegetarians, the poor, substance abusers, women carrying multiple gestations, and so on.

The only clear teratogenic vitamin is vitamin A which, when used at over 10,000 IU per day, can cause cranial neural crest anomalies. It would be prudent to not exceed 5,000 IU per day in supplementation.

Supplementation of iron can improve hematocrit at the time of delivery and 6 weeks postpartum. Some studies have shown a benefit of calcium in reducing the risk of gestational hypertension and preeclampsia, although other studies fail to confirm this finding. Zinc may increase birth weight and head circumference in populations with zinc deficiency, but probably not in the United States.

RECREATIONAL DRUG USE

Recreational drug use is a major problem in the United States. Anonymous testing studies have found rates of positivity from 7.5% to over 13% in a variety of populations, the drugs found including opiates, cocaine, or cannabinoids.

As concerning as the illicit drugs are, the effects of tobacco also are well described and of great impact. Some studies suggest that one sixth of low birth weight incidence could be prevented if women stopped smoking during pregnancy. Nicotine reduces uteroplacental blood flow and increases the risk of preterm birth, low birth weight, and sudden infant death syndrome.

Maternal alcohol use can cause the fetal alcohol syndrome characterized by craniofacial changes and impaired cognitive development. Although the full-blown picture can be seen with excessive consumption, no safe level of alcohol use has been established.

The effects of recreational opioid use appear to be confined to an increased risk of growth restriction, intrauterine fetal death, and neonatal withdrawal. No clear long-term effects have been proven.

Marijuana use during pregnancy has not been linked with any clear teratogenic effect or long-term developmental consequences.

Cocaine use has been associated with an increased risk of placental abruption, preterm premature rupture of membranes, and low birth weight. A variety of congenital abnormalities have been described with maternal cocaine use, but no definite connection has been established. A variety of neurobehavioral effects have been described also, but long-term problems are not clear.

Amphetamine, described as a stimulant for depressed patients, is becoming a commonly abused drug. Although no clear pattern of malformations has been seen, increases in cleft lip and palate have been seen in some, but not all, studies. Concern has been raised about impact on long-term physical growth and intellectual and behavorial development.

ANTICONVULSANT AGENTS

Epilepsy is the most common neurologic disorder in pregnancy. Five percent of the population report having had a seizure at some point in their lives. All antiepileptic drugs (AEDs) cross the placenta and, therefore, have potential for teratogenicity (Table 7.7). Given the incidence of epilepsy, 1 in 250 fetuses is exposed to an AED. Recent studies are making it clear that the AEDs are responsible for the congenital malformations found in the offspring of pregnant women with epilepsy, not the epilepsy, itself, as has been conjectured in the past.

Drug	Dosage and comments
Phenytoin (Dilantin)	300–600 mg/d in divided doses, therapeutic level: 10–20 μg/mL
Carbamazepine (Tegretol)	200–1,200 mg/d, therapeutic level: 4–12 μg/mL
Phenobarbital	60–240 mg/d, therapeutic level:10–40 μg/mL
Valproic acid (Depakote)	10–15 mg/kg per day, therapeutic level: 50–100 μg/mL
Ethosuximide (Zarontin)	500–2,000 mg/d in divided doses, therapeutic level: 40–100 μg/mL
Clonazepam (Klonopin)	1.5–20 mg/d
Gabapentin (Neurontin)	New agent
Lamotrigine (Lamictal)	New agent

Source: Hansen WF, Yankowitz J. Pharmacologic therapy for medical disorders during pregnancy. *Clin Obstet Gynecol* 2002;45:136–152, with permission.

TABLE 7.7. *Anticonvulsants*

Phenytoin (Dilantin) is a hydantoin AED. The fetal hydantoin syndrome includes a constellation of anomalies including craniofacial, limb, and neonatal growth and performance delays. The risk of teratogenicity is about 2 times the background risk. Phenytoin is compatible with breast-feeding.

Carbamazepine (Tegretol) causes a group of defects similar to the fetal hydantoin syndrome, in addition to the increased risk of spina bifida. The risk of spina bifida is about 0.5% to 1.0%. Carbamazepine is compatible with breast-feeding.

Phenobarbital is in the barbiturate class. It has been associated with findings similar to the hydantoin syndrome, as well as with congenital heart defects and orofacial

clefting. Breast-feeding is acceptable unless the infant becomes sedated, in which case breast-feeding should be discontinued.

Valproic acid (Depakote) has a 1% to 2% risk of causing spina bifida. These neural tube defects tend to be in the lumbosacral area. Valproic acid use also has been associated with cardiac defects, orofacial clefting, and genitourinary anomalies. There is a fetal valproate syndrome that includes facial, central nervous system, and limb anomalies. Breast-feeding is permissible while using this medication.

Several newer AEDs have been developed and include felbamate, gabapentin, lamotrigine, and others. Many patients make their first visits to prenatal clinics while taking these medications and having completed the first trimester. We counsel them that, at present, there is no evidence of teratogenicity but that little information is available.

HEADACHES

Headache is a very common problem in pregnancy. Evaluation of headaches requires categorizing the headache as primary or secondary. Secondary headache is due to another condition such as flu, while in the primary category the headache, itself, is the disorder. Primary headaches include migraine, tension-type headache, and cluster headache. Criteria have been developed for differentiating these categories and include frequency, degree of pain, and location of pain.

Sumatriptan is a selective serotonin receptor agonist. There is no evidence that it is a human teratogen, based on limited numbers of patients reported to the Sumatriptan Pregnancy Registry maintained by GlaxoWellcome and patients who contacted a teratogen hotline. Even less data is available about three newer drugs in this class: naratriptan, zolmitriptan, and rizatriptan.

ß-Adrenergic blockers, such as propranolol have been used as preventive therapy. ß-Blockers, calcium channel blockers, and many of the antidepressants discussed earlier have been used as preventive therapy and appear safe in pregnancy and lactation.

ANTINEOPLASTIC AGENTS

Cancer is relatively common during pregnancy, complicating 1 in 1,000 to 1 in 1,500 pregnancies. The most common malignancies include carcinoma of the cervix and breast, lymphoma, melanoma, leukemia, and carcinoma of the ovary and colon. Chemotherapeutic agents act on rapidly dividing cells and are, therefore, potentially harmful to the fetal tissue. The trimester of exposure is, of course, critically important to what potential effect the drug may have. Teratogenesis is a concern in the first trimester, but impact on the continued development of the brain in the second and third trimester is of import. Delivery planning is also important, because both maternal and neonatal blood counts may be adversely affected by the chemotherapy. For the most part, chemotherapeutic drugs are secreted into the breast milk, making breast-feeding contraindicated for the woman receiving this therapy.

Many classes of drugs can be used as chemotherapy. The alkylating agents cross-link DNA. These drugs, including busulfan, chlorambucil, cyclophosphamide, and nitrogen mustard, are all considered teratogens in the first trimester. The antimetabolites are also teratogenic, possibly due to their effects on folic acid metabolism. This class includes aminopterin and methotrexate. Other antimetabolites that do not affect folic acid metabolism, such as the pyrimidine antagonist 5-fluorouracil, 6-mercaptopurine, and cytarabine, have much less frequently been associated with birth defects.

The taxanes, including paclitaxel, have not been used in pregnancy enough to comment on safety. Cisplatin has been used in pregnancy, but most experience is in the second and third trimesters. Growth restriction is common.

The therapy of a pregnant woman with cancer must be individualized and must be based on collaboration among the primary care provider, perinatologist, oncologist, and neonatologist.

ANTICOAGULATION

Thromboembolism is a leading cause of morbidity and mortality in pregnancy and postpartum. In is the second most common cause of pregnancy-related maternal mortality in the United States. Anticoagulation is used for thromboembolism, valvular heart disease, inherited thrombophilias, and acquired thrombophilias such as antiphospholipid antibody syndrome. The agents available (Table 7.8) are the coumarin derivatives, unfractionated heparin, and low-molecular-weight heparin (LMWH).

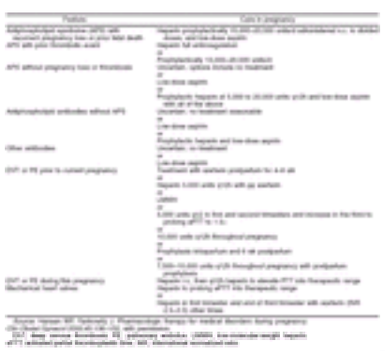

TABLE 7.8. *Anticoagulation in pregnancy*

Thromboembolism occurs in 0.5 to 3.0 of every 1,000 pregnancies. Treatment of acute deep vein thrombosis includes bed rest, elevation of the extremity to promote venous return, and heparin. Heparin is used with a target activated partial thromboplastin time (aPTT) of 1.5 to 2.5 times control. For pregnant patients, a switch to subcutaneous heparin takes place after 3 to 5 days, as opposed to the initiation of warfarin in the nonpregnant state.

Anticoagulation in a patient with artificial heart valves can be a difficult dilemma. For those with particularly thrombogenic valves it may be necessary to consider oral anticoagulation. For the inherited and acquired thrombophilias, use of unfractionated or LMWH probably is acceptable.

Use of the oral anticoagulant warfarin sodium (coumadin) is problematic, because there is a known teratogenic effect. This agent easily crosses the placenta. Warfarin depresses the vitamin K-dependent clotting factors (II, VII, IX, and X). Its effectiveness is measured by the prothrombin time (PT), expressed as an international normalized ratio (INR). The first case of teratogenicity of warfarin was reported in 1966, and this infant had nasal hypoplasia, bilateral optic atrophy, blindness, and mental retardation. In a review of all published cases up to 1980, one sixth had abnormalities, and another one sixth ended in stillbirth or spontaneous abortion. Two thirds of exposed pregnancies had a normal outcome. Some reports cite a teratogenic effect in up to two thirds of fetuses exposed between 6 and 12 weeks gestation. Other reports state that the embryopathy affects as few as 5% to 10% of fetuses exposed in the first trimester. The problem is in differing dosages and nature of neonatal evaluation.

It appears that neither unfractionated heparin nor LMWH crosses the placenta to any appreciable degree and is, therefore, not teratogenic. Patients can develop heparin-induced thrombocytopenia at about 2 weeks after initiation of therapy. Osteopenia is a problem with prolonged use. Both of the latter complications are more common with unfractionated heparin.

All three classes of anticoagulants are compatible with breast-feeding.

RADIOLOGIC EXAMINATIONS

Many women require diagnostic imaging studies during pregnancy. The two main concerns are exposure to ionizing radiation and effects of contrast agents. The vast majority of data derives from relatively few pregnant women exposed to high doses of radiation from the atomic bombs dropped over Hiroshima and Nagasaki. From these few individuals it has been extrapolated that there is a threshold dose of at least 5 rads required to cause concerning effect on the developing fetus. The particular effect depends on gestational age at exposure and radiation dose (Table 7.9). Lethality may be possible during preimplantation with doses as low as 5 rads, but by 9 days postconception at least 25 to 50 rads is needed. Malformations occur only between about 9 and 60 days postconception, and the threshold is at least 10

rads. Mental retardation is possible between 61 and 104 days postconception, with a threshold of 12 rads.

Defect and gestational age	Occurrence	Threshold	Risk per rad
Lethality			
0–8 days (PC) maximum	+++	5–10 rads	1%
9–60 days	+	25–50 rads	ND
61–104 days	+	50 rads	ND
105–175 days	—	—	—
>175 days	—	—	—
Malformation			
0–8 days	—	—	—
9–60 days	+++	10–20 rads	0.50%
61–104 days	—	—	—
105–175 days	—	—	—
>175 days	—	—	—
Mental Retardation			
0–8 days	—	—	—
9–60 days	—	—	—
61–104 days	+++	12 rads	0.40%
105–175 days	+	65 rads	0.10%
>175 days	—	—	—
Microcephaly			
0–8 days	—	—	—
9–60 days	++	10–20 rads	1%
61–104 days	++	10–20 rads	1%
105–175 days	—	—	—
>175 days	—	—	—
Growth Retardation			
0–8 days	—	—	—
9–60 days	+++	5–25 rads	ND
61–104 days	++	5–25 rads	ND
105–175 days	—	—	—
>175 days	—	—	—

Source: The American College of Obstetricians and Gynecologists. *Guidelines for Diagnostic Imaging During Pregnancy.* ACOG Committee Opinion #158, September, 1995; Heinonen OP, Sloane D, Shapiro S. *Birth defects and drugs in pregnancy.* Littleton, MA: Publishing Sciences Group, 1977; Teratology Society of Public Affairs Committee. FDA Classification of drugs for teratogenic risk. *Teratol* 1994;49:445–447; Friedler M, Thorp JM. Radiologic examinations during pregnancy. In: Yankowitz J, Niebyl JR, eds. *Drug therapy in pregnancy.* third ed. New York: Lippincott Williams & Wilkins, 2001, with permission.

PC, postconception; ND, no data; —, no observed effect; +, demonstrated effect; ++, readily apparent effect; +++, occurs in high incidence.

TABLE 7.9. *Risks of irradiation per gestational age*

Due to increasing concern about the escalating number of rads of exposure inherent in newer computed tomography (CT) technology, the University of Iowa Department of Radiology has developed a protocol to avoid unnecessary exposures and adequately counsel the pregnant patient. Counseling includes a discussion of a 1.5-fold to 2-fold increased risk in childhood leukemias for a 1-rad to 2-rad exposure in the midtrimester and into the third trimester. It is important to be aware of typical radiation exposures of commonly used examinations (Table 7.10) but also to enlist the expertise of a radiation physicist to assist in calculation of doses in specific cases.

Chest x-ray	2–8 millirads
Dental x-rays	<1 millirad
Mammography	7–10 millirads
Abdominal x-ray	200–700 millirads
Lumbar spine x-ray	300–600 millirads
Hip x-ray	200–500 millirads
Upper GI series	100–550 millirads
Barium enema	800–1,300 millirads
Intravenous pyelogram	600–1,000 millirads
Cholecystography	100 millirads
CT head	50 millirads
CT chest	1,000 millirads
CT abdomen	3,000–4,000 millirads
CT pelvimetry	250 millirads
Cardiac catheterization	<500 millirads

Source: Friedler M, Thorp JM. Radiologic examinations during pregnancy. In: Yankowitz J, Niebyl JR, eds. *Drug therapy in pregnancy.* third ed. New York: Lippincott Williams & Wilkins, 2001, with permission.

GI, gastrointestinal; CT, computed tomography.

TABLE 7.10. *Typical radiation exposure to the fetus for selected diagnostic studies (1 rad = 1,000 millirads)*

Nuclear medicine studies involve exposure to ionizing radiation from a variety of isotopes. In most cases the fetal dose will be less than 1 rad except for sodium iodide, Ga67, iodinated red blood cells, or Ti201. Iodine-131 can cause fetal thyroid damage, goiter, and local effects when concentrated by the fetal thyroid after 70 days post-LMP. Use of iodine-131 to treat hyperthyroidism or ablate the thyroid can result in substantial fetal dosage.

The most widely used radioisotope in pregnancy is technetium-99. It can cross the placenta, but the amount of radiation from any routine study is small.

Magnetic resonance imaging (MRI) involves exposure to magnetic fields rather than ionizing radiation. There are few studies evaluating the effects of MRI on fetuses. There are also virtually no data on gadolinium, a nonionic contrast agent typically used for MRI evaluations. For this reason, MRI is reserved for situations when it clearly is clinically warranted.

COMPLEMENTARY AND ALTERNATIVE THERAPY

Complementary and alternative therapy includes acupuncture, acupressure, massage, aromatherapy, and herbal preparations (phytomedicine). A wide variety of herbs are used but they have received limited scientific evaluation. Thus, safety and efficacy cannot be addressed clearly. Certain ingredients should be avoided altogether and include anthraquinone and berberine, which may stimulate uterine contractions. Many other herbs are thought to have similar properties and should be avoided. Patients should be queried about use of complementary medicines. An effort should be made to determine the constituents of a preparation and then evaluate the safety of each component.

SUMMARY POINTS

- Disease treatment in the pregnant patient should be similar to that given to other patients.
- Rather than using the FDA Drug Classification System, references and information in databases should be sought for particular medications in specific clinical situations.
- Most drugs are safe to use during pregnancy, including most antibiotics and medications to treat common conditions, such as upper respiratory tract and gastrointestinal complaints.
- A few medications are known teratogens, and the list includes coumadin, lithium, the anticonvulsive medications, several antineoplastic drugs, and vitamin A and its derivatives.
- Most drugs are safe during lactation because the amounts that appear in breast milk are subtherapeutic, approximately 1% to 2% of the maternal dose. One notable exception is lithium.

USEFUL DATABASES AND WEB RESOURCES

REPROTEXT, REPROTOX, TERIS, and Shepard's Catalog of teratogenic agents are useful resources. These and other databases can be purchased and installed in personal computers.

http://www.perinatology.com/exposures/druglhttp://www.reprotox.org/.%20Accessed%20December%206,%202002.http://depts.washington.edu/terisweb/.%20Accessed%20December%206,%202002.
http://www.rxlist.com/.%20Accessed%20December%206,%202002.ist.htm

Organization of Teratology Information Services, http://orpheus.ucsd.edu/otis/links.htm

American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 1994;93:137–150. http://www.aap.org/policy/0036.html

The Organization of Teratology Information Services has a collection of fact sheets on exposure during pregnancy to a variety of diseases, medications, and herbal remedies.

http://www.OTISpregnancy.org/fact_sheet.htm. Accessed December 6, 2002.

General information regarding drugs and medications during pregnancy:

http://www.vh.org/Patients/IHB/ObGyn/MedicinesPregnancy.html. Accessed December 6, 2002.

http://www.perinatology.com/exposures/druglist.htm. Accessed December 6, 2002.

http://www.motherisk.org/. Accessed December 6, 2002.

The National Library of Medicine, http://www.ncbi.nlm.m.nih.gov/PubMed/

The National Center for Complementary and Alternative Medicine, http://nccam.nih.gov/

The NIH Office of Dietary Supplements, http://dietary-supplements.info.nih.gov/

The American Botanical Council, http://www.herbalgram.org/ Accessed December 6, 2002.

The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine, http://www.rosenthal.hs.columbia.edu/

A drug name and “pregnancy” or “lactation” can be entered into a search engine such as Dogpile (http://www.dogpile.com/) or Google (http://www.google.com/).

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Chapter 8

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Ultrasound in Obstetrics

GENERAL PRINCIPLES
INDICATIONS
FIRST TRIMESTER
SECOND TRIMESTER
DOCUMENTATION AND THE BASIC ULTRASONOGRAPHIC EXAMINATION
THIRD TRIMESTER
TECHNIQUES OF FETAL TESTING
INTERVENTIONAL ULTRASONOGRAPHY
FUTURE DIRECTIONS
CONCLUSION
SUMMARY POINTS

RECOMMENDED READINGS
Introduction
General Principles
Documentation and the Basic Ultrasonographic Examination
Techniques of Fetal Testing

The use of ultrasonography in obstetrics and gynecology has made sweeping changes in the management of pregnant patients. The purpose of this chapter is to review existing recommendations regarding the use of ultrasonography in pregnancy. The background setting of a patient's progress in pregnancy—from her initial visit confirming an intrauterine pregnancy through the anatomic survey to her third-trimester testing—was chosen. Many excellent textbooks dedicated to obstetric ultrasonography already exist. This chapter is intended to provide information about current ultrasonographic practice, guidance for performing the examination, and assistance in recognizing common anomalies. Future ideas and new technology will be reviewed at the end of the chapter.

Most ultrasound providers recognize two categories of examination: a basic ultrasonographic examination that includes a routine anatomic survey, estimate of gestational age, evaluation of placenta and amniotic fluid, and evaluation of maternal anatomy; and a more comprehensive examination that may be targeted based on the abnormal findings in a basic examination. In the past, the terms “level I” and “level II” examination were used erroneously to describe these two categories. Such classification schemes must be avoided to prevent misguided patient and physician expectations for the purposes of the examination. Every ultrasonographic examination should be as complete as possible within the limits of the provider and equipment. An ultrasonogram performed simply for the purpose of sex determination that fails to identify an anencephalic fetus has certainly done only harm. A limited ultrasonographic examination for a specific purpose, such as evaluation of fetal presentation, is appropriate in cases in which the pregnancy has been examined previously or in a clinical emergency.

GENERAL PRINCIPLES

Ultrasound images are generated using the same principle as sonar. High-frequency sound waves (3.5-7.5 MHz) pass from the surface of the ultrasound transducer through the tissues of the imaging target. Echoes of the transmitted sound waves return to the transducer. Because the average speed of ultrasound in human tissue is known (1,540 m/s), the distance of the reflector from the transmitter can be calculated using the time required for the echo to return. The resulting depth and signal strength data are plotted on a display screen. The position on the screen corresponds to the depth in the tissue. The brightness of the picture element corresponds to the strength of the return signal. Ultrasound systems display a black background and use increasingly bright shades of gray and white to represent stronger echoes.

The acoustic impedance for a tissue determines the degree to which that tissue reflects or transmits ultrasound energy. Because the acoustic impedance of tissue varies by density and consistency, interfaces between dissimilar tissues and within heterogeneous tissues act as reflectors that echo part of the transmitted signal back to the transducer. The degree of dissimilarity between one tissue type and the next determines the strength of the return echo received. Simple fluids such as water or amniotic fluid generate very few echoes, because they are homogeneous. Bone generates very strong echoes because the adjacent soft tissues have very dissimilar acoustic properties, producing a marked acoustic impedance mismatch. The strength of the return echo also depends on the angle between the face of the reflector and the ultrasound beam. As the reflector becomes closer to perpendicular with the transmitting source, a greater proportion of the echo is received. This property is well illustrated by the midline structures of the fetal brain, which are imaged best when perpendicular to the incident beam. The strength of the transmitted signal, which is controlled by the ultrasound operator, also contributes to the strength of the return echo.

Transducers spend only a small fraction of the time generating the ultrasound signal compared with the time spent detecting return echoes. The duty factor, expressed as the time spent transmitting divided by the time spent listening, is on the order of 0.01 for modern equipment. When a patient has an ultrasonographic examination lasting 20 minutes, the maternal and fetal total exposure to ultrasound energy is only 12 seconds. This exposure increases when Doppler sonography is employed due to the longer energy pulses.

The American College of Obstetricians and Gynecologists (ACOG) and American Institute of Ultrasound in Medicine (AIUM) recommend that ultrasound systems used for obstetrics display the thermal index (TI) and mechanical index (MI) of acoustic output on the screen. The TI is an estimate of the increase in temperature in tissue due to conversion of mechanical energy from the ultrasound beam to heat. Values of the TI less than 1.0 are not of concern for generating significant temperature changes. Temperature increases are most likely to occur during Doppler ultrasonography because of the larger duty factors. The MI estimates the compressive and decompressive forces caused by the ultrasound beam. If these mechanical forces are excessive, microscopic bubbles might form in the tissue being imaged. This bubble formation is called cavitation. As long as the MI values are less than 1.0, cavitation is not a concern.

The Food and Drug Administration has set the upper limit of acoustic intensity at 94 mW/cm ^{2} (spatial peak temporal average) for obstetric ultrasonography. For other applications, ultrasound systems are limited to a maximum output of 720 mW/cm ^{2}. Furthermore, the systems must display the TI and MI if either or both of these indices can exceed 1.0. Because many systems can be used for both obstetric and nonobstetric ultrasonography, the provider should be aware of the acoustic output and TI and MI of the system in use. Overuse of power Doppler and color Doppler imaging is especially noteworthy as settings in which the recommended maximums could be exceeded. The ALARA principle (*a*s *l*ow *a*s *r*easonably *a*chievable) has been suggested to govern the amount of fetal exposure to ultrasound energy while obtaining useful image data. The ultrasound provider should also remember that although there are no *known* bioeffects of diagnostic ultrasonography, future discoveries of adverse effects are certainly possible. As such, obstetric ultrasonography should be used only when indicated (Table 8.1).

TABLE 8.1. *Indications for ultrasonography in pregnancy*

Ultrasonographic images are most correctly described using terms that acknowledge sound as the source of the image. Highly sound-reflective structures that produce large reflections and correspondingly bright screen images are called hyperechoic or hyperechogenic structures. Regions that produce very few echoes are termed hypoechoic or hypoechogenic. Regions that are echo free are termed anechoic. The reader is encouraged to avoid terms such as translucent or sonolucent, which are derived from the Latin root *lucere*, meaning “to shine.”

INDICATIONS

The currently accepted ACOG recommendations for ultrasonographic examination in pregnancy are based on the opinion of a National Institutes of Health consensus

panel and are summarized in Table 8.1.

Several studies have addressed the question of whether routine ultrasonographic screening for all pregnancies should be performed. Recommendations from ACOG, based on an analysis of existing literature, suggest that women with low-risk pregnancies should not receive screening ultrasonography unless medically indicated. Thus far the evidence indicates that there is no reduction in perinatal morbidity or mortality from routine ultrasonographic screening in the low-risk population. The rate of unnecessary interventions in pregnancies screened with routine ultrasonography is also unchanged. There are not yet enough data to conclude whether fetuses with life-threatening anomalies have an improved outcome because of routine ultrasound use.

Although these studies demonstrate that routine ultrasonography in the low-risk pregnancy is not effective in improving perinatal mortality or morbidity, there are articles and editorials challenging those conclusions. Many of these studies offered routine screening to all patients except those who would stand to benefit most. Furthermore, a population agreeing to participate in a randomized study of routine screening does not necessarily constitute an accurate cross-section of the intended study population. The ability to perform a physical examination on the second patient—the fetus—is important. When performed with adequate equipment by properly trained personnel, prenatal ultrasonographic examinations can and do offer important information to the provider and patient.

Good evidence exists to demonstrate that fetal anatomic surveys are over 99% specific in detecting anomalies; that is, when ultrasonographic examination findings are normal, the fetus will indeed be normal over 99% of the time. The sensitivity of the anatomic survey, or the probability that an ultrasonogram will demonstrate an anomaly if one is present, varies widely depending on the ultrasound provider, the quality and age of the ultrasound system, the anomaly in question, and the frequency of the anomaly in the practitioner's own population. For this reason, it is recommended that ultrasound specialists perform examinations for genetic screening or evaluation of abnormal scan results.

FIRST TRIMESTER

With the advent of extremely sensitive home pregnancy tests which can detect human chorionic gonadotropin (hCG) levels down to 20 to 30 mIU/mL, the early diagnosis of pregnancy is now within reach of the typical consumer. Initial visits to the obstetrician can occur earlier instead of later, sometimes even before the first missed menstrual period.

Ultrasonographic examinations in the first trimester should be performed with transvaginal imaging and augmented with transabdominal imaging, if necessary. Although first-trimester detection of an intrauterine gestation is possible, it still is limited by the size of the gestation. Corresponding levels of serum ß-hCG help to determine a threshold level at which sonographic evidence of an intrauterine pregnancy should be detected. Various sources place this level between 1,500 and 2,000 mIU/mL for transvaginal sonography and 3,000 and 5,000 mIU/mL for the transabdominal approach. Protocols have been developed for the management of patients with a positive pregnancy test but no ultrasonographic evidence of intrauterine gestation. This scenario may be of concern for ectopic pregnancy, especially when there is pain or vaginal bleeding. In the clinically stable patient, a repeat ultrasonogram in 3 to 7 days may yield more useful information and help avoid errors in management.

Two methods are commonly used for determining the gestational age in the first trimester. These are the mean sac diameter (MSD) and the more accurate crown-rump length (CRL). The MSD is determined by two methods. The method selected depends on the reference table used to determine the gestational age. The first method involves imaging the sac and measuring the longest axis (length) and the largest axis perpendicular to the long axis (width). These two orthogonal measurements are averaged and the value used to estimate a gestational age. The second technique requires the addition of the depth of the sac from an image that is transverse and perpendicular to the length. The three values are averaged and an appropriate table used (Fig. 8.1). The CRL is measured from an image of the fetus that includes the maximum distance from the cephalic pole to the caudal pole. Although the CRL is regarded as highly accurate in determining the gestational age, the biparietal diameter (BPD) in the late first trimester and before 20 weeks of gestation offers comparable accuracy. The MSD is more useful if no embryo is present in a gestational sac. The identification of a yolk sac or an embryo determines that a gestational sac is present. Using transvaginal ultrasonography, an embryo should be seen by 5 to 6 weeks of gestation as measured from the first day of the last menstrual period. By the time the CRL equals 5 millimeters, cardiac activity should be seen. If the CRL is less than 5 millimeters, the examination should be repeated. Table 8.2 lists the signs of an abnormal gestation. If the patient is at 6 weeks of gestation with a positive pregnancy test and there is no gestational sac visualized in the uterus, an ectopic pregnancy is highly suspect.

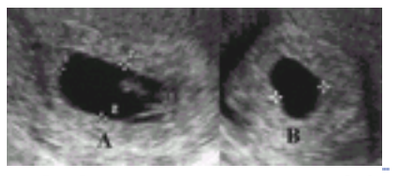

FIG. 8.1. Measurement of the mean sac diameter (MSD). The distances measured by the calipers in the longitudinal axis (**A**, number one) and the depth (**A**, number two) and the transverse diameter measured in **(B)** are added together and divided by three to produce the MSD. Some authors use only the sum of the longitudinal and depth measurements divided by two.

Greater than 16 mm MSD without an embryo
Greater than 13 mm MSD without a yolk sac
No fetal heart activity in an embryo with a CRL greater than 5 mm
Yolk sac without an embryo by 6 wks gestation
No gestational sac by 6 wks
Markedly distorted gestational sac
Visualization of the amnion without an embryo

MSD, mean sac diameter; CRL, crown-rump length.

TABLE 8.2. *Signs of an abnormal gestation*

The obvious diagnosis of an ectopic pregnancy, in which a small gestational sac with cardiac activity present is seen outside the uterus, can be made even when serum ß-hCG levels are not at the threshold for determination of intrauterine pregnancy. The more difficult ectopic pregnancy cases usually involve abnormal adnexal findings such as ovarian or paratubal cysts, free peritoneal or pelvic fluid, but no definite pregnancy sac. The pseudogestational sac may be seen when the endometrium responds to chemical changes of pregnancy and may resemble a fluid-filled structure within the endometrial cavity. Some authors describe a *ring of fire* that may be seen around ectopic pregnancies developing in the adnexa when evaluated with color Doppler interrogation or power Doppler imaging (Fig. 8.2). The ring represents increased blood flow about the developing embryo, but it is possible for a corpus luteal cyst or even normal ovarian tissue to demonstrate such a ring. It is recommended that further diagnostic information be gathered, using sequential determination of serum ß-hCG levels and clinical findings, as long as the clinical situation is stable.

FIG. 8.2. Ring of fire. A corpus luteum **(A)** can be confused with an ectopic pregnancy **(B).** The *arrow* indicates blood flow in the embryo **(B).** (From Diana M. Strickland, RDMS, RDCS; with permission.) See color figure 8.2.

When the serum ß-hCG levels are abnormally high (greater than 100,000 mIU/mL) for the estimated gestational age by last menstrual period dating or by the uterine size, the diagnosis of molar gestation should be entertained. The classic “snowstorm” description of ultrasonographic imaging in molar gestation has been discarded to reflect the improved resolution of ultrasound transducers. A complete molar pregnancy, in which no fetal tissue is identified, may demonstrate clusters of vesicles on ultrasonographic examination. Identification of a partial molar pregnancy is more difficult, but it may be suggested by the presence of a fetus with a cystic or multicystic placenta (Fig. 8.3). The fetus might demonstrate numerous anomalies, including findings consistent with triploidy.

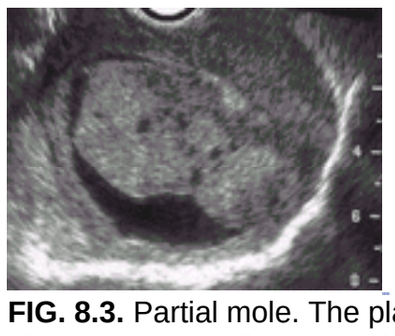

FIG. 8.3. Partial mole. The placenta appears cystic and enlarged for gestation. No fetal heartbeat was noted and, although fetal tissue was found at pathology, no chromosome studies were obtained.

During imaging of the early fetus several important features should be visualized. The number of fetuses in the uterus should be reported. A multiple gestation should not be diagnosed until the yolk sacs or embryos can be counted. This will avoid counting the empty gestational sac of an anembryonic pregnancy or blighted ovum as a viable pregnancy. Early gestation may be the best possible time to determine the amnionicity and chorionicity of multiple gestations, information of crucial importance in the later management of these pregnancies. A thick rim of tissue surrounding each fetus is more suggestive of dichorionic, diamniotic gestations. If the intervening tissue is thin or absent, monochorionic, diamniotic, or even monoamniotic gestations are more probable. Conjoined twins may also be detected in the first trimester (Fig. 8.4). Determination of zygosity is possible only if a monoamniotic with monochorionic or diamniotic with monochorionic configuration is found, in which case the twins are monozygotic. Placentation in multiple gestations is often an important clue in determining zygosity and the risk of twin-to-twin transfusion syndrome. The single placenta associated with monochorionic monoamniotic twinning can be identified during the first and second trimesters. A fused placenta will appear as a single placenta but with the additional finding of dichorionic diamniotic membranes (Fig. 8.5). Determination of fetal sex also may be helpful in determining zygosity.

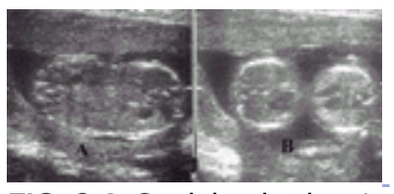

FIG. 8.4. Conjoined twins. In **(A)** the twins are joined at the abdomen (abdominophagus) and separated at the chest **(B).**

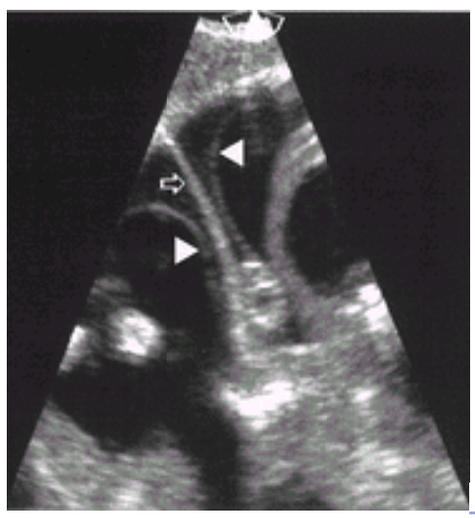

FIG. 8.5. Fused placenta with diamniotic, dichorionic membranes. The fused chorions *(open arrow)* are noted between the amnions *(closed arrow)* of each twin. The twins could be either mono- or dizygotic.

The fusion of the expanding amnion with the chorion, obliterating the intervening space, occurs around 12 weeks. Prior to this union, the unfused amnion may be seen as a wispy echogenic membrane surrounding the developing fetus and should not be confused with a gestational sac (Fig. 8.6). It is theorized that rupture of the unfused amnion followed by settling of the fragmented ends onto the surface of the developing embryo is the source of amniotic band syndrome. These disruptions of normally developing fetal anatomy may lead to amputations of random fetal parts or even to fetal death.

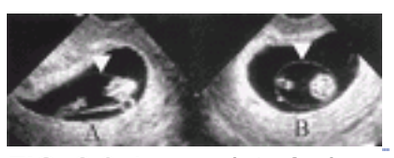

FIG. 8.6. Incomplete fusion of the amnion in the first trimester **(A).** The amnion in the singleton gestation resembles the membrane in a multiple gestation. However, in a different plane **(B)** the amnion surrounds the embryo in a more characteristic manner.

Later in the first trimester it may be possible to identify the normal rotation of the fetal gut, which occurs in the proximal part of the umbilical cord (Fig. 8.7). Such normal development may be confused with an omphalocele, an abnormality of the abdominal wall at the umbilical ring. Completion of gut rotation occurs by week 14, with subsequent resolution of the normal developmental hernia.

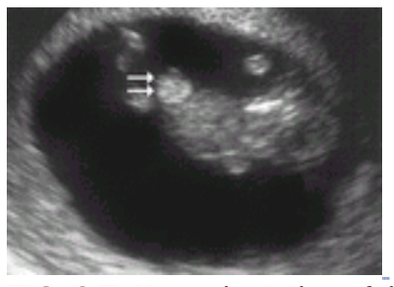

FIG. 8.7. Normal rotation of the fetal gut. The *double arrow* indicates the portion of the umbilical cord transiently occupied by the fetal gut during migration and rotation.

One of the earliest markers for aneuploidy in the developing fetus is an abnormally thick but hypoechoic ridge of skin over the nuchal portion of the skull. This may be detected in the first trimester and is suggestive of, but not diagnostic of, Down syndrome (trisomy 21). Some authors believe that this thickened region represents a resolving cystic hygroma that is characteristic of many fetuses with Down syndrome. Further discussion of nuchal hypoechogenicity can be found in the “Second Trimester” section.

The placenta is due more than the typical cursory glance during the first trimester. Early detection of placenta previa is possible but should be interpreted with caution. As the lower uterine segment develops in pregnancy, placentas that were previously low lying or covering the internal cervical os may no longer occupy that precarious location. The placenta may seem to migrate away from the os. The change actually occurs due to preferential placental development in areas of improved blood flow

and regression in poorly supplied regions. Blood flow in the lower uterine segment is less marked than in the fundus, encouraging placental development away from the lower uterine segment. Other abnormalities such as succenturiate lobes and circumvallate or circummarginate placentas may also be seen in the first trimester (Fig. 8.8). In cases of suspected placenta previa, transvaginal imaging can be performed to confirm the placental location relative to the cervix. Doppler flow studies may also reveal a vasa previa, in which the fetal vessels lie across the internal cervical os. This phenomenon may occur secondary to a succenturiate lobe or velamentous umbilical cord insertion.

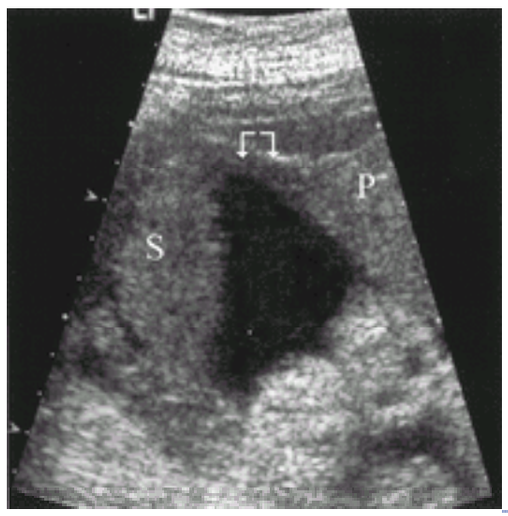

FIG. 8.8. Succenturiate lobe. The succenturiate lobe *(S)* is connected to the placenta *(P)* by the bridge of tissue and vessels.

Careful imaging of maternal anatomy should not be neglected in the excitement of finding a new pregnancy. Abnormal uterine masses such as leiomyomata (Fig. 8.9) or maternal embryologic abnormalities such as a bicornuate or septate uterus (Fig. 8.10) may be identified most easily when the pregnancy is not large enough to occlude good visualization. More unusual developments such as anterior and posterior sacculation of the uterus may be visualized, but these findings are extremely rare. Abnormalities of the adnexal structures in pregnancy may include any of the typically encountered abnormalities in the nonpregnant state. The most commonly encountered ovarian neoplasm in pregnancy is the mature teratoma or dermoid. Hemorrhagic cysts of the corpus luteum have the sonographic appearance of complex adnexal masses, but they usually will resolve over time (Fig. 8.11).

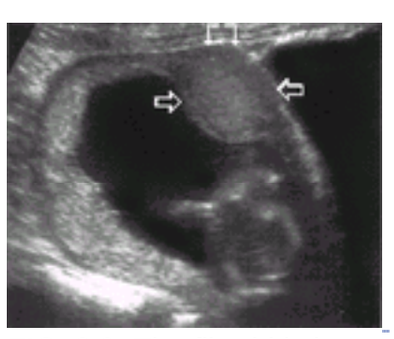

FIG. 8.9. The fibroid is located anteriorly in the uterine wall and distorts the outer contour of the uterus, which helps to differentiate this from a uterine contraction.

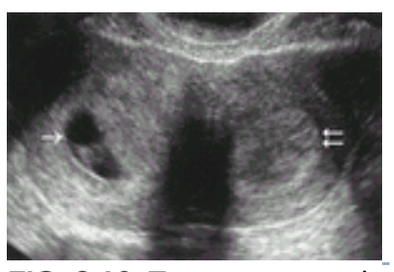

FIG. 8.10. Transverse section of a bicornuate uterus in the first trimester. The gestational sac is in the right horn and the left horn shows decidual changes.

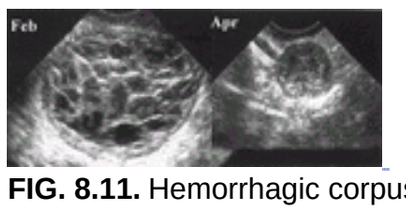

FIG. 8.11. Hemorrhagic corpus luteum cyst. In February **(Feb)** the cyst is complex, but by April **(Apr)** it has resolved and a normal ovary is present.

SECOND TRIMESTER

A complete fetal anatomic survey can be performed most comprehensively in the late second trimester. This head-to-toe examination of the fetus identifies normal fetal anatomy, many but not all structural abnormalities, and markers for aneuploidy. As previously mentioned, there is not a consensus on the best use of ultrasonography in screening for abnormal pregnancies in low-risk populations. Additional information should be used to identify patients who will benefit from ultrasonographic examination. This information includes a family history of abnormal pregnancies or genetic anomalies, teratogenic exposures, abnormal laboratory findings including the maternal serum a-fetoprotein-human chorionic gonadotropin-estriol triple test, and abnormal clinical findings in the developing pregnancy.

In some cases, the second trimester marks the first prenatal visit for patients. Such patients often will depend on ultrasonography for an accurate estimation of the gestational age. This estimation is based on ultrasonographic measurements of the BPD, head circumference (HC), abdominal circumference (AC), and femur length (FL). These values are averaged to generate a composite score that is compared with standards. Some equipment calculates the average automatically. Additional measurements that may improve the accuracy of age determination include other long bone lengths, foot length, cerebellar width, and intraocular distance.

The physician must ascertain that only normal measurements are averaged. For example, adding the abnormal measurement of a shortened femur in skeletal dysplasia to the head and abdominal measurements will produce an incorrect gestational age. Two approaches can be used to calculate the gestational age if the anatomy is abnormal. One is to omit the data from the abnormal part. For example, obtaining the estimated fetal weight of an anencephalic fetus using the ultrasound system may require the BPD or HC. Because cranial measurements will be abnormal in this case, an equation that uses only the AC and FL can be used. The other option is to substitute a normal measurement from a table containing such data for the same point in the gestation as the patient. In the case of the anencephalic fetus, the appropriate head measurements for gestational age can be found in a reference table and substituted for the abnormal measurements.

The anatomic survey seeks to identify major structures in the developing fetus. During this survey, many abnormal ultrasonographic findings may be discovered. Such findings will lead to referral or subsequent diagnosis of abnormal conditions. Table 8.3 contains only a few of the more commonly encountered findings and anomalies that warrant further investigation.

TABLE 8.3. *Abnormal ultrasonographic findings by location and potentially associated diagnoses*

DOCUMENTATION AND THE BASIC ULTRASONOGRAPHIC EXAMINATION

Standards for performing an ultrasonographic examination can be found on the Web sites of the national organizations involved in ultrasound practice: the American College of Obstetricians and Gynecologists (ACOG.org), the American Institute of Ultrasound in Medicine (AIUM.org), and the American College of Radiology (ACR.org). Because these standards are being updated continually, they are not repeated here. These standards are developed with the intention of improving patient care and assisting the physicians and sonographers performing the examinations. The flow of the basic examination is important because, with a disciplined approach, the examiner will have the opportunity to recognize a majority of congenital defects while obtaining information about the normal pregnancy. The examiner should develop a technique for performing the examination that is logical and consistent with published standards. The technique that follows is not the only method but is one that has proved helpful to the initiate and the experienced.

Standard orientation should be used. On a transverse scan, the patient's right is on the left of the image. On a longitudinal scan, the patient's head is placed on the left of the image. If standard orientation is not used, the images should be labeled to provide orientation to the interpreter. Any measurement should be accompanied by an image. Documentation can be by any combination of thermal photographs, videotape, digital images, or radiographic film. Thorough documentation of the ultrasonographic examination is imperative for providing a historical reference for future examinations, images for referrals, and a permanent record for the patient's file.

After fetal heart activity is confirmed, begin imaging in the long axis of the uterus and move to the maternal adnexae to look for ovarian and adnexal masses. The large venous complexes in the adnexae during pregnancy should not be confused with pathology. Return to the midline of the uterus, and locate and document the lowest edge of the placenta. Although this image will not help with the lateral location of the placenta, it will document anterior or posterior orientation and the extent to which the edge approaches the cervical os. A transvaginal or translabial ultrasonographic examination may be necessary to locate the lower edge of the very low-lying placenta (Fig. 8.12). Document the area of the cervix unless the bladder is overly filled. Document the placental umbilical cord insertion site in order to diagnose possible marginal or velamentous cord insertions and to assess for vasa previa. The number of vessels in the umbilical cord should be documented in a cross-section of the cord, at the fetal cord insertion, or by visualization of the umbilical arteries around the bladder (Fig. 8.13). By this point in the examination, there should be a general impression of amniotic fluid volume. An amniotic fluid index (AFI) is not required in most standards; a subjective determination is acceptable. If more examinations are anticipated during the pregnancy or there is a question about the trend in fluid volume, the AFI provides consistency among examiners.

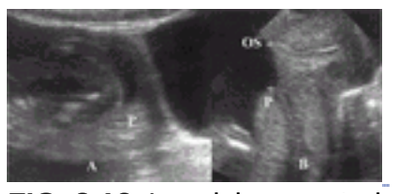

FIG. 8.12. Low-lying, posterior placenta. In **(A)** the placenta *(P)* could be mistaken for a posterior placenta previa. Transvaginal ultrasound **(B)** demonstrates the lower border of the placenta *(P)* separate from the internal os *(OS)* by the distance indicated between the plus signs *(+)*.

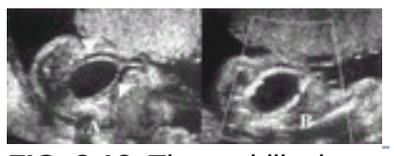

FIG. 8.13. The umbilical arteries around the fetal bladder frequently can be seen without the use of color Doppler as in **(B).**

Document the lie and presentation of the fetus with a longitudinal scan of the fetal axis. Subsequent imaging of the fetus transverse to the longitudinal fetal axis is usually most helpful. Begin with the fetal head. This provides an opportunity to diagnose cranial defects, which are both common and serious, and to locate the anatomy for the head measurements (BPD and HC) used in determining gestational age (Fig. 8.14). A normal cavum septum pellucidum eliminates the diagnoses of agenesis of the corpus callosum, hydranencephaly, hydrocephaly, holoprosencephaly, and anencephaly (Fig. 8.15). The plane used for measurements should be documented. The choroid plexuses are near the anatomic plane for the BPD. Choroid plexus cysts will appear as smooth-walled anechoic spaces within the echogenic choroid plexus (Fig. 8.16). The risk of a chromosomal anomaly with the isolated finding of choroid plexus cysts during a routine ultrasonographic examination is less than the risk associated with amniocentesis, regardless of the number or persistence of the cysts.

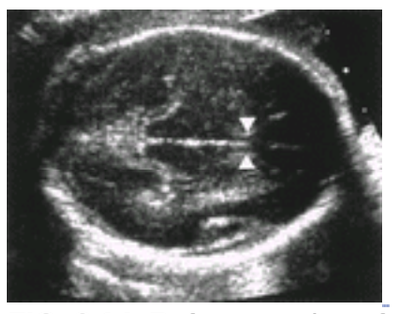

FIG. 8.14. Reference plane for the biparietal diameter and head circumference. The cavum septum pellucidum is a major landmark for this reference plane and for anomaly screening.

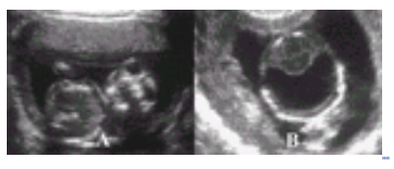

FIG. 8.15. The cavum septum pellucidum is absent in anencephaly **(A)** because the cranium and majority of the brain are absent. In holoprosencephaly **(B)** it is absent because the normal brain midline is not developed.

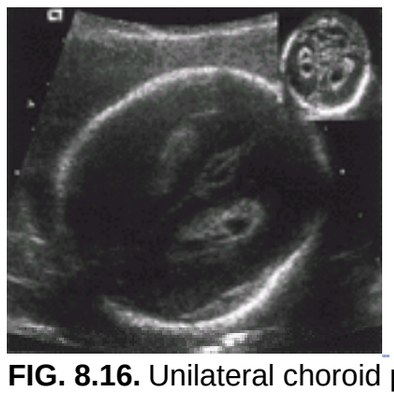

FIG. 8.16. Unilateral choroid plexus cyst. In the absence of other ultrasonographic findings or risk factors, the chances for trisomy 18 are less than the risk from an amniocentesis. This is also the case even if there are multiple or bilateral cysts **(inset).**

Posterior and inferior to the BPD plane is the cerebellum. Documentation of a normal configuration will provide assurance that there is a minimal chance of an open neural tube defect (Fig. 8.17). Slightly more inferior, the nape of the neck is visualized. Abnormalities in this area include cystic hygromas or posterior encephaloceles (Fig. 8.18). Identification of nuchal translucency, more properly termed nuchal hypoechogenicity, is accomplished in the same plane. Although the finding of nuchal hypoechogenicity in the first trimester appears to be a promising tool to screen for aneuploidy, it should be regarded as investigational. The most recent ACOG recommendation is that nuchal skin measurements should not be used clinically until better standardization is developed and more convincing data support such a practice. The fetal neck is smaller than the fetal head, so any enlargement should be evident. Fetal goiters or teratomas may be seen anteriorly (Fig. 8.19).

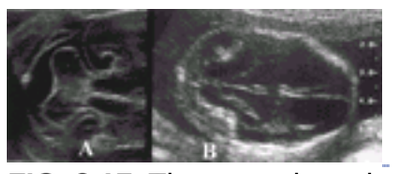

FIG. 8.17. The normal cerebellum **(A)** has a characteristic “doughnut” shape compared with the elongated cerebellum **(B)** described as the “banana sign” associated with an open neural tube defect.

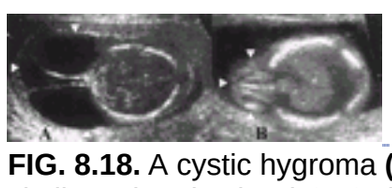

FIG. 8.18. A cystic hygroma **(A)** is more fluid filled than a cephalocele **(B)**, which contains brain tissue and generally contains a septum. Usually the bony defect in the skull can be also be detected in the latter case.

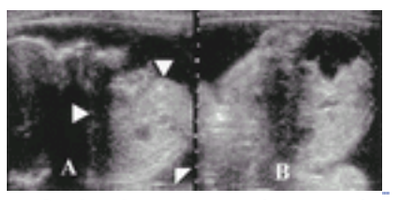

FIG. 8.19. An anterior cervical teratoma is seen in longitudinal section **(A)** and transverse **(B).** Although the diagnosis was made prenatally, intubation at delivery was unsuccessful. Tracheal compression is a significant risk with cervical tumors in the fetus and generally is the cause of death.

The upper part of the fetal chest is symmetric and consists mostly of lung tissue and the fetal thymus, which is difficult to image. The normal orientation of the fetal heart lies along a 45-degree left axis relative to the anterior-posterior thoracic diameter. The apex of the heart overlying the fetal stomach is an important relationship. Malrotations and situs inversus can be missed if careful correlation with the fetal lie is not included (Fig. 8.20). A lack of homogeneous lung tissue with or without displacement of the heart suggests cystic adenomatoid malformations, diaphragmatic hernias, teratomas, or other lesions. The fetal heart can still maintain a normal 45-degree axis but be displaced laterally by these and other anomalies (Fig. 8.21). Documentation of a normal four-chamber view eliminates the majority of fetal heart defects (Fig. 8.22). A short-axis view is not currently a requirement of a basic examination but increases the sensitivity for detecting cardiac defects.

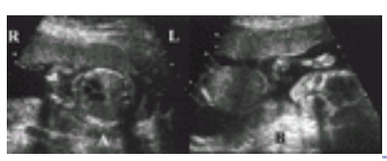

FIG. 8.20. Situs inversus. Using standard orientation, in a transverse image **(A)**, the maternal right *(R)* and left *(L)* appear on the left and right of the image, and in the longitudinal image **(B)**, the maternal feet are to the right of the image. This indicates a vertex presentation with the fetal back to the left side of the mother, which means the apex of the fetal heart points to the right side of the fetus in **(A).**

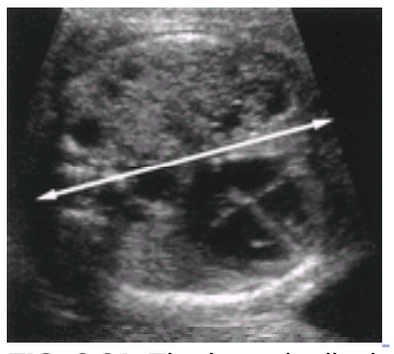

FIG. 8.21. The heart is displaced from a more central position by the cystic adenomatoid malformation in the right side of the chest, but the normal 45-degree axis of the heart is preserved. The line from the fetal spine to the sternum normally should pass through the atria.

FIG. 8.22. A normal four-chamber view **(A)** compared with the same view in Ebstein anomaly **(B)** and in transposition of the great vessels **(C).** *RV*, right ventricle; *LV*, left ventricle; *RA*, right atrium; *LA*, left atrium; *AO*, aorta; *PA*, pulmonary artery. (From Dr. Alfred Abuhamad; with permission.)

With the transducer held in the same orientation for the four-chamber heart view, move inferiorly in the fetus to locate and document the plane for the AC measurement. The fetal gall bladder, which may be seen during this transition, is one of the three anechoic areas normally seen in the fetal abdomen. The other two are the stomach and urinary bladder. The observation of additional areas requires explanation. The fetal liver occupies most of the abdominal cavity in the plane used for the circumference measurement, which is why that measurement is sensitive for fetal weight and disturbances in growth. Below the AC plane, the abdomen consists mostly of fetal bowel and the kidneys posteriorly. An image showing both kidneys is useful for eliminating unilateral agenesis, horseshoe kidney, and multicystic or polycystic kidneys (Fig. 8.23). The fetal umbilical cord insertion site should be documented. If a gastroschisis or omphalocele is present, further investigation is needed (Fig. 8.24).

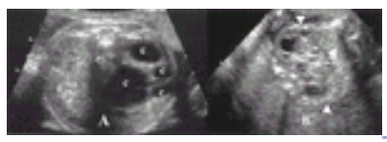

FIG. 8.23. The cysts *(c)* of the multicystic kidney **(A)** involve the left kidney. A normal contralateral kidney with normal amniotic fluid volume portends a good prognosis. In **(B)** the polycystic horseshoe-shaped kidney is accompanied by oligohydramnios, a poor prognosis.

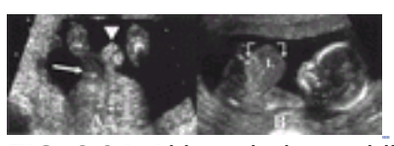

FIG. 8.24. Although the umbilical cord insertion site is normal, a gastroschisis will appear as a mass to the right of the insertion site. **B:** The umbilical cord inserts into the sac of an omphalocele which, in this case, contains fetal liver *(L).* Isolated gastroschisis is not associated with an increased risk of chromosomal anomalies, contrary to an omphalocele which has significant associated risk. A smaller omphalocele has further increased risks.

Moving caudally in the fetus, document the fetal urinary bladder. Following that image, rotate the transducer to image the femur. Although documentation of the FL suggests that a portion of the lower extremity has formed, an additional image of the fetal feet is helpful. Be aware of the orientation of the foot with respect to the tibia in order to diagnose clubfoot (Fig. 8.25). Images of the fetal hands, although difficult and not required in standards, are useful in finding soft markers of aneuploidy such as shortened phalanges, characteristic posturing of the fetal hands, or polydactyly.

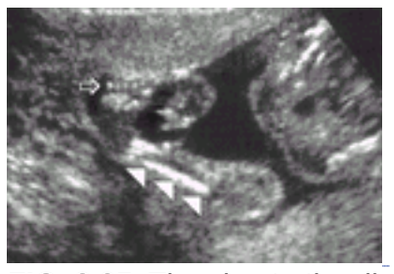

FIG. 8.25. The clue to the diagnosis of clubfoot is that the sole of the foot and the toes are in the same plane as the longitudinal axis of the leg.

THIRD TRIMESTER

There are a few anatomic structures that may be seen in the second trimester that can be visualized more easily in the third trimester. The fetal adrenal glands can be located on the superior poles of the kidneys. It is usually possible to distinguish the adrenal cortex and adrenal medulla. The lens of the eye and fetal scalp hair are more easily distinguished in the early third trimester.

Helpful adjuncts to estimation of gestational age also appear in the third trimester. Ossification of the distal femoral epiphysis occurs predictably around 32 weeks. The proximal tibial epiphysis ossifies around 35 weeks. These two ossification centers of the long bones are seen as prominent echoes distinct from the ends of the long bones. Because fetal growth rate varies widely in the third trimester, estimation of fetal weight alone may not accurately predict the gestational age. Finding the additional ossification centers of the long bones may provide more guidance for the patient who has not entered prenatal care until late in the pregnancy.

A worrisome source of third-trimester bleeding is placental abruption, which is mainly a diagnosis made on clinical grounds. In some cases ultrasonography provides information about gestational age and fetal life, allowing for more informed management decisions. In extreme cases, ultrasonography may reveal a portion of an abruption (Fig. 8.26) or a free-floating placenta and intrauterine fetal death.

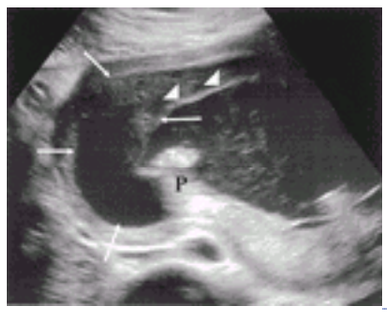

FIG. 8.26. Placental abruption. The edge of the placenta *(P)* has been elevated by the bleeding. A portion of the amnion and chorion attached to the edge appears to be floating in the uterine cavity.

Transvaginal scanning with appropriate caution in cases of undiagnosed vaginal bleeding in pregnancy can be very useful. The transducer should be inserted slowly while the sonographer watches the path of the transducer on the monitor. The ability to guide the tip of the transducer relative to maternal anatomy avoids the pitfalls of blind digital or speculum examination. Placental tissue overlying the internal os is seen clearly (Fig. 8.27), so the uncertainty of terms such as *partial placenta previa* or *low-lying placenta previa* can be avoided. The percentage of placenta overlying the internal cervical os can be reported to provide more information. The largest reportable percentage is 50%, indicating a central placenta previa (Fig. 8.28).

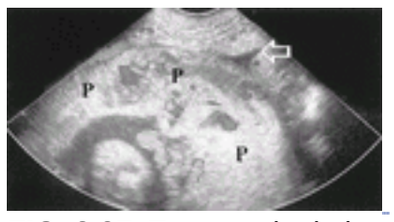

FIG. 8.27. Transvaginal ultrasonogram of a placenta previa. The placenta *(P)* covers the internal os. The tip of the transvaginal probe is in the anterior fornix. See color figure 8.27.

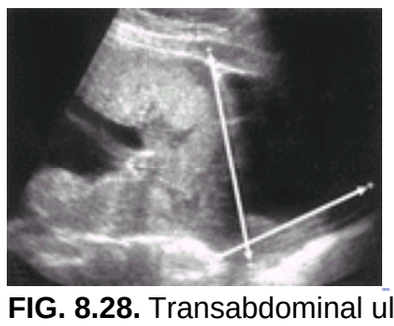
FIG. 8.28. Transabdominal ultrasonogram of a central placenta previa. The intersection of arrows indicates the approximate location of the cervix, which cannot always be visualized using transabdominal sonography. The arrows are drawn along the bladder-uterine interface and the axis of the vagina.

TECHNIQUES OF FETAL TESTING

The amount of amniotic fluid surrounding the fetus has been shown to be a very sensitive indicator of fetal status. Poor placental blood flow in cases of maternal hypertension or diabetes results in a diminished substrate for fetal kidney filtration and a subsequent decrease in the amount of fetal urine. A low AFI is one of the early indicators of such compromise, although a wide variation in the normal range is possible. Estimation of the fluid index requires measurement of the deepest vertical pocket of amniotic fluid not occupied by fetal parts or umbilical cord. This measurement is performed in each of four quadrants of the uterus. Measurements should be performed with the patient supine and the transducer held perpendicular to the floor. The sum of the four measurements expressed in centimeters equals the AFI. Two approaches have been suggested to define oligohydramnios and polyhydramnios using the AFI. One method is to use fixed values of less than or equal to 5 centimeters for oligohydramnios and greater than or equal to 18 centimeters for polyhydramnios. The second approach is to use gestational-specific percentiles below or equal to the fifth percentile for oligohydramnios and above or equal to the 95th percentile for polyhydramnios. Some authors have also proposed defining adequate amniotic fluid volume as the presence of a pocket of fluid measuring at least 2 centimeters horizontally and vertically. The method selected should depend on the experience and data from each sonographer's institution and further correlation with outcomes.

Manning and Platt described the biophysical profile (BPP) as a method for noninvasive monitoring of fetal status. There are five parts to the BPP. Four of these parameters are ultrasonographic variables that are evaluated during a 30-minute observation period: fetal breathing, fetal movement, fetal tone, and amniotic fluid volume. Fetal breathing can be observed by watching the fetal diaphragm or chest wall for characteristic breathing motion. The fetus must breathe continuously for 30 seconds during the 30-minute observation period to receive a normal score. Fetal movement of the limbs or body must occur at least 3 times to be considered adequate. Normal fetal tone is demonstrated by one active extension and flexion of the limbs or trunk. Opening and closing of the fetal hand also qualifies for a normal tone score. Slow extension of the extremity or trunk with incomplete return to flexion is not considered normal. The fourth part of the BPP is measurement of the amniotic fluid volume. Originally the normal fluid volume was described as the presence of at least one pocket of amniotic fluid measuring 1 centimeter in vertical dimension. Manning and colleagues later modified this definition to 2 centimeters measured vertically. Many centers use a normal AFI as a substitute measurement. Each ultrasonographic variable is scored zero (abnormal) or two points (normal). The fifth component of the BPP is a nonstress test, which receives a score of two points when reactive and zero when nonreactive. The best possible BPP score is ten. A detailed discussion of the use of the BPP in antepartum care can be found in Chapter 9.

Doppler velocimetry of both maternal and fetal vessels is based on the principle that sound waves returning from a moving reflector will be affected by the direction and speed of that reflector relative to the transmitting or receiving source. A reflector traveling toward the receiver will cause the return signal to be higher in frequency. The opposite is true for a reflector moving away from the receiver. Return echoes from the receding reflector will be lower in frequency than the transmitted pulse. The degree of change in the returning signal can be used to calculate the velocity (speed and direction) of the reflector. By applying this property to the red blood cell mass moving within maternal or fetal vasculature, characteristic profiles were obtained for mother and fetus. Doppler interrogation of the maternal uterine artery may reveal a characteristic notch during diastole, which is a sensitive predictor for preeclampsia during the pregnancy. The umbilical artery Doppler waveforms can be used to evaluate the resistance of the placental circuit. The systolic-to-diastolic (S/D) ratio is defined as the ratio of peak velocity in systole to the velocity nadir in diastole. This value is typically between 1.5 and 2.5 in the third trimester. As placental flow resistance increases with vascular compromise, the S/D ratio also increases. Increased resistance to the point of stopping or reversing diastolic blood flow is worrisome for fetal outcome and should prompt further evaluation (Fig. 8.29).

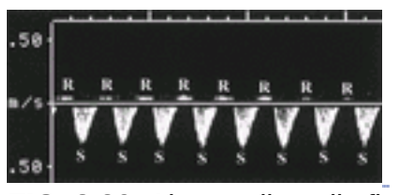

FIG. 8.29. Absent diastolic flow with or without reverse flow *(R)* is an indicator of poor fetal health. *S*, systole. (From Diana M. Strickland, RDMS, RDCS; with permission.)

INTERVENTIONAL ULTRASONOGRAPHY

Ultrasonography is now a standard adjunct for amniocentesis, chorionic villus sampling, percutaneous umbilical blood sampling (PUBS), and other invasive procedures. Amniocentesis for genetic studies generally is performed after 13 weeks gestation. The tip of the amniocentesis needle is visualized during insertion to reduce the number of attempts. Post-procedure determination of fetal heart rate usually is performed to assure that the procedure was well tolerated. Chorionic villus sampling can be performed blindly, but many providers find that the procedure is easier and less risky when transabdominal imaging provides visualization of the uterus and guidance of the catheter. PUBS depends heavily on ultrasonographic imaging to locate the placental umbilical cord insertion for needle placement, for monitoring the fetus during sampling, and for post-procedure monitoring to watch for hemorrhage.

Ultrasonographic guidance may be employed during interventional procedures for fetal benefit. Intrauterine fetal blood transfusion can be performed in severe cases of isoimmunization when the fetus is too premature to deliver. Replacement of fetal thyroid hormone in cases of maternal thyroid dysfunction can also be performed. The fetus can then be treated and followed with ultrasonography for resolution of the goiter, indicated by return of the thyroid gland to normal size. Selected obstructions of the fetal urinary tract can be bypassed with percutaneous catheters that are removed after birth. This procedure may also be performed in cases in which fluid-filled areas are found to be compressing thoracic structures (Fig. 8.30). In cases of twin-to-twin transfusion syndrome, therapeutic drainage of the polyhydramnic twin may permit the pregnancy to progress to a reasonable chance of viability.

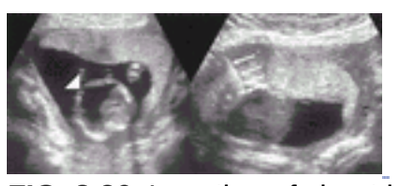
FIG. 8.30. Insertion of shunt in unilateral hydrothorax. The anechoic, fluid-filled area is drained by the needle during insertion of the shunt. The baby was delivered at term with no pulmonary complications.

FUTURE DIRECTIONS

New developments in the field of diagnostic ultrasonographic imaging include power Doppler imaging, harmonic imaging, three-dimensional (3D) ultrasonography, real-time 3D ultrasonography (often called four-dimensional [4D] imaging), compound imaging, B-flow imaging, and panoramic ultrasonographic imaging.

Power Doppler imaging uses the same principle as Doppler velocimetry. However, instead of targeting a single vessel, power Doppler imaging is used over a region of tissue. When the Doppler shift is detected in the return echoes, that region of tissue is assigned flow data that appear on the screen as colors different than those of the surrounding image. Direction of flow is not indicated. The resulting image contains a standard ultrasonographic image of the target tissue, with a color overlay representing vascular flow. This type of imaging may become useful in placental flow studies, analysis of the umbilical cord, or detection of ectopic pregnancy. Use of power Doppler should be monitored carefully, because the acoustic output increases dramatically with its use.

Harmonic imaging utilizes the harmonics of the transmitted pulse to receive double the transmitted frequency. This improves the image by removing clutter and artifact and improving resolution. This feature is very useful for the patient whose body habitus makes imaging difficult.

Three-dimensional ultrasonography relies on a special transducer that can sample tissue in multiple sections simultaneously and on computer processors that can reconstruct the data as a virtual block of tissue. This block can then be viewed at any angle and in any section. Proponents of 3D ultrasonography advocate its use in first-trimester anatomic surveys, monitoring of cervical cerclage, and evaluation of fetal surface defects such as cleft lip or myelocele. This technology requires good fetal position and a moderate amount of amniotic fluid in front of the targeted tissue in order to create adequate images. Special transducers, for both transvaginal and transabdominal imaging, are required to insonate the tissue of interest. The extra graphics processors and memory required to generate 3D images are the rate-limiting steps to producing real-time 3D ultrasonography. Also known as 4D ultrasonography, real-time 3D ultrasonography is currently in development. This technology requires the same transducers as 3D ultrasonography but uses faster processors to generate 3D images in actual real time. The same limitations apply to fetal position and amniotic fluid. It might be possible eventually to assess the functional status of fetal organs with 4D ultrasonography. The results from current research will provide the evidence for using real-time ultrasonography in different applications.

Compound imaging utilizes electronic beam focusing to emit ultrasound energy at angles to the axis of the transducer. A single target will be insonated from numerous different angles by the array of emitters across the transducer face. Shallow reflectors that would otherwise block tissue penetration are bypassed by the angled signals from and to the transducer. Reflectors from deeper in the tissue are imaged more precisely and a more detailed grayscale image is produced.

The increased resolution of modern transducers and data processing capabilities of systems have led to the development of B-flow imaging. Rather than using the Doppler effect to calculate velocities of blood flow, the B-mode function actually collects the tiny echoes emitted from blood cells. The resulting image is a real-time anatomic image combined with grayscale flow imaging. Color is not required for the display. An advantage of B-flow is the decreased exposure of the patient to ultrasound energy compared with Doppler interrogation.

Panoramic imaging relies on the ultrasound system to link a series of images into a large single image, much as a vacationer would align snapshots into a panoramic landscape photo. Although this mode is not real time, it has the advantage of displaying images much larger than the transducer's field of view.

CONCLUSION

In the changing spectrum of obstetric practice, ultrasonography has established a niche that is unlikely to be challenged significantly. It is a safe imaging modality when used properly. Numerous applications exist, from anatomic surveys to guidance during interventional procedures. The skills of the provider and the quality of the equipment have a direct impact on the sensitivity of the examination in detecting anomalies. Although the usefulness of screening every pregnant woman with an ultrasonographic examination is still in question, there is no doubt that under the guidelines of accepted medical indications, ultrasonography improves prenatal care.

SUMMARY POINTS

- Every ultrasonographic examination should be as complete as possible within the scope of the provider and the equipment.
- There is no evidence to suggest that medical ultrasonography carries a risk to the mother or fetus; nevertheless, such risks might be identified in the future. An ultrasonographic examination should be performed only when medically indicated.
- The sensitivity of ultrasonography in detecting fetal anomalies is variable and relies on the experience of the provider and the quality of equipment. Specialists with additional training in ultrasonography, such as a maternal-fetal medicine fellowship, should perform ultrasonographic examinations for abnormal findings or for genetic indications.

RECOMMENDED READINGS

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Chapter 9

Catherine Y. Spong

Fetal Monitoring

WHY PERFORM FETAL MONITORING?
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SUGGESTED READINGS
Asphyxia and Cerebral Palsy
Fetal Heart Rate Monitoring
Fetal Scalp Stimulation/Vibroacoustic Stimulation
Prolonged Decelerations in Fetal Heart Rate Baseline
Contraction Stress Test/Oxytocin Challenge Test
Modified Biophysical Profile
Fetal Scalp Blood Sampling
Doppler Ultrasound
Fetal Pulse Oximetry
Fetal Cardiotocography Plus Pulse Rate-Interval Analysis
ST Waveform Analysis

In the beginning of the 19th century, reports on the presence of fetal heart tones were published, and nearly 150 years later, continuous fetal heart rate (FHR) monitoring became a reality. By 1998, electronic fetal monitoring was used in 84% of all U.S. births, regardless of whether the primary caregiver was a physician or a midwife. With the advent of these technologies, fetal monitoring is implemented in nearly all pregnancies, either in the antepartum or intrapartum period. The challenge of fetal surveillance is to identify those fetuses whose physiological defense mechanisms are compromised, in order to be able to act before decompensation has occurred. The goal is to prevent fetal and neonatal morbidity, and especially mortality.

WHY PERFORM FETAL MONITORING?

Since its inception, the primary objective of FHR monitoring has been to identify the fetus in distress so that measures might be taken in time to avert permanent fetal damage or death. However, a clear consensus regarding the definition of “fetal distress” has not been established. It has been described as “a condition in which fetal physiology is so altered as to make death or permanent injury a probability within a relatively short period of time,” and is usually considered to denote disruption of normal fetal oxygenation, ranging from mild hypoxia to profound fetal asphyxia. The term *hypoxia* refers to the reduction of tissue oxygen supply below physiologic levels. *Asphyxia*, derived from the Greek word meaning “a stopping of the pulse,” implies a combination of hypoxia and metabolic acidosis. Historically, the clinical diagnosis of birth asphyxia has been based on findings such as meconium-stained amniotic fluid, abnormal FHR patterns, low Apgar scores, abnormal blood gases, and neonatal neurologic abnormalities. When present together, these findings are highly suggestive of a recent asphyxial insult. Isolated abnormalities, however, correlate poorly with birth-related asphyxia and subsequent neurologic impairment. In 2002, the American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy stated the criteria to define an acute intrapartum event sufficient to cause cerebral palsy.

Essential criteria (must meet all four):

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH <7 and base deficit =12 mmol/L).
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation.
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type.
4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, eg., 0–48 hours) but are nonspecific to asphyxial insults:

1. A sentinel (signal) hypoxic event occurring immediately before or during labor.
2. A sudden and sustained fetal bradychardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal.
3. Apgar scores of 0–3 beyond 5 minutes.
4. Onset of multisystem involvement within 72 hours of birth.
5. Early imaging study showing evidence of acute nonfocal cerebral abnormality.

At the cellular level, asphyxia triggers a cascade of events, including membrane depolarization, disruption of energy metabolism, altered neurotransmission, ion shifts, protease activation, free radical production, and phospholipid degradation. Profound and prolonged asphyxia may result in cell death and, eventually, death of the organism. Sublethal asphyxia may lead to multi-organ system dysfunction. Severe asphyxial brain injury may lead to long-term neurodevelopmental impairment.

Cerebral palsy (CP) is a major disorder of neurodevelopment, defined as “a chronic disability, characterized by aberrant control of movement and posture, appearing early in life and not the result of recognized progressive disease.” It may be accompanied by mental retardation (41%), seizures (23%), or cortical visual impairment. The insult responsible for the development of CP may occur at any time during the prenatal, perinatal, or postnatal periods. Unlike other major neurodevelopmental disorders, the relationship between CP and abnormal or difficult birth has long been recognized, publicly dating back to a treatise presented by William John Little in 1862. In 1943, Windle demonstrated clinical and histopathologic evidence of neural damage in experimentally asphyxiated fetal guinea pigs. He later reported the effects of prolonged anoxia on fetal rhesus monkeys. Total anoxia for less than 8 minutes did not produce consistent injury, whereas anoxia for more than 10 minutes invariably resulted in neuropathology. There were no survivors beyond 20 to 25 minutes of anoxia. The pattern of injury produced by prolonged anoxia, however, did not correlate with the cerebral injury, mental retardation, and spasticity seen in CP. Later work demonstrated that prolonged partial asphyxia in monkeys produced acidosis, late FHR decelerations, and neuropathologic defects consistent with the findings in the common forms of CP. In addition to lesions in the thalamus and basal ganglia, prolonged partial asphyxia caused generalized cerebral necrosis or focal necrosis in the parasagittal regions and the border zones between the parietal and occipital lobes.

Although early studies created and fostered the assumption that birth-related asphyxia was the primary cause of CP, recent evidence challenges this assumption. In 1986, Nelson and Ellenberg reported a multivariate analysis of risk in 189 cases of CP. After accounting for major congenital malformations, low birth weight, microcephaly, and alternative explanations for the disorder, they were able to attribute only 9% of CP cases to birth asphyxia. Others have reached similar conclusions. Although birth asphyxia nearly tripled the odds of developing CP, only 8.2% of CP cases were potentially attributable to birth asphyxia.

As early as the 19th century, researchers using auscultation recognized that certain FHR patterns were associated with adverse perinatal outcome. The introduction of

direct electronic fetal monitoring and fetal scalp blood sampling in the 1960s provided tools for evaluating the fetus. FHR decelerations have been found to be correlated with fetal acidosis. Fetuses with no decelerations, early decelerations, or mild variable decelerations had average scalp pH values greater than or equal to 7.29, whereas those with severe variable or late decelerations had pH values less than or equal to 7.15. In addition, FHR variability was found to be correlated with scalp pH values as fetuses with normal FHR variability had higher scalp pH values than those with decreased variability. The absence of FHR accelerations was correlated with poor perinatal outcome and the presence of FHR accelerations has been shown to predict normal scalp pH values. With the development of indirect monitoring techniques, the experience derived from direct intrapartum monitoring became applicable to the antepartum period, leading to the development of antepartum testing.

Antepartum fetal monitoring has the goal of identifying the fetus at risk, allowing sufficient time to intervene before permanent injury or death occur. Intrapartum fetal monitoring should be able to identify three groups of fetuses:

- the fetus that is not affected by labor
- the fetus that is negatively affected by labor but has enough reserve to compensate fully and is in no immediate danger
- the fetus that is negatively affected and lacks the reserve to compensate, thus uses its key resources to survive and is in danger for morbidity/mortality.

It is the third group that would most benefit from intervention.

WHO SHOULD BE MONITORED?

Antepartum fetal monitoring is typically offered to patients at increased risk of fetal or neonatal morbidity/mortality. These include maternal medical complications (e.g., diabetes mellitus, chronic hypertension, systemic lupus erythematosis), fetal conditions (Rh isoimmunization, fetal growth restriction), and pregnancy complications (multiple gestation, oligohydramnios). Overall, the studies supporting the methods of testing, the timing, and initiation are extremely varied; thus absolute guidelines based on scientific evidence cannot be established. However, recommended gestational ages for initiation of testing, timing, and methods for specific maternal conditions, and the supportive evidence can be found in Table 9.1.

Uterine activity assessment
Contraction frequency
Contraction duration
Baseline uterine tone
Contraction strength
Fetal heart rate assessment
Baseline rate
Tachycardia
Bradycardia
Sinusoidal pattern
Variability
Increased variability
Average or normal variability
Decreased variability
Absent variability
Periodic patterns
Accelerations
Decelerations
Early decelerations
Variable decelerations
Late decelerations

TABLE 9.1. *General guidelines for initiation of antenatal testing*

Intrapartum fetal monitoring has remained controversial since its inception. The FHR many be evaluated by auscultation or by electronic monitoring. Auscultation is typically performed with a DeLee stethoscope or Doppler ultrasound. Electronic monitoring can be either performed externally or internally, external monitors use a Doppler device with computerized logic to interpret and count the signals. Internal monitoring uses a fetal electrode that records the fetal electrocardiogram (ECG). Well-controlled studies have shown the equivalence of intermittent auscultation to continuous fetal heart monitoring when auscultation was performed at specific intervals with a 1:1 nurse-to-patient ratio. The intensity of monitoring is based on risk factors, with more intensive surveillance required for high-risk pregnancies.

WHAT CAN WE MONITOR?

Fetal Heart Rate

The FHR can be monitored and recorded indirectly through the use of an ultrasound transducer or directly via a subcutaneous ECG electrode placed on the fetus (Fig. 9.1). The indirect method can be used throughout pregnancy and has no contraindications. Using the indirect method, ultrasound waves originating from the transducer penetrate the tissues and are reflected by tissue interfaces. Waves reflected from the moving structures of the fetal heart return to the transducer and are translated into electrical signals. In the direct method, the subcutaneously placed ECG electrode detects electrical impulses originating in the fetal heart. Amplified signals are processed by a cardiotachometer, comparing each incoming QRS complex to the one immediately preceding it. The interval between the two complexes is used to calculate a heart rate. The process is repeated with each cardiac cycle yielding a graphic beat-to beat display of the FHR. The direct method requires rupture of the fetal membranes for placement of the ECG electrode. In addition, in light of the potential risk of infection, the electrode for direct assessment should only be used when the benefits outweigh this risk.

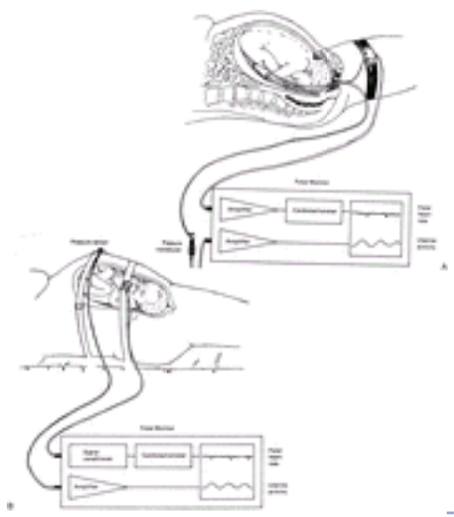

FIG. 9.1. Direct and indirect fetal monitoring. **A:** Direct method. Recordings are made from a fetal electrocardiograph electrode applied directly to the fetus. A transcervical intrauterine pressure catheter is used to monitor the strength of uterine contractions. **B:** Indirect method. The fetal heart rate is derived from a Doppler ultrasound transducer applied to the maternal abdominal wall. A pressure sensor (tocodynamometer) detects uterine contractions. (Courtesy of Richard H. Paul.)

Uterine Activity

Similar to FHR, the detection and measurement of uterine activity can be performed indirectly or directly (see Fig. 9.1). Indirect assessment of uterine activity is performed with a pressure ransducer (tocodynamometer) applied tightly to the maternal abdomen over the uterine fundus. Uterine contractions exert pressure on the abdominal wall that is transmitted to the tocodynamometer. Changes in pressure are converted into signals and plotted on the uterine activity graph. The indirect method is noninvasive and can be performed at any time during pregnancy. The limitations of the indirect method are that the readout can only be used to determine contraction frequency, not strength of the contraction (a tightly fit belt will record larger contractions than a loosely fitting or misplaced belt) and the ability to detect contractions in extremely obese women may be difficult. Direct assessment of uterine activity employs a thin, flexible intrauterine pressure catheter (IUPC) placed transcervically into the amniotic cavity. Intrauterine pressure is transmitted from the amniotic fluid through the fluid-filled IUPC to a pressure transducer. The transducer converts pressure measurements into electrical signals, and continuous pressure readings are displayed on the uterine activity graph. The direct assessment is invasive and requires ruptured membranes. Aside from some research indications, the IUPC should only be used in patients when the benefits outweigh the risk of infection. The direct method allows the readout of both the frequency and the strength of the uterine contractions. This can be especially useful in the evaluation and

assessment of patients with prolonged labor.

Fetal State (Tone/Breathing/Movements)

Using real-time ultrasound, the state of the fetus can be evaluated. Typically included in this evaluation are assessments of fetal tone, movements, and breathing. Fetal voiding and swallowing can also be evaluated. Specific assessments of fetal tone, breathing, and movements are discussed later in the chapter “Biophysical Profile.”

Amniotic Fluid Volume

The volume of amniotic fluid is a measure of fetal well-being. By the second trimester the predominant source of amniotic fluid is fetal urine. The level of amniotic fluid is thought to represent “long-term” fetal well-being. A compromised fetus will preferentially shunt blood to the major organs (central nervous system, adrenals) and away from others, such as the kidney. Decreased fetal renal perfusion results in a decrease in fetal renal function and subsequent oligohydramnios. The amniotic fluid can be assessed ultrasonongraphically. There are a number of methods to quantitate the volume, including the amniotic fluid index, single deepest pocket, two-dimensional pocket, and a subjective assessment.

HOW DO WE MONITOR?

Equipment

The fetal monitor tracing is a continuous paper strip composed of two Cartesian graphs. The FHR tracing is displayed on the upper graph, with time on the x-axis and heart rate on the y-axis (range 30 to 240 beats per minute). Uterine activity is displayed on the lower graph, with time on the x-axis and pressure on the y-axis (range 0 to 100 mm Hg). Heart rate and uterine activity are plotted separately on the heat-sensitive paper by two thermal pens. On both grids, fine vertical lines represent 10-second intervals, and heavy lines denote 1-minute intervals. In the United States, the standard paper speed is 3 cm per minute.

INTERPRETATION OF THE FETAL MONITOR

Analysis of the fetal monitor strip requires a systematic approach. First, the FHR is analyzed with respect to (a) the baseline, (b) variability, and (c) periodic patterns, including FHR accelerations and decelerations (Table 9.2). Uterine activity is evaluated with attention to the frequency, duration, and strength of contractions, as well as the baseline uterine tone between contractions.

Uterine activity assessment
Contraction frequency
Contraction duration
Baseline uterine tone
Contraction strength
Fetal heart rate assessment
Baseline rate
Tachycardia
Bradycardia
Sinusoidal pattern
Variability
Increased variability
Average or normal variability
Decreased variability
Absent variability
Periodic patterns
Accelerations
Decelerations
Early decelerations
Variable decelerations
Late decelerations

TABLE 9.2. *Fetal monitor interpretation*

FETAL HEART RATE INTERPRETATION

Baseline Fetal Heart Rate

The normal FHR baseline ranges from 120 to 160 beats per minute. Early in pregnancy, it is closer to 160 beats per minute, declining as gestational age advances. Likewise, the FHR may decrease gradually toward 120 beats per minute during the course of labor. An FHR baseline below 120 beats per minute is termed *bradycardia*, and a rate in excess of 160 beats per minute is termed *tachycardia.* Abnormalities in the FHR baseline may have very different causes and consequences. It is important therefore to characterize the underlying etiology as accurately as possible and to institute appropriate therapy at the earliest possible time.

Bradycardia Bradycardia is defined as an abnormally low baseline FHR (< 120 beats per minute) and must be differentiated from the episodic FHR changes characteristic of decelerations. Although FHR decelerations are very common, true fetal bradycardia is not. A bradycardic FHR baseline between 100 and 120 beats per minute observed in association with otherwise reassuring FHR patterns probably represents a normal variant. Rarely, fetal bradycardia may be seen in association with maternal ß-blocker therapy, hypothermia, hypoglycemia, hypothyroidism, or fetal cardiac conduction defects (congenital atrioventricular block). Documentation of fetal heart block should prompt a search for structural fetal cardiac abnormalities, which may be present in 20% of cases. Other causes of heart block include viral infections (e.g., cytomegalovirus) and damage to the cardiac conduction system by transplacental passage of maternal anti-Ro (anti–SS-A) antibodies. Most congenital causes of fetal bradycardia do not present as abrupt changes in the FHR and rarely require emergency intervention. Any abrupt decline in the FHR below 120 beats per minute more likely represents a deceleration than a change in the baseline, and should be considered pathologic until proven otherwise.
Tachycardia Fetal tachycardia has many possible etiologies. Most often, it is the result of decreased vagal or increased sympathetic outflow, associated with fever, infection, fetal anemia, or fetal hypoxia. Other causes include maternal hyperthyroidism, fetal tachyarrhythmias (e.g., paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter, and ventricular tachyarrhythmias), and medications including sympathomimetics (e.g., ritodrine, terbutaline) and parasympatholytics (e.g., atropine, phenothiazines).
Sinusoidal Pattern The sinusoidal FHR pattern is an uncommon FHR baseline abnormality. It has the appearance of a smooth sine wave with an amplitude of 5 to 15 beats per minute and a frequency of 2 to 5 cycles per minute. There is little beat-to-beat variability, and accelerations are absent. Although the pathophysiologic mechanism is unclear, this pattern classically is associated with hypoxia and severe fetal anemia. Additionally, it has been reported in association with fetomaternal hemorrhage, chorioamnionitis, fetal sepsis, and administration of narcotic analgesics. A persistent sinusoidal pattern that is not attributable to medications is a concerning finding and demands immediate evaluation.

Fetal Heart Rate Variability

Variability in the FHR results from constant interplay between the sympathetic and parasympathetic arms of the fetal autonomic nervous system. Modulation of vagal tone occurs in response to changes in blood pressure detected by baroreceptors in the fetal aortic arch. Oxygen and carbon dioxide fluctuations, detected by chemoreceptors in the carotid bodies, similarly influence vagal outflow. In the absence of stress, sympathetic outflow is thought to be relatively tonic. Continual adjustments in vagal tone are manifested in the FHR tracing as “short-term” (beat-to-beat) variability superimposed on broader, cyclical fluctuations of 3 to 5 cycles per minute, referred to as “long-term” variability. In clinical use, the term *FHR variability* refers to the composite of short-term and long-term variability and is quantitated by measuring the difference between the peaks and troughs of the long-term fluctuations (Fig. 9.2). FHR variability is considered normal or average when both short-term and long-term variability are present, and the difference between the peaks and troughs of the long-term fluctuations is 6 to 25 beats per minute. Average variability reflects a nonacidotic vagal connection between the fetal central nervous system (CNS) and the cardiac conduction system. Increased variability (more than 25 beats per minute), or *saltatory* FHR pattern, is uncommon and most often represents an exuberant autonomic response of a normal fetus. On occasion, it may reflect increased catecholamine release in the early stages of fetal hypoxia. Careful evaluation of the associated FHR findings should help to clarify such cases. Decreased (3 to 5 beats per minute) or absent (0 to 2 beats per minute) FHR variability reflects diminished fetal CNS activity, usually attributable to fetal sleep cycles or to medications administered to the mother (e.g., analgesics, magnesium sulfate, benzodiazepines, phenothiazines, atropine). Persistently decreased variability, however, may signal fetal acidosis. This is particularly true in the presence of other FHR findings suggestive of hypoxia, including tachycardia, loss of reactivity, or repetitive decelerations.

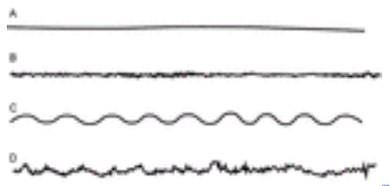

FIG. 9.2. Fetal heart rate variability. **A:** Short-term variability absent, long-term variability absent—abnormal. **B:** Short-term variability present, long-term variability absent—abnormal. **C:** Short-term variability absent, long-term variability present—abnormal. **D:** Short-term variability present, long-term variability present—normal.

Periodic Patterns

The FHR baseline is frequently interrupted by accelerations or decelerations in rate. These periodic patterns have important clinical implications regarding the well-being of the fetus.

Accelerations Accelerations in the FHR occur with 90% of fetal movements as early as the second trimester, probably as a result of increased catecholamine release and decreased vagal stimulation of the heart (Fig. 9.3). By 32 weeks gestation, nearly all normal fetuses will have 15 to 40 spontaneous accelerations per hour, reflecting normal oxygenation of the CNS–cardiac axis. The frequency and amplitude of accelerations may be diminished by fetal sleep states, medications (narcotics, magnesium sulfate, atropine), prematurity, or fetal acidosis. Often, fetal scalp stimulation or vibroacoustic stimulation will provoke fetal movement and FHR accelerations. If these measures fail to induce FHR accelerations, hypoxia should be suspected, particularly if other FHR characteristics are not reassuring.

FIG. 9.3. Fetal heart rate accelerations.

Decelerations Decelerations in the FHR are most commonly encountered during the intrapartum period. They are divided into three categories: early, variable, and late decelerations (Fig. 9.4). Classification is based on the characteristic appearance of the deceleration and its temporal relationship to the onset of a uterine contraction.

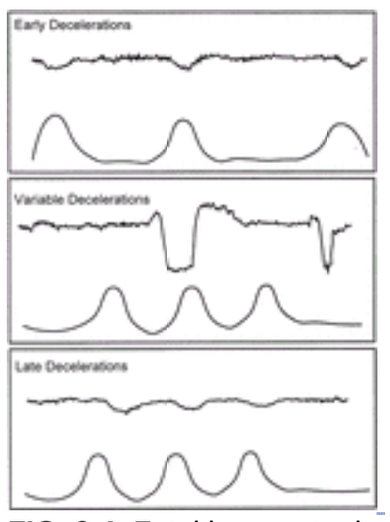

FIG. 9.4. Fetal heart rate decelerations.

Early Decelerations Early decelerations are typically uniform, shallow dips in the FHR (rarely below 100 beats per minute) that mirror uterine contractions, beginning at the onset of the contraction and ending when the contraction ends. They are thought to result from fetal head compression, transient elevation of intracranial pressure, and reflex augmentation of vagal tone. Early decelerations classically appear during labor when the cervix is dilated 4 to 6 cm. Perinatal outcome is not adversely affected by these decelerations, and they are considered clinically benign.

Variable Decelerations and Prolonged Decelerations Variable decelerations result from umbilical cord compression. They are abrupt and angular in appearance and have a variable temporal relationship to uterine contractions. As the umbilical cord is compressed, the thin-walled, compliant umbilical vein is the first vessel occluded, resulting in decreased fetal venous return, relative hypovolemia, and a reflex increase in the FHR. This observation often is termed a “shoulder.” Further compression of the umbilical cord leads to occlusion of the umbilical arteries, removing the low-resistance placenta from the circuit and dramatically increasing fetal peripheral resistance. This leads to elevation of the fetal blood pressure and a baroreceptor-mediated slowing of the FHR in an attempt to return the blood pressure to normal. Maximum vagal tone may result in a junctional or idioventricular escape rhythm that appears as a relatively stable rate of 60 to 70 beats per minute at the nadir of the deceleration. As cord compression is relieved, this sequence of events occurs in reverse, at times resulting in transient tachycardia or “overshoot” at the end of the deceleration. Variable decelerations are classified as:

- Mild—duration less than 30 seconds, depth of deceleration less than 70 beats per minute
- Moderate—duration 30 to 60 seconds, depth less than 70 beats per minute
- Severe—duration greater than 60 seconds, depth less than 70 beats per minute.

Isolated, infrequent variable decelerations have little clinical significance. Repetitive severe variables, however, may not allow sufficient fetal recovery between decelerations, resulting in persistent hypoxemia, hypercapnia, and respiratory acidosis. Prolonged tissue hypoperfusion may lead to metabolic acidosis and, ultimately, fetal death. In animal models, Clapp reported that frequent episodes of hypoxemic stress, produced by intermittent umbilical cord occlusion over a period of hours, produced fetal injury even in the absence of acidosis. When repetitive, severe variable decelerations are present, prolapse of the umbilical cord must be excluded. Other causes include nuchal cord, true knot in the cord, uterine rupture, placental abruption, uterine hypertonus, and tachysystole. Occasionally, variable decelerations fail to return promptly to the baseline and may more accurately be termed *prolonged* decelerations. Prolonged decelerations usually result from umbilical cord compression (cord prolapse, nuchal cord) or other acute interruption of uteroplacental transfer of oxygen (tetanic contraction, uterine rupture, maternal hypotension, maternal apnea, placental abruption).

Late Decelerations Late decelerations reflect inadequate uteroplacental transfer of oxygen during contractions. Typically, they are smooth, uniform decelerations that begin after the onset of a contraction and end after the contraction stops. During uterine contractions, decreased maternal perfusion of the uteroplacental unit causes a decline in fetal PO_2. Fetal PO_2 levels below a critical threshold of 15 to 18 mm Hg trigger a complex chemoreceptor- and baroreceptor-mediated reflex. Initially, centralization of blood volume (favoring perfusion of the brain, heart, and adrenals) occurs via vasoconstriction in the vascular beds of the limbs and gut. The resulting increase in peripheral resistance provokes a reflex deceleration in the FHR. Isolated late decelerations within an otherwise normal tracing have little clinical significance. However, repetitive hypoxemia and centralization of blood volume, as evidenced by repetitive late decelerations, may force hypoperfused tissues to convert from aerobic to anaerobic metabolism. Organic acid by-products of anaerobic metabolism (pyruvate, lactate) diffuse slowly across the placenta and may accumulate in the fetus, leading to metabolic acidosis, asphyxia, and possibly death. Late decelerations may be caused by any factor that (a) reduces the normal placental transfer of oxygen or (b) increases the fetal oxygen demand beyond the available supply. Such factors include uterine hypertonus or tachysystole (oxytocin, prostaglandins, uterine rupture, placental abruption), maternal hypertension (chronic hypertension, preeclampsia, collagen vascular disease, renal disease, diabetes), suboptimal maternal cardiac output (cardiac disease, hypovolemia, supine hypotension, sympathetic blockade from regional anesthesia, sepsis), maternal hypoxia (apnea, cardiac disease, pulmonary disease), reduced oxygen-carrying capacity of maternal blood (anemia, hemoglobinopathy), and fever (increased fetal metabolism and increased oxygen consumption).

Uterine Activity Uterine activity is evaluated with attention to the frequency, duration, and strength of contractions, as well as the baseline uterine tone between contractions. The frequency is assessed by counting the number of contractions as recorded over a period of time. The normal frequency of uterine contractions during labor is every 2 to 3 minutes; however, cervical change may result from contractions occurring less frequently. In most cases, five to seven uterine contractions within a 15-minute period reflect adequate uterine activity. Increased contraction frequency is termed uterine tachysystole and is defined by six or more uterine contractions within a 10-minute window for two consecutive windows. Tachysystole may be seen in cases of placental abruption or hyperstimulation of the uterus by oxytocin or prostaglandin cervical-ripening agents. The duration is assessed by calculating the length of the contraction, the fine vertical lines represent 10-second intervals, and heavy lines denote 1-minute intervals (run at 3 cm per minute). Normal uterine contractions last approximately 40 to 60 seconds. Prolonged contractions may result from “coupling” of contractions, uterine hyperstimulation, or acute complications such as placental abruption or uterine rupture. The strength of the contractions can only be assessed with the direct IUPC. The normal baseline uterine pressure between contractions is approximately 10 mm Hg. Abnormally high baseline pressures in excess of 20 mm Hg may result from hyperstimulation or occasionally from overdistention of the uterus by excessive amnioinfusion, polyhydramnios, or fetal macrosomia. During contractions, normal uterine pressure ranges from 30 to 80 mm Hg, although pressures in excess of 80 mm Hg may be observed during the second stage of labor. A calculation of the strength of the contraction is based on the sum of contraction pressures (peak minus baseline) and is expressed in Montevideo units. For example, four contractions in a 10-minute window, each 50 mm Hg above the baseline, would yield 200 Montevideo units. Montevideo units in

excess of 180 to 200 usually are considered to reflect adequate uterine activity to effect cervical change in labor.

Antepartum Testing/Fetal Monitoring Early in its development, electronic FHR monitoring required direct access to the fetus and was limited to the intrapartum period. Later, Doppler ultrasound technology made it possible to monitor the FHR before labor. The experience gained from intrapartum monitoring was applied to the antepartum period and led to the development of antepartum testing. The goals of antepartum testing are (a) to identify fetuses in jeopardy so that permanent injury or death might be prevented and (b) to identify healthy fetuses so that unnecessary intervention might be avoided. The key measure of the effectiveness of an antepartum test is the false-negative rate, defined as the incidence of fetal death within 1 week of a normal antepartum test. Reported false-negative rates range from 0.4 to 1.9 per 1000 with current testing methods. Another important measure is the false-positive rate. A false-positive test may be defined as an abnormal test that prompts delivery but is not associated with evidence of acute fetal compromise (e.g., meconium-stained amniotic fluid, intrapartum fetal distress, low Apgar scores) or chronic fetal compromise (e.g., fetal growth restriction). False-positive rates range from 30% to 90% with current testing methods. Antepartum testing is used primarily in patients who are considered to be at increased risk for fetal hypoxia or asphyxia secondary to suboptimal uteroplacental transfer of oxygen. It is expected that the use of antepartum testing in these high-risk patients will reduce their risk of fetal/neonatal morbidity/mortality to the level of the low-risk patient. The optimal gestational age at which to begin antepartum testing is not known and varies according to the underlying condition. However, for most medical indications, testing is initiated by 32 to 34 weeks. In view of the high false-positive rates of most testing protocols, earlier initiation of testing should be expected to increase the incidence of unnecessary intervention and iatrogenic prematurity, with its attendant complications.

Fetal Movement Counts Maternal perception of normal fetal movement has long been recognized as a reliable indicator of fetal well-being. Conversely, prolonged absence of fetal movement may signal fetal death. Cessation of fetal movement in response to hypoxia has been demonstrated in animal studies; however, controlled data in human fetuses are lacking. Nevertheless, any acute decrement in the number or strength of fetal movements should raise the suspicion of fetal compromise and should prompt further evaluation. Many clinicians recommend routine fetal movement counting, particularly in patients who are considered high-risk. A common approach is to recommend daily counting of fetal movements for 1 hour. Ten fetal movements in a 1-hour period are considered reassuring. If fewer than 10 movements are appreciated, counting is continued for another hour. Fewer than 10 movements in a 2-hour period should alert the patient to contact her physician for further evaluation. Another protocol calls for movement counting two to three times daily for 30 minutes. With this approach, further evaluation is recommended if there are fewer than four strong movements in a 30-minute period. Although controlled trials in low-risk patients have not demonstrated a significant benefit of formalized movement counting over routine questioning during prenatal visits, evidence from one study using nonconcurrent controls suggests a lower rate of fetal death and a higher incidence of intervention for fetal distress in patients using a formalized protocol of fetal movement counting. Fetal movement counting is an inexpensive method of involving the patient in her own care and may be a valuable adjunct to routine prenatal care, regardless of risk category. Some fetal monitors have the capability to display a Doppler-detected fetal movement profile. This technology may aid the clinician in determining the true baseline FHR and has been shown to reduce the incidence of nonreactive nonstress tests by half.

Nonstress Test FHR accelerations occurring in association with fetal movements form the basis of the nonstress test (NST). Although many criteria have been reported, a normal or “reactive” NST usually is defined by two accelerations in a 10- to 20-minute period, each lasting at least 15 seconds and peaking at least 15 beats per minute above the baseline. In most institutions, the test is repeated once or twice weekly. Boehm and colleagues (1986) reported that the latter approach yielded a three-fold reduction in the incidence of fetal death, although the difference was not statistically significant. Freeman and co-workers (1982) reported a false-negative rate of 1.9 per 1000 among 1542 women tested weekly with the NST. Manning and associates (1983) reported an average false-negative rate of 6.4 per 1000 among nine large clinical trials using the NST as the primary method of surveillance. Assessment of FHR characteristics other than reactivity (baseline rate, variability, decelerations) may improve the sensitivity of the test. The findings from an NST must be interpreted in the context of the pregnancy. Preterm infants commonly do not meet the 15 beats per 15 seconds criterion for reactivity. Once the fetus is 34 weeks, the tracing should be reactive. However, once a fetus demonstrates FHR reactivity, even if earlier than 34 weeks gestation, it should continue to have reactive tests. Reported false-positive rates of the NST vary widely, with an average rate of approximately 50%. When performed twice weekly and interpreted in the context of associated FHR patterns, the NST alone appears to be an acceptable, though not optimal, method of antepartum testing. Advantages include ease of use and interpretation, low cost, and minimal time requirement. The chief disadvantages include a high false-positive rate and a higher false-negative rate than achieved with other methods. Commonly the NST is used as a screening test, and if abnormal, a backup test such as the contraction stress test or biophysical profile is used.

Contraction Stress Test and Oxytocin Challenge Test The first antepartum testing technique, the contraction stress test (CST) or oxytocin challenge test (OCT), arose from intrapartum observations linking late FHR decelerations with poor perinatal outcome. The test sought to identify uteroplacental insufficiency by demonstrating late decelerations in fetuses exposed to the stress of spontaneous (CST) or induced (OCT) uterine contractions. Late decelerations occurring during uterine contractions were associated with increased rates of fetal death, growth retardation, and neonatal depression. The CST is performed weekly and is considered negative if there are at least three uterine contractions in a 10-minute period with no late decelerations on the tracing. Failure to produce three contractions within a 10-minute window or inability to trace the FHR results in an unsatisfactory test. Prolonged decelerations, variable decelerations, or late decelerations occurring with fewer than half of the contractions constitute a suspicious or equivocal test. Unsatisfactory, suspicious, or equivocal tests require repeat testing the following day. The CST or OCT is considered positive when at least half of the contractions during a 10-minute window are associated with late decelerations. Freeman and colleagues (1982) tested more than 4600 women with the CST and reported a false-negative rate of 0.4 per 1000. When the last test before delivery was a reactive, negative CST, the perinatal mortality rate was 2.3 per 1000, compared to a mortality rate of 176.5 per 1000 when the last test was a nonreactive, positive CST. Reported false-positive rates for the CST range from 8% to 57%, with an average of approximately 30%. Principal advantages of this form of testing include excellent sensitivity and a weekly testing interval. Limitations include a high rate of equivocal results requiring repeat testing, increased expense and inconvenience (particularly if oxytocin is required), and increased time requirement compared to the NST. Additionally, use of the CST is contraindicated in several clinical settings, including preterm labor, placenta previa, vasa previa, cervical incompetence, multiple gestation, and previous classic cesarean section.

Biophysical Profile The biophysical profile (BPP) assesses five biophysical variables: FHR reactivity, fetal movement, tone, and breathing reflect acute CNS function, while amniotic fluid volume serves as a marker of the longer-term adequacy of placental function. Two points are assigned for each normal variable and zero for each abnormal variable for a maximum score of 10. A BPP score of 8 to 10, with normal amniotic fluid volume, is considered normal. A score of 6 is considered suspicious, and testing usually is repeated the following day. Scores less than 6 are associated with increased perinatal morbidity and mortality; they usually warrant hospitalization for further evaluation or delivery. Among 12,620 women tested weekly using the BPP, Manning and co-workers reported a false-negative rate of 0.6 per 1000. The false-positive rate of the BPP varies with the score of the last test prior to delivery. Manning and co-workers reported a false-positive rate of zero among 11 patients in whom the last BPP score before delivery was zero, compared to a false-positive rate greater than 40% among 182 patients with a last BPP score of 6. The BPP is a reliable predictor of fetal well-being. The false-negative rate is superior to that of the NST alone and compares favorably with the false-negative rate of the CST. Advantages of BPP include excellent sensitivity, a weekly testing interval, and a low false-negative rate. The primary limitation is the requirement for personnel trained in sonographic visualization of the fetus. Additionally, although the duration of ultrasound observation is less than 10 minutes in the majority of cases, the complete BPP is more time-consuming than other noninvasive tests.

Modified Biophysical Profile The modified biophysical profile (MBPP) combines the strengths of the NST (ease of use, low cost) and the complete BPP (improved sensitivity, low false-negative rate), while minimizing the requirement for additional training in sonographic visualization of the fetus. The test is performed once to twice weekly and uses the NST as a short-term marker of fetal status and the amniotic fluid index (AFI) as a marker of longer-term placental function. Interpretation of the NST incorporates assessment of reactivity, baseline rate, variability, and FHR decelerations. Late, prolonged, or significant variable decelerations, particularly in the setting of borderline amniotic fluid volume (AFI 5 to 10 cm), are considered abnormal. Regardless of reactivity, oligohydramnios (AFI < 5 cm) constitutes an abnormal test. Nageotte and co-workers (1994) evaluated 2774 high-risk pregnancies with twice weekly MBPPs and reported one unexplained fetal death within 1 week of a normal test result, for a false-negative rate of 0.36 per 1000. Miller and colleagues (1996) reported 54,617 MBPPs in 15,482 high-risk pregnancies. Antepartum testing in high-risk pregnancies yielded a fetal death rate that was nearly sevenfold lower than that in the untested, low-risk population. The overall false-negative rate of the MBPP was 0.8 per 1000, and the false-positive rate was 60%. Abnormal test results prompted intervention in 15.5% of the tested population; however, iatrogenic prematurity occurred in only 1.5% of women tested before 37 weeks. The false-negative rate of the MBPP is similar to the CST and the complete BPP. Additionally, it is easier to perform and less time-consuming than the CST or the complete BPP. The sensitivity of the MBPP is superior to that of the NST alone. Limitations include the need for backup testing in 10% to 50% of patients, a high false-positive rate, and a twice weekly testing interval.

Doppler Velocimetry Doppler velocimetry of fetal, umbilical, and uterine vessels has been the focus of intensive study in recent years. This technology uses systolic-to-diastolic flow ratios and resistance indices to estimate blood flow in various arteries. Studies have shown statistically significant improvement in perinatal outcome with the use of Doppler ultrasonography in pregnancies complicated by fetal growth restriction. Although severe restriction of umbilical artery blood flow, as evidenced by absent or reversed flow during diastole, has been correlated with fetal growth restriction, acidosis, and adverse perinatal outcome, the predictive values of less extreme deviations from normal remain undefined. In conditions other than fetal growth restriction, Doppler velocimetry does not appear to be a useful screening test for the detection of fetal compromise and is not recommended for use as a screening test in the general obstetric population. Doppler velocimetry is used in some settings as an adjunct to standard methods of fetal assessment but should not be considered a replacement for traditional fetal monitoring.

OTHER METHODS AND INTRAPARTUM EVALUATIONS

Fetal Scalp Blood Sampling

Fetal scalp blood sampling allows for the determination of the fetal acid–base status during labor. The technique requires dilation of the cervix, rupture of the membranes, and access to the fetal presenting part. A lighted plastic endoscopic cone is inserted into the vagina and through the cervical os so that it rests against the fetal presenting part. Care should be taken to ensure that it is not placed over a fontanelle. The area to be sampled is dried with a sponge and coated with a thin layer of silicone to facilitate the formation of a blood globule. The scalp is then punctured with a microscalpel, and blood is collected by capillary action in a heparinized capillary tube. After the sample is mixed, it is transported on ice to the laboratory for blood gas analysis. During labor, a normal scalp blood pH is 7.25 to 7.35. A fetal scalp pH of greater than or equal to 7.25 provides evidence of a nonacidotic fetus. A scalp pH of 7.20 to 7.25 is considered suspicious, and sampling should be repeated within 30 to 60 minutes. Historically, pH values less than 7.20 have been considered acidotic; however, minor deviations below normal correlate poorly with perinatal outcome. Because abnormal perinatal outcome has not been consistently observed with values greater than 7.0, there is debate regarding the specific pH value that should be considered acidotic. In addition, fetal scalp sampling reflects the status of the peripheral blood, where acidosis is inherent, owing to the accumulation of CO_2. Since respiratory acidemia is generated in the blood and metabolic acidemia is generated in the tissues, a scalp sample may not reflect the state

of the fetus. In light of the technical difficulty of the procedure and the uncertainty regarding interpretation of results, many centers have reduced their reliance on fetal scalp blood sampling.

Percutaneous Umbilical Blood Sampling

Electronic FHR monitoring, ultrasound, and fetal scalp blood sampling can provide useful information regarding the acid–base status of the fetus. Occasionally, however, direct access to circulating fetal blood is necessary. A classic example is the fetus with severe anemia secondary to Rh-isoimmunization. In this condition, maternal antibodies directed against fetal red blood cell antigens cross the placenta and bind to fetal red blood cells, resulting in hemolysis. At term, suspected fetal anemia can be managed by delivery and treatment of the neonate. Earlier in pregnancy, however, it may be preferable to delay delivery by assessing the fetal hematocrit and, if necessary, performing intrauterine blood transfusion. Percutaneous umbilical blood sampling (PUBS) is a procedure that affords direct access to fetal venous blood. Using sterile technique and direct ultrasound guidance, a fine needle is passed transabdominally into the umbilical vein. Medications or blood may be infused through the needle once fetal blood samples have been obtained. Other indications for PUBS include suspected antibody-mediated fetal thrombocytopenia and fetal cardiac arrhythmias requiring assessment of fetal drug levels or direct fetal administration of antiarrhythmic agents.

Fetal blood sampling can be used along with cardiotocography (CTG) to assess fetal acid–base status during labor. However it requires additional expertise, is time-consuming, has some significant risks, and has only intermittent information. For these reasons, it is not widely used.

Fetal Scalp Stimulation and Fetal Vibroacoustic Stimulation

FHR accelerations of 15 beats per minute for 15 seconds in response to fetal scalp stimulation have been shown to predict a scalp pH greater than or equal to 7.19. Among fetuses without an acceleratory response to scalp stimulation, 39% were considered acidotic (pH < 7.19). A similar relationship has been reported between fetal scalp pH and the FHR response to vibroacoustic stimulation with an artificial larynx applied to the maternal abdomen over the fetal head for 1 to 3 seconds. Among 30 fetuses with FHR accelerations in response to this stimulus, all had scalp pH values greater than or equal to 7.25. Half of the fetuses that did not respond to acoustic stimulation had pH values less than 7.25. FHR accelerations in response to external stimuli are thought to have the same predictive value as spontaneous accelerations. Fetal stimulation is used in antepartum testing to shorten the time of the NST and in the intrapartum period to confirm fetal well-being when spontaneous accelerations are absent. There is no evidence in humans of adverse long-term effects of vibroacoustic stimulation.

Fetal Pulse Oximetry (Fetal Oxygenation)

The aim of fetal pulse oximetry is to provide a continuous assessment of fetal oxygen saturation. The fetal pulse oximeter provides a noninvasive continuous measurement of fetal arterial oxyhemoglobin saturation once membranes have been ruptured. A sensor, similar to an IUPC is placed transvaginally between the uterine wall and fetal face and measures oxyhemoglobin saturation. The system includes an optoelectronic sensor and a microprocessor-based monitor. It has two low-voltage, light-emitting diodes as light sources and one photodetector. One of the light-emitting diodes emits red light (735 nm) and the other emits infrared light (890 nm). When light from each light-emitting diode passes through fetal tissues at the sensor application site, a fraction is absorbed. The photodetector measures the reflected (nonabsorbed) light using a process similar to measurement of transmitted light in conventional pulse oximetry. The amount of light absorbed is related to the amount of oxy- and deoxyhemoglobin. Their ratio determines fetal oxygen saturation during each arterial pulse. The potential is that this technology will provide a practical and easy method for better evaluation of fetal well-being during labor.

In 1994, fetal oximetry was marketed in countries outside of the U.S., including Europe and Canada. In January 2000, the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee of the Food and Drug Administration (FDA) recommended approval of a fetal oximeter for use in obstetrics (OxiFirst: N-400 Fetal Oxygen Monitoring System, Nellcor).

A U.S. multicenter, randomized, controlled trial of fetal oximetry enrolled 1010 women with abnormal FHR patterns. The objective of the trial was to determine whether fetal pulse oximetry with fetal monitoring would reduce the rate of cesarean delivery performed for non-reassuring fetal status. The rate of cesarean delivery for fetal distress was significantly lower in the fetal oximetry group (4.5%) compared to 10.2% in the conventional fetal monitoring group. Unexpectedly, however, the cesarean rate for dystocia was significantly higher in the oximetry group (18.5%) versus 8.6% in the control group), thus the overall cesarean rates were not different (29% oximetry plus FHM vs. 26% FHM).

Clearly, continuous measurement of fetal oxygen saturation could be an important addition to the interpretation of heart rate patterns. The device is attractive in that it offers a direct measure of fetal oxygenation during labor. However, like its predecessor, electronic FHR monitoring, oximetry has the potential for widespread application without conclusive evidence that it is efficacious. The use of this technology is the focus of several ongoing clinical studies and trials.

Fetal Cardiotocography Plus Pulse Rate-Interval Analysis Normally there is a negative relationship between the pulse rate (PR) interval and the FHR: as the FHR slows, the PR interval lengthens, and vice versa. In acidemic infants, this relationship is reversed. A retrospective study of 265 women suggested that the addition of time-interval analysis of the fetal ECG would decrease the rate of unnecessary fetal blood sampling or assisted delivery for presumed fetal distress. However, in a prospective randomized trial of the use of fetal ECG time-interval variables in addition to cardiotocography in fetal surveillance during labor there was no difference in operative intervention or neonatal outcome. The use of fetal cardiotocography plus PR-interval analysis is presently considered investigational.
ST Waveform Analysis Since different fetuses may be able to tolerate varied oxygenation levels based on their situation prior to the hypoxic event, reliance on the level of oxygenation may not be the most applicable measure. In the search for other parameters, an evaluation of the changes in specific end organs, such as the fetal heart, have been pursued. One development is the ST waveform analysis to aid in the interpretation of ominous FHR patterns. ST analysis of the ECG during exercise is a method for assessing myocardial function in the adult. As a corollary, ST waveform analysis of the fetus during labor is analogous to a fetal “stress test” and should provide information on the ability of the fetal heart to respond. An ST segment rise indicates a fetus responding to hypoxia. A negative ST indicates a fetus that is unable to respond or has not had time to react. The fetal ECG is readily obtainable during labor from the same scalp electrode used to obtain the FHR. The evidence from experimental work indicates that ST waveform elevation reflects compensated myocardial stress and a switch to anaerobic myocardial metabolism. A study of 4966 women with CTG versus CTG plus ST analysis revealed that intrapartum monitoring with cardiotocography combined with automatic ST waveform analysis increased the ability of the obstetrician to identify fetal hypoxia. Currently, the use of ST segment elevation in clinical interpretation of fetal heart tracings is considered investigational and studies are ongoing to assess its effectiveness.

SUMMARY POINTS

- Fetal evaluation and interpretation of the findings has made some significant advances. However, there are many limitations with the available technology.
- Electronic FHR monitoring is a very sensitive tool for the detection of fetal compromise; truly compromised fetuses rarely fail to exhibit abnormal FHR patterns. The converse, however, is not true. Abnormal FHR patterns frequently are observed in the absence of fetal compromise. The limited positive predictive value is the principal shortcoming of FHR monitoring.
- Accuracy may be improved by combining FHR analysis with assessment of biophysical variables such as amniotic fluid volume, fetal movement, breathing, tone, and blood flow characteristics.
- Other variables under investigation include continuous intrapartum fetal pulse oximetry, fetal ECG interpretation, and ST waveform analysis.
- To date, the most effective combination of variables has not been defined, and no one approach to fetal surveillance has demonstrated clear superiority over the others. Yet, despite the limitations, antepartum testing in “high-risk” pregnancies has been reported to yield a fetal death rate nearly seven times lower than that in untested, “low-risk” pregnancies. If this observation is substantiated, future investigation will be needed to address the role of antepartum fetal surveillance in uncomplicated, low-risk pregnancies.

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Chapter 10

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Preterm Labor and Delivery

MECHANISMS OF LABOR ONSET
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Oxytocin
Prostaglandins
Cytokines
Other Factors
INFECTION AS A CAUSE OF PRETERM BIRTH
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ANCILLARY THERAPY FOR WOMEN IN PRETERM LABOR
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SUMMARY POINTS

SUGGESTED READINGS

Over the past two decades we have seen a marked increase in survival of very low birth weight infants. This increase in survival has been attributed to increased use of corticosteroids, regionalization of perinatal care, improved methods of mechanical ventilation, availability of exogenous surfactant, and improved nutritional therapy. However, the reduction in mortality has not been accompanied by a reduction in neonatal morbidity or long-term handicaps. It is estimated that 50% of all major neurologic handicaps in children result from premature births.

Despite widespread awareness of the problem and use of therapies believed to be beneficial to prevent preterm births, the rate of preterm delivery is increasing in the United States. The majority of spontaneous premature births occur to women who develop preterm labor or preterm premature rupture of the membranes (PPROM). Cervical incompetence may also result in preterm delivery. Historically, researchers and epidemiologists have approached these conditions as being distinct processes that were mutually exclusive of one another. Recent evidence would suggest that many women have overlapping conditions, which predispose them to deliver preterm. This concept is depicted in Figure 10.1. For example, a women who has preterm delivery secondary to PPROM at 27 weeks gestation, may have had weeks of “silent” or painless contractions or cervical dilation prior to developing ruptured membranes and delivery. Using this broader conceptual framework, this chapter will review the epidemiology, etiology, prevention, and treatment of women with preterm labor.

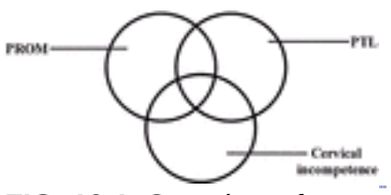

FIG. 10.1. Overview of spontaneous preterm birth.

MECHANISMS OF LABOR ONSET

Labor occurs when mechanisms are present that convert the uterus from a state of containment to an environment that attempts to expel the fetus. In humans, the average gestational period is 280 days ± 14 days. Therefore, term labor is defined as *labor that occurs between 37 and 42 weeks gestation*. Preterm labor is defined as *labor that occurs between 20 and 37 weeks gestation*. In theory, pathologic activation of the normal parturition process results in preterm labor and delivery.

In both term and preterm labor, following an unknown stimulus, the mechanisms that produce labor override those that maintain the pregnancy. Activation of the parturition process results in membrane activation, cervical ripening, and an increase in myometrial responsiveness to endogenous and exogenous signals. Subsequently, labor progresses along a common pathway that results in uterine contractions that are sufficient to cause progressive cervical dilation to allow for expulsion of the fetus. A number of inciting events have been implicated in premature births. These events include decidual hemorrhage (abruption), mechanical factors (overdistension of the uterus, cervical incompetence), hormonal changes (fetal or maternal stress) or subclinical/clinical infection. Infection is associated with as many as one third of preterm deliveries, particularly those occurring at the earliest gestational ages. The role of infection in preterm labor will be reviewed separately in this chapter.

Animal models have helped in understanding labor. Important findings in animal labor models include an increase in oxytocin receptors present in the myometrium, gap junctions developing between myometrial cells, an increased response to agents capable of producing contractions in the uterus, and physical and biochemical changes of the cervix resulting in a softened consistency. Uterine smooth muscle contractility is produced by the actin–myosin interaction, following myosin light chain phosphorylation, which is controlled by myosin light chain kinase. Myosin light chain kinase is activated by calcium as a calmodulin–calcium complex. Cyclic adenosine monophosphate (cAMP) also regulates kinase by inhibiting phosphorylation. Many factors are involved in this control. Some of the proposed theories of labor will be discussed in the following sections.

Hormonal

Alteration in systemic or local levels of steroid hormones is an initiating factor of labor in some animals. The understanding of their possible role in human labor has been continuously evolving. The withdrawal of the uterine inhibitor hormone progesterone has been shown to play a major role in many animals (e.g., sheep, rats, rabbits). In sheep, this withdrawal seems to be caused by an increased responsiveness of fetal adrenal cells to adrenocorticotropic hormone (ACTH) that results in increased production of cortisol. Through several steps, cortisol redirects placental steroid biosynthesis and decreases progesterone secretion. The decreased circulating progesterone in the sheep permits increased myometrial gap junction formation, an increase in prostaglandin formation, and increased response of the uterus to agents capable of producing contractions. In this sheep model, fetal ACTH secretion has control of the onset of labor.

Major differences exist, however, between sheep hormonal status and that of primates, including humans. In humans, there is no great increase in cortisol from the fetal adrenal gland before labor, nor has a dramatic decrease in progesterone been consistently demonstrated. Progesterone, however, is important in human pregnancy, and numerous studies have examined the role of the progesterone-to-estrogen ratio before the onset of labor. In 1974, investigators demonstrated a significant fall in serum progesterone levels and a rise in estrogen levels in many women before labor. This finding has not been reproduced consistently. Estriol may be a signal from the fetus indicating that it is mature and ready for delivery. Production of estriol increases during the last month of pregnancy. In the large amounts produced, estriol is as active as estradiol in stimulating uterine growth. There are reports of an elevation in the estradiol/progesterone ratio at the end of pregnancy.

Administration of progesterone has not been demonstrated to delay term or preterm labor in primates. The antiprogesterones—RU-486 or mifepristone and ZK-98299 or onapristone—in humans and other primates can enhance the responsiveness of the uterus and induce cervical change within 12 to 48 hours, again suggesting a role for progesterone in preventing labor onset.

Oxytocin

It is well known that oxytocin produces uterine activity when administered to pregnant women. The role of endogenous oxytocin as an initiator of term or preterm labor is less well defined. Some reasons to suspect that oxytocin is a universal initiator of labor are its ability to induce labor when given exogenously, and the increase in blood levels that accompanies labor in most species. Because of the pulsatile manner of oxytocin release and the difficulty in measuring the hormone, its precise role in humans has been difficult to ascertain. Compared with oxytocin levels in nonlaboring patients, levels appear to be significantly increased during the first stage of labor and increase to a greater amount during the second stage of labor. Oxytocin levels are higher in umbilical artery blood than in umbilical vein or maternal blood. This finding suggests that the fetus is a source of oxytocin production and release during labor. It is clear that the uterus becomes more sensitive to oxytocin in the days preceding labor. The number of myometrial cell membrane oxytocin receptors greatly increases as pregnancy advances, with a further increase during labor itself. In humans as well as in other species, the concentration of oxytocin receptors is a major reason for increased contractility of the uterus. The increase in oxytocin receptors is the result of increased estrogen levels.

Prostaglandins

Another important part of the parturition model is the synthesis and release of prostaglandins E_2 and F_2. This is supported by an increase in prostaglandins or metabolites in the amniotic fluid, endometrium, decidua, myometrium and blood at the time of labor, the administration of prostaglandins inducing labor, and inhibitors to prostaglandin synthesis delaying labor. It is likely that the prostaglandins have a role in parturition originating from the decidua and myometrium. Oxytocin has the ability to stimulate prostaglandin release through the decidual receptors. In addition, infection of the membranes can release prostaglandins and may be an initiating factor in many cases of preterm labor.

Bacterial by-products may be directly responsible for the stimulation of prostaglandin release in the following ways: Bacterial phospholipase releases the precursor arachidonic acid from the amnion, leading to increased prostaglandin synthesis. Gram-negative organisms may also be able to produce prostaglandins through endotoxin stimulation of the decidua or membranes. Gram-positive organisms may also have prostaglandin-stimulating abilities through peptidoglycans. Phospholipase A_2 is contained within the lysosome of the fetal membranes. As phospholipase A_2 is released from the lysosome, prostaglandin may be synthesized, resulting in uterine contractions.

Cytokines

Cytokines are substances secreted by the immune system in response to infection. There is recent interest in the role of cytokines and growth factors, (e.g., epidermal growth factor, insulin-like growth factors 1 and 2) as potential initiators of labor. The cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF) stimulate the amnion and decidua to produce prostaglandins and increase at time of labor, while transforming growth factor-ß (TGF-ß) inhibits prostaglandin production by other cytokines and may have antiprogestin properties. Finally, several different cytokines have been found in the amniotic fluid of patients with preterm labor.

Other Factors

Endothelins are potent vasoconstrictors in the sarafotoxin-like family. Some isoforms of endothelins are potent uterotonics. Although endothelin does not appear to increase at time of labor, uterine sensitivity and endothelin-receptor numbers do increase in the pregnant uterus. There is some decrease of endothelin-1 in the amniotic fluid of patients in labor, but this may be a consequence rather than an initiator of labor. Nitric oxide, produced from L-arginine by the enzyme nitric oxide synthase (NOS), mediates relaxation of vascular smooth muscle. It has been shown in various animal tissues, including human, that the NOS enzyme is decreased in myometrial tissue at term. Thus, nitric oxide may have a role in maintaining a quiescent uterus.

It can be hypothesized that parturition is a development of an estrogen environment. This estrogen environment promotes changes in the maternal pituitary with increased oxytocin synthesis and release. Estrogen may also be acting directly on the placenta and cervix. As the antiestrogen progesterone level decreases, estrogen can act to increase oxytocin receptors, prostaglandin production, and gap junction number and size. As the cervix ripens, the underlying membranes and decidua become exposed to the vaginal bacteria, triggering an inflammatory response with release of cytokines and prostaglandins. At this point, the paracrine events take dominance over the endocrine effects. Some conditions, such as infection, can overwhelm the endocrine phase of parturition.

INFECTION AS A CAUSE OF PRETERM BIRTH

Preterm birth has been linked with symptomatic nongenital infections, such as acute pyelonephritis and pneumonia. In the last 15 years, new information has suggested that subclinical infection may be an important cause of premature labor, especially labors resulting in very early delivery.

The hypothesis linking subclinical infection and premature birth may be summarized as follows: microbes or their products such as endotoxin enter the uterine cavity during pregnancy, most commonly ascending from the lower genital tract. Blood-borne infection from a nongenital focus occurs less commonly. Microbes or their products then interact, most likely with the decidua or possibly with the membranes, producing prostaglandins or directly leading to uterine muscle contraction. This interaction is most likely mediated through a cytokine cascade. As a result, there is cervical dilation, entry of more microbes into the uterus, and continuation of “the viscous cycle” resulting in premature birth.

The first piece of evidence linking subclinical infection to preterm birth is that the prevalence of histologic chorioamnionitis is increased among preterm births. In membranes from preterm deliveries, there is a consistent and very strong association between positive membrane cultures and the likelihood of membrane infiltration. For example, when the birth weight is greater than 3,000 g, the percentage of placentae showing histologic chorioamnionitis is less than 20%; when the birth weight is below 1,500 g, the percentage was fully 60% to 70%. Most cases of histologic chorioamnionitis are caused by infection.

Second, clinically recognized infection is increased in mothers and neonates after preterm birth. This association is also consistent. Sepsis and meningitis are increased three- to ten-fold in preterm infants. Less widely recognized is the increase in maternal infection after preterm birth. These observations suggest that subclinical infection underlies preterm birth and that the infection became clinically evident during or shortly after birth. Alternatively, the preterm infant may be more susceptible to infection that develops after delivery.

Third, there are associations of preterm birth with various maternal lower genital infections or microbes (Table 10.1). Although *Ureaplasma urealyticum* in the lower genital tract has been associated with low–birth-weight (LBW) infants in earlier studies, a large National Institutes of Health (NIH) study reported no associations of *U. urealyticum* in the vagina with any adverse pregnancy outcome (preterm birth, PPROM, LBW, or BW <1,500 g). Interestingly, then, *U. urealyticum* in the lower genital tract is *not* associated with LBW/preterm pregnancies, even though this organism is one of the most common isolated in the amniotic fluid of women in preterm labor. Lower genital infection with *Chlamydia trachomatis* has also not been consistently associated with adverse pregnancy outcome. However, women with active chlamydial infection and with a positive serum antichlamydial immunoglobulin M (IgM) have shown an increase in rates of preterm delivery. Although a consistent association has not been observed between maternal group B streptococci (GBS) colonization and premature birth in several small studies, a large investigation of approximately 13,000 women showed that pregnant women with heavy GBS colonization had a small but significant increase in risk for LBW (odds ratio [OR] = 1.2; 95% confidence interval [CI] = 1.01–1.5). There were no significant increases in other adverse outcomes, including preterm birth, among heavily colonized women. Women with light colonization were not at an increased risk for any adverse outcomes. Results are also contradictory regarding an association between *Trichomonas vaginalis* and premature birth. Although small, earlier studies had conflicting results, the large Vaginal Infections and Prematurity Study found the presence of *T. vaginalis* in the vagina at midpregnancy was significantly associated with preterm LBW (7.1% of women with vs. 4.5% without *T. vaginalis*: OR = 1.6; 95% CI = 1.3–1.9). Considerable data have linked lower genital tract anaerobes with preterm labor. Further, bacterial vaginosis, in which there is a predominance of anaerobes, has been consistently associated with approximately a two- to three-fold increase in spontaneous preterm delivery. Among other infections, untreated pyelonephritis has been associated with a risk of preterm delivery of approximately 30%, and asymptomatic bacteriuria is associated with a 60% higher rate of LBW (95% CI =

1.4–1.9) and a 90% higher rate of preterm delivery (95% CI = 1.3–2.9).

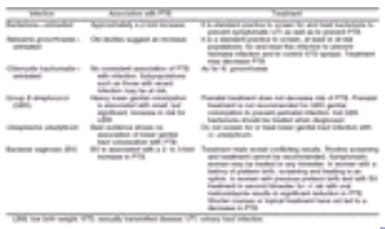

TABLE 10.1. *Prenatal infections as a cause of preterm birth (PTB): association and treatment recommendations*

Fourth, positive cultures of the amniotic fluid/membranes/decidua are found in some patients in premature labor. The range of positive amniotic fluid cultures obtained by amniocentesis from asymptomatic women in premature labor is 3% to 24%. When more sensitive testing for detection of bacteria (polymerase chain reaction) is carried out in amniotic fluid from women in preterm labor, bacteria are detected in 30% to 50%. The most widely discussed route of upper genital tract infection in preterm labor is an ascending path through the vagina and cervix. Similarities in organisms isolated from the amniotic fluid and the lower genital tract support this pathogenic route. It is also possible to speculate that bacteria may enter the uterine cavity hematogenously through spread via the placenta, by contamination at the time of instrumentation such as during amniocentesis or chorion villus sampling, or even by spread from the abdominal cavity via the fallopian tubes. Other sources of organisms for hematogenous spread include bacteremia from periodontal disease or procedures. Among women in spontaneous preterm labor with intact membranes, genital mycoplasmas and anaerobic organisms as well as *Gardnerella vaginalis* (the so-called bacterial vaginosis organisms) are in fact those organisms most commonly found in the amniotic fluid. Sexually transmitted organisms such as *Neisseria gonorrhoeae* and *C. trachomatis* are rarely found in the amniotic fluid, and GBS and *Escherichia coli* are found just occasionally. Patients in preterm labor with the highest likelihood of having a positive culture of the amniotic fluid are those in preterm labor at early gestational ages. It may be speculated that intrauterine infection occurs early in pregnancy (or even has preceded the pregnancy) and may remain without clinical detection for months.

Fifth, biochemical “markers” of infection are often present among women in premature labor. In infection-induced premature labor, the primary site of infection is probably not the amniotic fluid, but the decidua or membranes. More sensitive markers of infection potentially include amniotic fluid glucose concentrations, serum white blood cell counts, C-reactive protein, and amniotic or serum cytokines. Unfortunately, relatively few are clinically useful. Among patients in preterm labor, a low amniotic fluid glucose (<14 mg/dL) correlates well with the likelihood of a positive culture. Among the cytokines, an elevated amniotic fluid IL-6 level is probably the most sensitive marker for infection, but is not yet widely available for clinical use.

Sixth, bacteria or their products induce preterm birth in animal models. The evidence presented here that indicates that infection is a cause of preterm birth in humans is circumstantial. Animal models have provided direct evidence that infection triggers preterm birth in the rabbit, monkey, and mouse.

Seventh, in some clinical circumstances, use of antibiotics has led to a lower rate of preterm birth and to delayed delivery. Antibiotic treatment trials may be classified as one of three designs:

- those conducted prenatally in patients at high risk for preterm delivery
- those conducted among women in preterm labor with intact membranes, as adjuncts to tocolytic therapy
- those conducted among women with PPROM.

Chapter 11 discusses antibiotics in PPROM. Table 10.2 summarizes current practices for use of antibiotics to prevent preterm birth. The discordant results in antibiotic trials raise the question as to why antibiotics have not consistently prevented preterm birth or neonatal morbidity associated with preterm birth. One explanation is that infection is simply not a significant cause of preterm labor, but this seems unlikely in view of all the other evidence. Another explanation is that studies have had too low a power. However, large meta-analyses and the ORACLE trial appear to rule out this possibility. Further, because preterm labor has multiple causes, a true effect of antibiotics may be diluted by those cases of preterm labor not caused by infection. It may also be that only a subset of pregnant women (e.g., perhaps genetically predisposed women) with high cytokine response are at risk for preterm labor after subclinical infection. Another reasonable explanation is that the antibiotics studied in most of the trials were simply the wrong ones (e.g., not including antibiotics with better anaerobic activity) or the antibiotics were given too late or the antibiotic dose or timing were incorrect. It has also been speculated that bacterial lysis as a result of antibiotic therapy may lead to increased exposure to lipopolysaccharide and thus enhance preterm labor. Finally, because infection is more likely to cause very early preterm birth (<32 weeks), trials focusing on women at later gestational ages may not show an effect. For example, the ORACLE I trial enrolled women up to 37 weeks gestation, and only 10% delivered at less than 32 weeks.

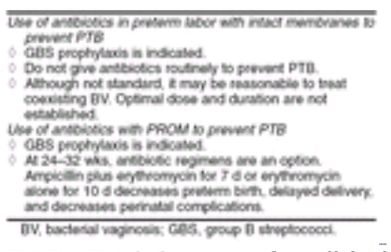

TABLE 10.2. *Use of antibiotics to prevent preterm birth (PTB) in women with preterm labor and premature rupture of the membranes (PROM)*

EPIDEMIOLOGY OF PRETERM LABOR

Currently, 11.8% of women deliver preterm. The vast majority of preterm deliveries are a result of preterm labor (50%), premature rupture of the membranes (33%), or cervical incompetence. The contributions of preterm labor and premature rupture of the membranes to preterm deliveries vary depending upon a number of factors including socioeconomic status (Fig. 10.2). In a large study from North Carolina, Meis and colleagues found that the most common reason for delivery less than 2,500 g in women who were receiving public assistance was PPROM (34%). In contrast, in women who had private insurance, the most common reason for early delivery was preterm labor (52%). Indicated preterm deliveries accounted for 14% and 18% of preterm deliveries, respectively.

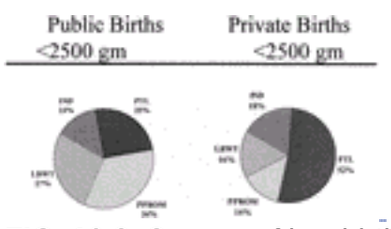

FIG. 10.2. Causes of low birth weight births in public and private patients. (Meis P, Ernest J, Moore M. Causes of low birth weight births in public and private patients. *Am J Obstet Gynecol* 1987;156:1165–1168, with permission). IND, indicated by maternal–fetal condition; PTL, preterm labor; PPROM, preterm premature rupture of membrane; LBWT, low birth weight.

Several major and minor risk factors are associated with development of preterm labor and premature rupture of the membranes (Table 10.3, Table 10.4). One of the most obvious and important risk factors for prematurity is a prior history of preterm delivery. To better quantify this relationship, Mercer and associates performed a subgroup analysis of data collected during a large population-based observational study evaluating risk factors for preterm delivery. In this study, gravid women with any prior spontaneous preterm birth had a 2.5-fold increased risk of spontaneous preterm delivery in the current pregnancy. This risk increased to 10.6-fold if the spontaneous preterm birth occurred prior to 28 weeks gestation. Interestingly, women with a history of loss between 13 and 22 weeks gestation had rates of prematurity that were similar to women who did not have this history (10.1% vs. 8.8%, *P* = .69).

	Relative risk
Prior preterm birth	6–8×
Multiple gestations	6–8×
African-American race	3.3×
Low socioeconomic status	1.9–2.6×

TABLE 10.3. *Major preterm labor risk factors*

Modifiable risks	Nonmodifiable risks
Poor maternal weight gain	Extremes of age (<17 or >40)
Physically demanding work	Prior multiple abortions
Smoking	History of DES exposure
Anemia	History of uterine abnormality
Bacteriuria	Short stature
Bacterial vaginosis	Low prepregnancy weight
Maternal systemic infections: pyelonephritis	

DES, diethylstilberol.

TABLE 10.4. *Minor preterm labor risk factors*

Another major risk factor for preterm labor and birth is multiple gestation. The rate of multiple gestations has increased dramatically over the past 15 years. The increase in twins and higher order multiples is largely a reflection of increased use of ovulation induction and assisted reproductive technologies. Fifty percent of twins deliver prematurely with a mean gestational age at delivery of approximately 35 weeks. As expected, the percent of preterm deliveries increases in proportion to the number of fetuses. Triplets and quadruplets deliver on average at 32 weeks and 30 weeks, respectively. Until researchers develop techniques to perform artificial reproductive technologies that minimize the risk of having high order multiples, then these women will continue to be at significant risk for delivering prematurely and suffering the consequences of preterm birth.

African Americans are 1.6 to 2.5 times more likely to deliver prematurely than Caucasian women of similar age and socioeconomic status. Although African Americans have higher rates of prematurity, the rates of neonatal morbidity are lower in African-American neonates when compared to Caucasians born at similar gestational ages. This suggests that the gestational period may be shorter in African-American women. Low socioeconomic status is also strongly associated with prematurity. It is not clear whether this is related to environment, genetic predisposition, infection or access to medical care.

Table 10.4 also lists a number of “minor” risk factors for preterm labor and delivery. Several of these will be discussed in more detail later in this chapter. In general, the minor risk factors can be broken into two categories: those that are potentially modifiable and those that are not. Many of the minor risk factors are common in pregnancy. Individually their contribution to prematurity is small; however, the risk is compounded by addition of other risk factors. The impact of work on preterm birth remains controversial. Prolonged, physically demanding work does appear to independently increase the risk of prematurity and is potentially modifiable.

PREDICTION OF WOMEN AT RISK FOR PRETERM LABOR

Over the past two decades many researchers have focused on identification of women who are at risk for preterm delivery. Theoretically, identification of asymptomatic women at risk for preterm delivery would allow obstetricians to effectively intervene to prevent preterm delivery or to decrease neonatal morbidity and mortality in preterm neonates. In an American College of Obstetricians and Gynecologists' (ACOG) Practice Bulletin titled *Assessment of Risk Factors for Preterm Birth*, the authors wrote “the ability to predict whether a women is at risk of preterm delivery has value only if an intervention is available that is likely to improve the outcome.” It is believed that identification of women at risk for preterm birth will be beneficial if it allows women to:

- receive a complete course of antenatal corticosteroids prior to delivery
- if necessary, receive tocolytic agents to maximize the probability that antenatal corticosteroids will be given
- be transported to a level III perinatal center.

Another potential benefit of screening is to identify women at low risk for preterm delivery and thereby avoiding administration of potentially dangerous medications or therapies to these women.

Table 10.5 is a review of “ideal” criteria for a screening test. An ideal screening test should have high sensitivity and positive predictive value as well as high specificity and high negative predictive value. Most screening tests do not meet these requirements and trade off sensitivity for specificity. Depending on the clinical scenario where screening tests are used and the consequences of treatment or no treatment, one must decide which test characteristic to stress. For example, one could argue that given the high morbidity associated with preterm birth, the ideal screening test should have a high sensitivity to allow treatment of the majority of women “at risk” and accept a lower specificity rate. On the other hand, one could argue, as ACOG did, that avoidance of treatment with potentially hazardous drugs is beneficial in women with symptoms who are at “low risk” for delivery, thus stressing the importance of the test's specificity and negative predictive value. The following will review available screening tests.

Ascertainment of early, asymptomatic disease
Early treatment alters health outcomes
Disease is important, prevalent
Screening acceptable to population
Diagnosis/treatment readily available
Screening test: simple, reliable, valid
Cost proportional to benefit

TABLE 10.5. *Criteria for screening tests*

Risk Scoring Systems

Risk scoring systems were promoted heavily in the 1980s to identify women at risk for preterm delivery. The risk scoring systems weigh major and minor risk factors for preterm birth as well as current pregnancy complications (see Table 10.3, Table 10.4). The scoring systems work best in multiparous patients and worst in privately insured nulliparas with singleton gestations. Overall, the sensitivity of the screening tool ranges from 3% to 30% and the positive predictive values from 0% to 20% depending on the population studied. While easy to use to identify women who may have modifiable risk factors for preterm delivery, the scoring systems do not reliably identify women at risk. They should not be used alone to institute interventions that may or may not be warranted.

Contraction Monitoring

Contraction monitoring has also been advocated to identify women at risk for preterm birth. Main and associates, in an inner-city clinic in Philadelphia, had low-risk women wear tocometers while waiting in the clinic to be seen between 28 and 32 weeks gestation. Women with 6 or more uterine contractions per hour were more likely to deliver prematurely than women who did not. Using this cutoff, the sensitivity was 75% and the specificity was 79%. As technology became more advanced, this concept was developed further and home uterine activity monitoring (HUAM) became possible. HUAM, as initially promoted, was a combination of telemetric recording of uterine activity and daily contact with perinatal nurses trained to identify signs and symptoms of early preterm labor. The following assumptions were used to establish a role for HUAM:

Women with preterm uterine activity are more likely to deliver prematurely than women who deliver at term.

Women at risk for preterm labor may be unaware of their contractions, thus they present too far along in established labor for treatment to be effective.

Effective treatment for preterm labor is available.

At least 13 randomized clinical trials have evaluated the role of HUAM. These trials differ dramatically depending on the inclusion and exclusion criteria, the use of adjunctive tocolytic agents, and the primary end points. Despite being “randomized clinical trials”, many of the reports were so severely flawed that they were not

included into several meta-analyses on the subject. After review of all of the evidence, both ACOG (HUAM: not recommended') and the U.S. Preventive Services (HUAM: devise not effective) discouraged the use of this expensive and unproven therapy. Additional research may be warranted in specific at-risk subgroups.

Salivary Estriol

Salivary estriol has also been promoted as a tool to identify women at risk for preterm birth. The basis for this theory is that estriol, a fetal product, is increased following activation of the fetal hypothalamic–pituitary–adrenal axis prior to spontaneous preterm birth. The estriol can be measured in maternal salivary secretions. Salivary estriol levels have a diurnal variation that peaks at night. Therefore, samples need to be collected in the morning to improve specificity. Using longitudinal sampling with morning collections, the sensitivity of SalEst is 71% and the specificity 77%. The false-positive rate is unacceptably high at 23%. Currently, there are no commercially available salivary estriol kits. Salivary estriol should be considered only as a research tool with limited, if any, clinical indications for use.

Screening for Bacterial Vaginosis

Bacterial vaginosis is a common alteration of normal vaginal flora affecting 10% to 25% of normal women. The majority of infections are asymptomatic. The presence of bacterial vaginosis has been clearly associated with preterm births in both prospective cohort studies and case-control studies. As a result, investigators and clinicians have attempted to eradicate bacterial vaginosis in an effort to reduce the incidence of preterm delivery. Brocklehurst and colleagues evaluated this treatment strategy using meta-analysis. They included five randomized clinical trials. As expected, treatment was highly effective in eradicating bacterial vaginosis (OR = 0.22; 95% CI = 0.17–0.27). The included trials used oral metronidazole, vaginal metronidazole, or vaginal clindamycin. Overall, treatment did not reduce preterm delivery prior to 37 weeks gestation (OR = 0.78; 95% CI = 0.60–1.02), preterm delivery prior to 34 weeks gestation (OR = 0.83; 95% CI = 0.32–2.08), or preterm delivery prior to 32 weeks gestation (OR = 1.51; 95% CI = 0.60–1.61). In a subgroup analysis, no effect was noted with vaginal administration of metronidazole or clindamycin. However, patients with a history of preterm delivery and bacterial vaginosis in the current pregnancy who received active treatment had a significant reduction in preterm delivery rates (OR = 0.37; 95% CI = 0.23–0.60). This meta-analysis has not been updated since the publication of the largest randomized controlled trial to date conducted by the Maternal–Fetal Medicine (MFM)-units network. In this double-blinded, randomized clinical trial, women with bacterial vaginosis were randomized to receive metronidazole 2 g orally for two consecutive days or placebo. Women were re-screened and re-treated, if indicated at 24 to 29 weeks gestation, according to the original treatment assignment. Figure 10.3 summarizes the principal findings of the trial. Overall, there was no reduction in preterm deliveries. This result was confirmed in women who had prior preterm delivery. This study has been widely criticized for using a short course treatment regimen and leaves the question of whether or not it is appropriate to “seek and treat” in high-risk women. In a statement by ACOG, the organization does not endorse routine, universal screening for bacterial vaginosis, but recommends further research on the subject in women with prior preterm delivery.

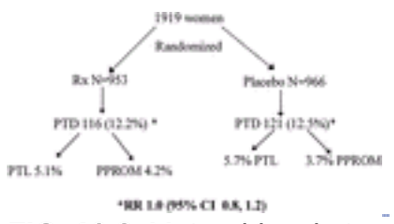

FIG. 10.3. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. (Carey J, Klebanoff M, Hauth J, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 2000;8:534–540, with permission.)

Fetal Fibronectin

Fetal fibronectin has been widely promoted as a tool to identify women at risk for preterm delivery. Fetal fibronectin, a basement membrane protein, is a normal constituent of the extracellular matrix of the maternal–fetal interface. It is present in normal human pregnancies prior to 20 weeks gestation and near term. Its presence between 20 and 34 weeks gestation has been strongly associated with preterm birth, but more importantly, its absence has been associated with low risk of preterm delivery.

Leitich and co-workers performed a comprehensive meta-analysis on the efficacy of fetal fibronectin in identifying women at risk for preterm delivery. They included 27 articles using fetal fibronectin in a variety of settings. Similar to other investigators, they noted that the test's usefulness was a result of its high specificity, and was limited by the low sensitivity in identifying women who would go on to deliver prior to 34 weeks gestation. The sensitivity of the test decreased further in identifying women who would deliver prior to 37 weeks but increased when it was used serially.

In order to maximize fetal fibronectin, its use should be restricted to women with intact membranes, cervical dilation less than 3 cm, and gestational age between 24 and 34 completed weeks gestation, and results should be available within 24 hours. False-positive fetal fibronectins may be obtained in women with recent intercourse or vaginal examinations, or in the presence of bacterial vaginosis and vaginal bleeding.

In general, the sensitivity of fetal fibronectin increases in symptomatic women, women with a cervical length less than 2.5 mm, women with a history of prior preterm delivery, and women with bacterial vaginosis. The negative predictive value in women with preterm contractions ranges from 69% to 92% before 37 weeks gestation. Importantly, a negative fetal fibronectin has a 95% likelihood that delivery will not occur within 14 days of sampling.

Will fetal fibronectin change management and improve outcomes? Fetal fibronectin results have been shown to alter clinical management in certain settings and may be cost-effective. Physicians may use the test to determine who will receive tocolytic therapy and antenatal corticosteroids as well as who is appropriate for a maternal transport. Clearly, this test has potential, yet further work is required to determine what interventions are appropriate and whether the test improves outcomes. An ACOG summary states, “fetal fibronectin may be useful in determining women at high risk for preterm labor. However, their clinical usefulness may rest primarily with their negative predictive value given the lack of proven treatment options to prevent preterm birth.”

Cervical Evaluation

It has long been noted that premature dilation or effacement of the maternal cervix is associated with preterm birth. There has been a great deal of research interest in precisely measuring the uterine cervix with ultrasound to identify women at risk for preterm birth. Several techniques for measuring the cervix have been advocated. In general, it is believed that vaginal measurements are superior to abdominal measurements. Furthermore, several measurements should be obtained and averaged given the variability in cervical lengths for a given individual at a single monitoring session. In order to improve inter-interpreter variability, individuals who are performing the ultrasound should undergo formal training and participate in continuing quality assurance.

Several large prospective cohort studies have been performed which have been useful in establishing cervical nomograms for low-risk and high-risk women. In general, as the cervix becomes progressively shorter or dilates, the risk of preterm delivery increases. Cervical length is also correlated with gestational age (i.e., as gestation advances the cervix matures and shortens). Different cutoff values have been tested. The sensitivity and positive predictive value depend on the prevalence of preterm birth in the population and the gestational age at testing and delivery. A cervical length of =30 mm or a dilation of the internal cervical os will identify 80% to 100% of women or 70% to 100% of women who will subsequently have a preterm delivery.

The proponents of cervical ultrasound evaluation stress the benefit in obtaining more precise measurements with vaginal ultrasound than digital evaluation and the improved ability to detect subtle changes. Furthermore, vaginal ultrasound allows one to avoid vaginal examinations. To date, only two published randomized clinical trials have evaluated the use of cervical cerclage in women with premature shortening of the cervix with no evidence of preterm labor. In the first, the cervical incompetence prevention randomized cerclage trial (CIPRACT), women with the following histories were approached:

- a history consistent with cervical incompetence
- PPROM prior to 32 weeks gestation
- history of cold-knife conization
- diethylstilbestrol exposure
- uterine anomaly

Consenting women who met the inclusion criteria and who had a cervical length less than 2.5 cm prior to 27 weeks were randomized to receive a McDonald cerclage and bed rest or bed rest alone. Placement of a cervical cerclage resulted in a significant decrease in preterm delivery prior to 34 weeks gestation (0 of 19 in cerclage

group vs. 7 of 16 in the expectant management group, *P* = .002). The decrease in preterm delivery prior to 34 weeks gestation was also associated with a decrease in composite neonatal outcome (1 of 19 vs. 8 of 16, *P* = .005). In contrast, Rust et al. randomized women with a shortened cervix detected on routine ultrasound evaluation between 16 and 24 weeks gestation were randomized to receive a cerclage (n = 31) or expectant management (n = 30). The groups were well balanced at randomization for potential confounders. Overall, there was no difference in gestational age at delivery (33.5 ± 6.3 weeks cerclage group vs. 34.7 ± 4.7 weeks in expectant management group, *P* = .4) or the perinatal death rate (12.9% cerclage group vs. 10.0% in expectant management group, *P* = .9).

At this time there does not appear to be sufficient evidence to recommend routine ultrasound screening of the uterine cervix since no treatment has been definitively established that will improve neonatal outcome.

Summary of Screening Tests Used to Identify Women at Risk for Preterm Labor

Several screening tests are available to identify women at risk for preterm delivery. All fail to meet the goals of an “ideal screening test”, since no therapy has been proven to be effective in preventing preterm labor and delivery. As a result, these tests should be considered experimental and used as part of randomized clinical trials with sufficient power to evaluate treatments for prevention of preterm birth.

PRETERM LABOR DEFINITION

Preterm labor is defined as *labor occurring prior to 37 weeks gestation.* Clinically it is difficult to distinguish women with true preterm labor from women who are experiencing preterm uterine contractions. In order to improve the accuracy of the diagnosis, Creasy has proposed using the following criteria: uterine contractions (>4 contractions per 20 minutes) *and* cervical dilation (=2 cm in a nullipara and =3 cm in a multipara) *and* cervical effacement (>80%) or uterine contractions and cervical change. Cervical change is the most well-accepted clinical criteria, yet it is the criteria most vulnerable to bias. For example, what constitutes minimal cervical change and over what time period does cervical change need to occur to be acute and warrant intervention? While this definition is more stringent than that proposed by ACOG and others, over 50% of women who fulfill Creasy's criteria will deliver at term with or without treatment. An alternate approach is to await cervical change during a prescribed period of observation. Utter and colleagues defined “minimal” cervical change as dilation of the cervix by at least 1 cm and effacement of at least 1 cm in women less than 3 cm dilated on admission. Is it appropriate to wait for cervical change and will waiting until labor becomes more established affect treatment success? In a retrospective case-control study, Utter et al. compared the outcomes of pregnancies in women who were treated with ritodrine upon admission who had uterine contractions and “minimal” cervical change to women who were observed and treated only when cervical change as defined above was determined. There were no differences in any maternal or neonatal outcomes including the number of days to delivery and “success” rates with tocolysis. Similarly, Guinn and associates randomized women with uterine contractions who were =2 cm to one of three therapies: observation alone, subcutaneous terbutaline, or intravenous hydration. Overall, there were no differences in any outcome measures between groups. Approximately 15% of women assigned to each of the groups went on to make cervical change during observation and were treated with parenteral tocolysis. In all cases, parenteral tocolysis was successful in delaying delivery for a minimum of 48 hours to allow treatment with antenatal corticosteroids. This approach avoided administration of tocolytic agents to 85% of women with no increase in morbidity or preterm delivery rates. An alternative strategy to awaiting cervical change is to use the rapid fetal fibronectin test and treat only women with a positive test. However, this strategy remains under investigation.

TREATMENT OF PRETERM LABOR

Once the diagnosis of preterm labor is made what treatments are available and do they work? Several agents have been used as tocolytic agents to suppress uterine activity in hopes that prolongation of pregnancy would improve neonatal outcomes (Table 10.6). The vast majority of placebo-controlled clinical trials were published during the 1970s and 1980s. Most of the placebo-controlled trials were small and the concurrent use of antenatal corticosteroids was low. Overall, women who received any tocolytic agent had a mean time to delivery of approximately 48 hours. Therefore, it is not surprising that tocolytic therapy has not been associated with improvements in neonatal outcomes. Despite this finding, tocolytic agents are widely prescribed throughout the world. The justification for the continued use of unproven drugs is the supposition that had the drugs been administered along with antenatal corticosteroids that the 48 hours gained in utero would be beneficial to the neonate and result in improved outcomes. This theory remains untested. However, given the current “standard of care” in the United States, it is unlikely that placebo-controlled trials will be performed to confirm the need to administer tocolytic agents in addition to antenatal corticosteroids. The individual agents that are commonly used throughout the world will be reviewed subsequently. The absolute and relative contraindications to administering tocolytic therapy are listed in Table 10.7 and Table 10.8.

- Hormone treatment
- Alcohol treatment
- Beta-mimetics
- $MgSO_4$
- Antiprostaglandins
- Anti-oxytocics
- Ca^{++} channel blockers

TABLE 10.6. *Overview of the tocolytic agents*

- Severe preeclampsia
- Severe abruptio
- Severe bleeding any cause
- Frank chorioamnionitis
- Fetal death
- Fetal anomaly incompatible with life
- Severe fetal growth restriction
- Mature lung studies
- Maternal cardiac arrythmias

TABLE 10.7. *Absolute contraindications to tocolytic therapy*

- Mild chronic hypertension
- Mild abruptio
- Stable previa
- Maternal cardiac disease
- Hyperthyroidism
- Uncontrolled diabetes mellitus
- Fetal distress
- Fetal anomaly
- Mild intrauterine growth restriction
- Cervix >4 cm

TABLE 10.8. *Relative contraindications to tocolytic therapy*

Beta-Adrenergic Agonists

The ß-mimetics are the most widely prescribed and best-studied tocolytic agents. The two most commonly used ß-mimetic agents in the United States are ritodrine and terbutaline. There are a number of treatment protocols for both ritodrine and terbutaline. In the acute setting, the medications can be administered intravenously (ritodrine and terbutaline) or subcutaneously (terbutaline). The dose is increased until uterine quiescence is achieved or maternal side effects develop that prevent the provider from increasing the dose further. Development of tachyphylaxis occurs rapidly. As a result it is common to need to increase the dose of the medication to maintain an acontractile state once steady-state levels are achieved.

The maternal side-effect profile with the ß-agonists is of particular concern. None of the ß-agonists used for tocolysis are completely ß-2 selective. Therefore, mothers can experience side effects from both ß-2 and ß-1-sensitive tissues. The negative ß-2 effects include: maternal hypotension, decreased urinary output, increased glucose secretion, hypokalemia, and pulmonary edema. The negative ß-1 effects include: tachycardia, palpitations, constipation, decreased gastric emptying, hypokalemia (decrease 0.6 to 1.5 mEq below pretreatment levels), agitation, and jitteriness. The most severe maternal adverse effects include cardiac arrhythmias, myocardial infarction, pulmonary edema, postpartum cardiomyopathy, and death. These risks can be minimized by judicious use of fluids, close monitoring of intake and output, and avoidance of other tocolytic agents.

Beta-mimetics rapidly cross the placenta. The fetal response is similar to the adult. Cardiovascular effects include tachycardia, increased cardiac output and redistribution of blood flow, increased thickness of the intraventricular septum, neonatal supraventricular tachycardia, myocardial ischemia, myocardial necrosis, hydrops, and hypoglycemia. Long-term follow-up studies demonstrated no overall difference in children exposed to ß-mimetics versus control groups that received placebo. However, evidence suggests that the ß-mimetics may increase the incidence of intraventricular hemorrhage in preterm neonates. This finding has been noted

in a couple of case-control studies performed in large neonatal databases. This finding was not previously noted in the randomized placebo-controlled trials of the ß-mimetics. Further studies are necessary to evaluate this potential adverse effect of ß-mimetics.

Are the ß-mimetics efficacious? The largest placebo-controlled trial of the ß-mimetics was performed in Canada and published in 1992. In this trial, 708 women with preterm labor, with or without ruptured membranes, were randomized to receive ritodrine or placebo infusions. Treatment with ritodrine did not reduce perinatal mortality or morbidity, prolong pregnancy, decrease the percent of preterm deliveries, or increase the percentage of women who completed a course of antenatal corticosteroids. The findings of this individual trial are consistent with a previously published meta-analysis of the ß-mimetics when used as tocolytic agents. The Canadian study has been widely criticized for including women with PPROM. Tocolytics and antenatal corticosteroids do not appear to be as efficacious in the setting of PPROM, thus potentially diluting any positive effect of the ritodrine.

At this time advocates for the use of the ß-mimetic believe that the benefit-to-risk ratio is favorable and that prolonging pregnancy may increase the proportion of women who complete a course of antenatal corticosteroids prior to delivery. As newer agents with less potential for maternal and fetal adverse effects become available, the use of the ß-mimetics will continue to decrease in the acute setting.

Magnesium Sulfate

Magnesium sulfate is probably the most widely prescribed tocolytic agent used in the United States. Although the exact mechanism of action is unknown, it likely decreases the free calcium ion concentration in the intracellular compartment of the uterine myometrial myosin light chains, which blocks kinase phosphorylation and therefore decreases the electrical potential of the cell. For acute tocolysis, magnesium sulfate is administered intravenously. A number of protocols for loading the patient and maintenance dosing exist. In general, the magnesium “bolus” is administered in doses that range from 4 to 8 g over a period of 20 minutes to 1 hour. Next, a maintenance infusion (2 to 4 g per hour) is started and adjusted until uterine contraction frequency decreases to less than 4 contractions per hour and no further cervical change is occurring. The infusion is stopped after the patient remains acontractile for 12 to 24 hours. In certain clinical situations (advanced dilation at early gestational ages, women who continue to contract despite high doses of magnesium sulfate, etc.) it may be warranted to continue the infusion for 48 hours to allow for administration of a full course of antenatal corticosteroids.

Magnesium sulfate is primarily cleared by the kidneys and is rapidly excreted in the pregnant woman with normal renal function. It is generally accepted that blood levels of 6 to 8 mg per dL of magnesium sulfate are optimal for tocolysis. However, there is a great deal of variation in the biological response to this agent including the level that is required to achieve uterine quiescence and the level associated with toxicity. For example, in one study investigators used a case-control study design and compared women who did and did not respond to magnesium sulfate tocolysis. Overall, there were no significant differences in serum levels of magnesium sulfate in the women who did and did not respond to tocolysis. This finding is similar to that of a randomized controlled trial comparing a high-dose magnesium protocol (8-g load, then 2–4 g per hour) to a low-dose magnesium protocol (4-g load, then 2–4 g per hour). The high-dose protocol did achieve tocolysis more rapidly than the low-dose protocol. However, there was a corresponding increase in maternal side effects with the high-dose protocol. Overall, there was no difference between the protocols with respect to prolongation of pregnancy or a reduction in neonatal morbidity. Finally, many physicians believe it is necessary to wean patients from magnesium sulfate tocolysis. This practice was evaluated in a randomized trial comparing a weaning protocol to immediate withdrawal of magnesium sulfate. Not surprisingly, weaning prolonged labor and delivery stays by approximately 8 hours. Overall, there was no difference in time gained in utero or differences in neonatal outcomes between the two groups. Women who were weaned had significantly higher rates of recurrent labor in the current admission and in the future.

Maternal side effects are common with magnesium sulfate and are presented in Table 10.9. As blood levels of magnesium increase, so does the potential for severe toxicity. Maternal deaths have occurred with magnesium sulfate as a result of respiratory depression and cardiac arrest. In general, these events should be preventable by following the patient's clinical status carefully. This monitoring should include hourly assessments of intake and output, level of deep tendon reflexes, and oxygen saturation using a pulse oximeter. Careful labeling of all medications as well as strict adherence to concentration should reduce the likelihood of an inadvertent bolus of large amounts of magnesium sulfate. In cases of extreme magnesium toxicity, administration of calcium gluconate may be useful to try and reverse the effects of magnesium sulfate.

◊ Common
Flushing
Sense of warmth
Headache
Nystagmus
Nausea
Dizziness
Lethargy
◊ Serious
Pulmonary edema
Neuromuscular blockage
Osteopenia

TABLE 10.9. *Maternal side effects related to* $MgSO_4$

Finally, long-term magnesium exposure has been associated with significant bone loss and fractures. Therefore, women receiving long-term magnesium therapy should receive supplemental calcium.

Magnesium sulfate also has significant fetal and neonatal effects. Magnesium sulfate crosses the placenta and accumulates in the fetus. As a result, it can affect fetal biophysical parameters (primarily fetal breathing activity) and decrease fetal heart rate variability. Neonates born with cord levels of magnesium sulfate greater than 4 mg per 100 mL may show signs of depression including decreased muscle tone, drowsiness, poor respiratory effort, and low Apgar scores. A case of neonatal osteoporosis with associated fractures has been reported in a woman undergoing long-term tocolysis with magnesium sulfate.

Controversy exists over the long-term effects of magnesium sulfate. A number of cohort and case-control studies have suggested that magnesium sulfate exposure at birth may reduce rates of cerebral palsy in preterm infants. The data are compelling enough that several investigators are now testing this hypothesis in randomized trials. The MagNet trial was the first trial published that formally evaluated this hypothesis. The MagNet trial randomized women with preterm labor and intact membranes to receive magnesium sulfate or other tocolytics if =4 cm dilated on admission or magnesium sulfate or placebo if more than 4 cm dilated. The trial was stopped at the first planned interim analysis because there were 7 pediatric deaths (n = 46) in the magnesium arm compared to no pediatric deaths (n = 47) in the tocolytic/placebo arm (OR = 15.2; 95% CI = 4.8–25.6). The groups were well balanced at randomization for potential confounders. Thus, there was no obvious explanation for the excess deaths in the magnesium arms of the trial other than magnesium sulfate exposure. The dramatic findings from this small trial have not been previously noted in large neonatal databases or in placebo-controlled trials. Ultimately, we will need to await the results of ongoing trials to either confirm or refute the findings of the MagNet trial.

Is magnesium sulfate efficacious? Only three small placebo-controlled trials have evaluated the efficacy of magnesium sulfate as a tocolytic agent. In the placebo-controlled trials, magnesium sulfate did not significantly prolong pregnancy or decrease neonatal morbidity. However, the majority of trials with magnesium sulfate compare it to the ß-mimetic agents. In these larger trials magnesium sulfate does appear to be equally “efficacious” to the ß-mimetics in prolonging pregnancy with a superior maternal side-effect profile. As a result, magnesium sulfate is generally used throughout the United States as a first-line tocolytic agent.

Calcium Channel Blockers

The calcium channel blockers are promising tocolytic agents. Calcium channel blockers or calcium antagonists are nonspecific smooth muscle relaxants. They prevent the influx of extracellular calcium ions into the myometrial cell. The effects are not specific to the uterus.

Numerous protocols for nifedipine exist. In general, 10 mg nifedipine is administered orally. If contractions persist the dose can be repeated every 20 minutes for a total of 30 mg in 1 hour. Maternal hypotension is relatively common. If hypotension develops, additional doses of nifedipine must be held. Once contractions decrease, the patient may receive 10 mg every 6 hours of nifedipine orally or receive 30 to 60 mg of the sustained-release nifedipine per day. Nicardipine, a potent uterine relaxant, may be administered as a 40-mg loading dose followed in 2 hours by a 20-mg dose to a maximum dose of 80 mg if uterine contractions do not abate. This can be followed by sustained-release nicardipine 45 mg every 12 hours.

The calcium channel blockers produce vasodilation and decrease peripheral vascular resistance. Maternal hypotension defined as either a 25% decrease in mean arterial pressure or symptomatic hypotension is relatively common. Many patients experience transient facial flushing or develop nausea and headache. Maternal side effects appear to be less common than in women treated with the ß-sympathomimetics but severe complications have been reported. For example, there has been a case of maternal myocardial infarction associated with high-dose nifedipine therapy following ritodrine treatment in women in preterm labor. We have had a similar case using a low dose of nifedipine following magnesium sulfate tocolysis. Nifedipine potentiates the toxicity of magnesium sulfate by causing neuromuscular blockade. There have been reports of profound hypotension, neuromuscular blockade, and maternal death resulting from the combination of magnesium sulfate therapy and calcium channel blockers. This complication may not be as frequent as initially believed. However, there are no protocols that establish the safety of using these

medications together. Therefore, they should not be used concurrently.

In general, the calcium channel blockers appear to be well tolerated by the fetus and neonate. There has been one case of neonatal heart block associated with their use. Concerns remain that the calcium channel blockers may have adverse effects on the fetal and placental circulation resulting in growth restriction, acidosis, and stillbirths. These concerns do not appear to be supported by the literature.

Prostaglandin Synthetase Inhibitors

Prostaglandins are integrally involved in cervical ripening and labor. Therefore, it would make sense that inhibiting prostaglandin synthesis should prevent preterm labor and delivery. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclooxygenase, thus preventing the conversion of arachidonic acid to prostaglandin. The effects are not limited to the uterus. Indomethacin is the most widely studied prostaglandin synthetase inhibitor used for treatment of women in preterm labor.

Our protocol for indomethacin tocolysis involves the administration of a 100-mg loading dose given as a suppository per rectum. If regular uterine contractions persist 1 to 2 hours after the initial 100-mg suppository, an additional 50 to 100 mg may be given. Oral therapy is then instituted at 50 mg every 6 hours for 48 hours while betamethasone is dispensed. The absorption of indomethacin is excellent from both the rectal and oral routes. Therefore, if rectal suppositories are not available, the oral formulation can be effectively substituted. Fetal echocardiography is not considered necessary when administering indomethacin as outlined above. Fetal contraindications to the use of indomethacin include growth restriction, renal anomalies, chorioamnionitis, oligohydramnios, ductal dependent cardiac lesions, and twin–twin transfusion syndrome.

Indomethacin is very well tolerated in the gravida in comparison to other tocolytic agents. Serious maternal side-effects are rare when the agent is used in a brief course of tocolysis. As with any NSAID, mild gastrointestinal upset may occur. More serious potential complications include gastrointestinal bleeding, alterations in coagulation, thrombocytopenia, and asthma in aspirin-sensitive patients.

Prolonged treatment can lead to renal injury, especially when nephrotoxic drugs such as aminoglycosides are employed. Drugs of this class are antipyretic agents and may obscure a clinically significant fever. Maternal contraindications to indomethacin include renal or hepatic disease, active peptic ulcer disease, poorly controlled hypertension, asthma, and coagulation disorders.

In contrast to the generally favorable maternal side-effect profile, the potential for fetal and neonatal complications of indomethacin tocolysis is worrisome. In actuality, serious complications are rare when limiting treatment to short courses and adhering to established protocols.

The principal side effects of indomethacin tocolysis have been constriction of the ductus arteriosus, oligohydramnios, and neonatal pulmonary hypertension. The ductal constriction occurs because formation of prostacyclin and prostaglandin E_2, which maintain ductal vasodilation, is inhibited by indomethacin. Moise and colleagues reported Doppler evidence of ductal constriction in 7 of 14 fetuses exposed to indomethacin between 27 and 31 weeks of gestation. Tricuspid regurgitation occurred in three fetuses. All ductal abnormalities resolved within 24 hours of discontinuation of indomethacin and none of the neonates had pulmonary hypertension. The Moise group later reported on the effect of advancing gestational age on ductal constriction in association with indomethacin and stated that “a dramatic increase in constriction was noted at 32 weeks gestation when the rate of compromise approached 50%.” However, ductal constriction was noted as early as 24 weeks, and occurred in 11 of the 23 fetuses prior to 30 weeks. This was a retrospective analysis of echocardiograms performed on 44 patients with premature labor or hydramnios treated with indomethacin. Although never clearly stated, these patients appeared to be on courses of therapy for greater than 48 hours. Indomethacin was the “third-line agent” in premature labor unresponsive to terbutaline or magnesium sulfate.

Oligohydramnios associated with indomethacin tocolysis is common, dose-related, and reversible. The oligohydramnios is a consequence of reduced fetal urine production due in turn to reduction by indomethacin of the normal prostaglandin inhibition of antidiuretic hormone and by direct effects on the renal blood flow. Indomethacin can be an effective therapy for hydramnios, especially when complicated by preterm labor.

Primary pulmonary hypertension in the neonate is a serious condition that has also been reported with prolonged (more than 48 hours) indomethacin therapy. This complication has not been reported when therapy was restricted to 24 to 48 hours, however, the incidence may be as high as 5% to 10% with long-term therapy.

Necrotizing enterocolitis and intraventricular hemorrhage have been observed in the LBW neonate exposed to indomethacin in utero when it was used outside of standardized protocols that did not limit the duration of treatment, or was the second or third agent added to recalcitrant preterm labor. Since such patients have an increased risk of subclinical intraamniotic infection, and since intraamniotic infection is associated with a greater risk of such complications, it is not clear that indomethacin incurs independent risk for these morbidities. Subsequently, two larger studies have not confirmed this finding or demonstrated any association between indomethacin exposure and any adverse neonatal outcome. Follow-up studies of children treated in utero with indomethacin have not found significant long-term effects although they did not specifically target the LBW neonate.

Indomethacin has been reported to be effective in two small randomized, placebo-controlled trials. The first found indomethacin was superior to placebo in delaying delivery for 48 hours (80% vs. 33%). The second demonstrated a sustained delay in delivery for patients treated with indomethacin (95% at 48 hours and 83% at 7 days) compared with placebo (23% at 48 hours and 16% at 7 days). Additional prospective, randomized trials have found indomethacin to be comparable to ritodrine and magnesium sulfate and superior to nylidrin for tocolysis. There are additional reports that describe indomethacin tocolysis favorably, but many used other tocolytic agents simultaneously or sequentially.

Indomethacin appears to be an effective tocolytic agent that is well tolerated by the mother, and appears to be tolerated by the fetus when used appropriately. Exposure should be limited to 48 consecutive hours to allow for administration of antenatal corticosteroids and should be restricted to gestational ages less than 32 weeks.

Other Tocolytic Agents

Several other tocolytic agents have been proposed for use. These include the oxytocin analogs, nitroglycerin, cyclooxygenase 2 (COX-2) inhibitors, ketorolac, progestins, and nitric-oxide inhibitors. The oxytocin analogs have been the most widely tested. These agents appear promising in delaying delivery and have acceptable maternal side-effect profiles. However, use of these agents did not appear to improve neonatal outcome. Therefore, the Food and Drug Administration (FDA) did not approve Antosiban for use in women with preterm labor. As a result of the failure to bring an “effective” drug to market, it is doubtful that any of the pharmaceutical companies will invest the capital necessary to develop new tocolytic agents in the near future.

MAINTENANCE TOCOLYIS FOLLOWING ARREST OF PRETERM LABOR

If preterm labor is arrested, the patient remains at high risk for a recurrent episode of preterm labor and preterm birth. Maintenance tocolytic therapy may decrease chances for delivery in some cases. Several agents including the ß-mimetics (ritodrine and terbutaline), magnesium sulfate, prostaglandin synthetase inhibitors, and the calcium channel blockers have been tested in randomized trials.

Efficacy of Oral Tocolysis with Beta-Mimetics

We have been able to identify eight randomized placebo-controlled trials of oral ß-mimetic maintenance therapy to prevent recurrent preterm labor and preterm delivery. A total of 915 patients were randomized in these eight trials. In six of the eight trials there was no decrease in the preterm delivery rate or a prolongation of pregnancy with maintenance tocolytic therapy when compared to controls receiving no treatment. Seven of the eight trials reported on the number of women treated for recurrent preterm labor. Overall, for women receiving a ß-mimetic, the rate of recurrent preterm labor was 32.5% (range, 2%–59%) and for patients receiving placebo or no therapy 28.3% (range, 12.9%–63%). Despite obvious differences in the trials, Sanchez-Ramos and colleagues combined these data using meta-analysis (Table 10.10). When they restricted the analysis to trials comparing ß-mimetics to placebo or no therapy, there was no benefit of treatment for prevention of preterm birth (OR = 1.08; 95% CI = 0.82–1.43) or risk of recurrent preterm labor (OR = 0.90; 95% CI = 0.63–1.28). One could argue that it is not appropriate to combine trials when there is no consistency between the trials in inclusion criteria and definitions of preterm labor and recurrent preterm labor. Regardless, whether the trials are evaluated individually, cumulatively as a review, or using meta-analysis, there does not appear to be any benefit of oral ß-mimetic tocolysis.

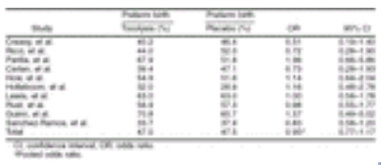

TABLE 10.10. *Impact of maintenance tocolysis on preterm delivery*

Several potential explanations can be offered as to why oral ß-mimetic therapy appears to be ineffective. Oral administration of terbutaline results in inconstant drug levels, characterized by peaks and troughs. The need to take the drug every 2 to 4 hours throughout the day, including awakening at regular intervals throughout the night, may decrease compliance. Finally, long-term exposure to ß-mimetic agents results in desensitization of the ß-adrenergic receptors in the myometrium. Development of tolerance is related to both the duration of therapy and the total dose of the ß-mimetics. As a result the drugs may lose effectiveness over time.

Efficacy of Continuous Subcutaneous Administration of Terbutaline

Terbutaline may be administered by a continuous portable subcutaneous pump for maintenance therapy. Its theoretical advantages over oral maintenance therapy are continuous low maintenance drug levels and the ability to bolus the drug if uterine contractions develop, thus preventing or decreasing the development of tolerance of the ß-receptors to the ß-agonist terbutaline.

A number of descriptive studies of terbutaline pump therapy for prevention of preterm birth have been published in peer review journals. It was not until 1997 that the first randomized, placebo-controlled trial of the terbutaline pump was published. In this study women with preterm labor were assigned to receive terbutaline pump therapy (n = 15), placebo pump therapy (n = 12), or oral terbutaline (n = 15). If women developed recurrent preterm labor, the blind was broken and women receiving placebo were crossed-over to terbutaline. Although conclusions were limited by the small number of patients in each group and the crossover design, there were no differences in the mean delay to delivery or in neonatal morbidity.

In 1998, Guinn and associates reported their randomized double-blind trial of terbutaline pump therapy. Preterm labor was defined prospectively as the presence of uterine contractions and =1 cm cervical dilation, =80% effacement or cervical change. Women received magnesium sulfate with or without indomethacin therapy for acute preterm labor. Women with singleton gestations and intact membranes between 22 and 33 $^{6}/_{7}$ weeks gestation were eligible. Consenting women were randomized to receive terbutaline pump (n = 24) or placebo pump therapy (n = 28). Pump therapy was initiated by the research nurse using a standard protocol. In addition to their programmed infusion, patients were allowed to administer up to two additional boluses (either 0.25 mg terbutaline or 0.25 cc saline depending on the treatment group) for uterine contractions. At randomization, the groups were well balanced with respect to parity, prior preterm delivery, gestational age, and cervical examination. Overall there was a 1-day difference in mean time to delivery between the groups (terbutaline 29 days and placebo 28 days, $P = .78$). There were no differences in the rates of preterm delivery at less than 34 and less than 37 weeks gestation, recurrent preterm labor (terbutaline 38% and placebo 37%, $P = .89$), or rates of neonatal morbidity.

Despite very limited information regarding terbutaline pump therapy, its use has been widely promoted by several home health care corporations that target the majority of their services to the obstetric patient. Terbutaline pump therapy whether used alone or in conjunction with HUAM programs is extremely expensive, averaging over $200 per day, when compared to oral therapy or no therapy. As its use has increased, so have reports of complications related to therapy. As a result, the FDA issued an alert regarding the potential dangers associated with terbutaline pump therapy and the lack of data supporting the efficacy of this treatment.

Risks Associated with Oral or Subcutaneous Beta-Mimetic Therapy

Frequent unwanted effects of ß-mimetic therapy include palpitations, tremor, nausea, vomiting, headache, thirst, nervousness, and restlessness. Complications of the oral ß-mimetics and the subcutaneous administration of terbutaline include sudden death, pulmonary edema, cardiac arrhythmias, hepatitis, glucose intolerance, and gestational diabetes. There has also been one case of neonatal myocardial necrosis in a woman receiving high doses of subcutaneous terbutaline.

Summary of Beta-Mimetics for Maintenance Therapy

There is no compelling evidence from the randomized controlled trials to support the use of ß-mimetics for maintenance therapy. Given the potential risks associated with the ß-mimetics, there is no justification for its continued use as a chronically administered therapy.

Other Maintenance Tocolytic Agents

Compared to the ß-mimetics, there have been relatively few trials exploring options for maintenance therapy. Magnesium sulfate has been administered on a chronic basis intravenously and orally. Long-term magnesium exposure can result in significant osteopenia, especially when used in conjunction with multiple doses of corticosteroids and bed rest. There have been reports of both mothers and neonates developing significant osteopenia following prolonged magnesium exposure. In the randomized trials that compare oral magnesium to placebo, no apparent benefits were noted in time to delivery or neonatal outcomes.

Long-term tocolysis with the prostaglandin synthetase inhibitors is contraindicated. The fetal risk is far in excess of any potential benefits. It is possible that more selective COX-2 inhibitors will be useful for maintenance therapy. The calcium channel blockers appear to be gaining popularity to reduce recurrent preterm labor. Two trials have compared nifedipine to ß-sympathomimetics agents. These investigations were equivalent or superior to the ß-mimetics for prolonging pregnancy, with lessened maternal side effects. Carr and colleagues published the only randomized trial of nifedipine compared to no therapy. They randomized 74 women to receive oral nifedipine (20 mg every 4 to 6 hours) or no treatment. The groups were well balanced at randomization for potential confounders. There were no differences in the time gained from initiation of therapy until delivery in the two groups (37 days nifedipine and 32 days no therapy) or gestational age at delivery (35.4 weeks nifedipine and 35.3 weeks no therapy). Oral nifedipine following successful tocolysis with magnesium sulfate did not improve pregnancy outcome. While this study did not report any significant complications of therapy, there has been a report of a myocardial infarction following treatment with nifedipine for maintenance tocolysis.

Conclusions Regarding Maintenance Tocolysis

At this time there is no evidence that any of the available maintenance tocolytic agents are effective in prolonging gestation, reducing preterm births, or improving neonatal outcome. Each of the therapies has been associated with significant complications. Therefore, we cannot recommend that any of these agents be used outside of properly designed randomized trials.

ANCILLARY THERAPY FOR WOMEN IN PRETERM LABOR

Several investigators have studied the impact of adjunctive antibiotic therapy in women with preterm labor and intact membranes. These studies have included women across the spectrum of gestational ages and cervical dilations and have used a variety of antibiotic regimens. This subject was reviewed by King and Flenady in the Cochrane Database. Beneficial effects of antibiotics included a significant prolongation of pregnancy (5.4 days), reduction in maternal infectious morbidity, and a trend toward reduction in neonatal sepsis. However, this was coupled with an increase in perinatal mortality (OR = 3.36; 95% CI = 1.21–9.32). The largest study published to date was ORACLE II. This study included women in preterm labor between 20 and 37 weeks gestation. In this trial, 6,295 women were enrolled, and data from 6,241 women was available for analysis. Overall, use of antibiotics was not associated with a reduction in neonatal morbidity or mortality or prolongation of pregnancy. The only exception was decreased use of postpartum antibiotic prescription in women who had received antibiotics. Based on the results of this trial and the Cochrane Database review, at this time, adjunctive antibiotic therapy for women in preterm labor is not indicated. GBS prophylaxis should be administered following the 2002 Centers for Disease Control and Prevention (CDC)/ACOG guidelines.

Hydration therapy, either oral or intravenously, is widely used as adjunctive therapy for women with preterm contractions and preterm labor. This practice was popularized during the 1980s when the ß-mimetics were being widely prescribed. Prior to administration of the ß-mimetics, women were hydrated to prevent hypotension. In many cases, as women were receiving their hydration therapy, their contractions reduced in frequency, thus obviating the need for parenteral tocolysis. Guinn and associates published a randomized trial comparing two commonly used therapies for preterm contractions to observation only. Women were included who had cervical dilation less than 2 cm, effacement less than 80%, gestational age 24 to 33 completed weeks gestation, and regular uterine contractions. Women were randomly assigned to receive intravenous hydration, one dose of subcutaneous terbutaline (0.25 mg), or observation only. There were no differences between the groups with time gained in utero, the proportion of women who delivered preterm, or the proportion of women who developed cervical change and received parenteral treatment with tocolytic agents. Intravenous hydration was associated with the highest hospital costs and charges and has the highest potential for adverse effects. Intravenous hydration should be reserved only for women who are obviously dehydrated.

Bed rest has also been widely prescribed for women in preterm labor. There is little if any data that suggests that bed rest is efficacious in women with threatened preterm labor or arrested preterm labor. There are significant costs associated with bed rest including hospital days, lost wages, and lost domestic productivity. It should not be routinely prescribed to women at risk for preterm labor or delivery.

Two therapies are extremely beneficial to women with preterm labor. The first is antenatal corticosteroids. There have been 15 randomized, placebo-controlled trials that tested the efficacy of antenatal corticosteroids in women at risk for preterm birth. Exposure to a complete course of antenatal corticosteroids (betamethasone 12 mg i.m. q24h ×2 doses or dexamethasone 6 mg i.m. q12h ×4 doses) significantly improves neonatal outcomes including a reduction in respiratory distress syndrome, intraventricular hemorrhage, and death. The data are so compelling that the ACOG and the NIH recommend that all women at risk for preterm birth prior to 34 weeks gestation receive antenatal corticosteroids. Repeat courses of antenatal corticosteroids are not recommended as they may reduce respiratory morbidity while increasing the potential for intraventricular hemorrhage and chorioamnionitis. Long-term follow-up studies are underway which will help to define the long-term risks and benefits of repeat courses of antenatal corticosteroids.

The other therapy that appears to be highly efficacious in improving neonatal outcomes is the administration of GBS prophylaxis to women at risk for preterm birth. The attack rates for preterm neonates colonized with GBS are significantly higher than in term infants. As a result, prophylaxis has been demonstrated to be highly beneficial in preventing invasive GBS and its sequelae in preterm neonates.

CONCLUSIONS

Prevention of preterm birth remains an elusive goal. Despite widespread recognition and interest in the problem, the rate of preterm delivery is increasing in the United States. Clearly continued research efforts are necessary to better elucidate the biology of parturition and abnormal parturition to allow us to develop more effective therapies. In the mean time, it is premature to incorporate screening tests to identify women at risk for preterm labor outside of randomized treatment trials since no treatment has been proven to prevent preterm delivery. In women with an acute episode of preterm labor, tocolysis can be administered with antenatal corticosteroids. All of the tocolytic agents are potentially dangerous and should be used with caution in a supervised setting. Currently, there is no data to support the use of maintenance tocolysis in women whose preterm labor is successfully arrested. All women in spontaneous preterm labor should receive a single course of antenatal corticosteroids and GBS prophylaxis following the 2002 CDC/ACOG guidelines.

SUMMARY POINTS

- The rate of preterm birth is increasing in the United States.
- Subclinical infection is an important cause of preterm labor and delivery.
- Risk factor screening misses the majority of women who deliver preterm.
- Fibronectin and vaginal ultrasound of the cervix are promising technologies to identify women at low and high risk for preterm delivery.
- Universal screening for bacterial vaginosis is not warranted.
- Management of women with asymptomatic shortening of the uterine cervix is controversial.
- The diagnosis of preterm labor should be made using objective and reproducible criteria to avoid over and under treatment of women at risk for delivery.
- Tocolytic therapy has not been associated with improvements in neonatal outcome.
- All tocolytic agents have the potential to adversely affect the mother and the neonate and should only be administered in a supervised setting.
- Currently, there is no data to support the use of maintenance tocolytic therapy.
- Tocolytic therapy should *not* be administered without concurrent administration of antenatal corticosteroids.
- Weekly courses of antenatal corticosteroids should not be routinely prescribed.

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Chapter 11

Ronald S. Gibbs

Premature Rupture of the Membranes

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SUMMARY POINTS

SUGGESTED READINGS

Premature rupture of the fetal membranes (PROM) is one of the most common problems in obstetrics, complicating approximately 5% to 10% of term pregnancies and up to 30% of preterm deliveries. Although the etiology of premature rupture of the membranes is often not clinically evident, a degree of consensus has arisen regarding management options. Indeed, the problem is intricate. Considerations in selecting management in a particular patient are gestational age and patient demographics. The clinician is confronted by a complex set of options including use of corticosteroids, tocolytics, more potent antibiotics, and innovative approaches using various tests (such as amniocentesis, ultrasound, and biophysical testing). Of major importance is the marked improvement in survival of low–birth-weight infants.

DEFINITIONS

PROM is usually defined as rupture *at any time before the onset of contractions*. Unfortunately, “premature” also carries the connotation of preterm pregnancy. To avoid confusion, we use the word *preterm* to refer to gestational age of less than 37 weeks. Thus, preterm PROM (PPROM) refers to PROM prior to 37 weeks gestation. The *latent period* is defined as the time from membrane rupture to onset of contractions. It is to be distinguished from a similar term, *latent phase*, designating the early phase of labor before the active phase. Various terms have been used to describe presumed *maternal or perinatal infections* related to PROM. During labor, designations have included “fever in labor,” “intrapartum fever,” “chorioamnionitis,” “amnionitis,” and “intrauterine infection.” The degree of temperature used to define “fever” has varied. After delivery, maternal infection is referred to as “endometritis” or “postpartum infection.” These diagnoses are usually based upon fever, uterine tenderness, and exclusion of other sources of fever. In neonates, the most common term used to report infection was *neonatal sepsis*, but this may mean strictly a positive blood culture or simply clinical signs or symptoms of sepsis.

INCIDENCE

The incidence of PROM ranges about 5% to 10% of all deliveries, and preterm PROM occurs in approximately 1% of all pregnancies. Approximately 70% of cases of PROM occur in pregnancies at term, but in referral centers, more than 50% of cases may occur in preterm pregnancies. PROM is the clinically recognized precipitating cause of about one third of all preterm births. Despite some progress in prolonging the latent period after preterm PROM and prevention of recurrence (in women with bacterial vaginosis), PPROM remains a leading contributor to the overall problem of premature birth.

ETIOLOGY

In the vast majority of cases, the etiology is not clinically evident. Earlier studies had identified selected clinical conditions such as cervical incompetence and polyhydramnios as being risk factors evident in some cases of PROM.

A scholarly review of the etiology of PPROM identified numerous potential causes in any given case. These included: a generalized decrease in tensile strength of membranes, local defects in the membranes, decreased amniotic fluid collagen and a change in collagen structure, uterine irritability, apoptosis, collagen degradation, and membrane stretch. The Maternal-Fetal Medicine (MFM) Network found that risk factors for PPROM were previous PPROM, positive fetal fibronectin at 23 weeks, and short cervix (<25 mm) at 23 weeks.

Substantial evidence is available to show that subclinical infection may be a cause of PROM, not merely its result. Support for a role of infection is provided by studies showing an association between clinically diagnosed bacterial vaginosis (or isolation of anaerobes in the vagina) and preterm birth/preterm premature rupture of the membranes. Some genital bacteria elaborate enzymes such as proteases, phospholipases, and collagenases that may act to weaken the membranes. Positive cultures of the amniotic fluid in cases of PPROM are obtained in approximately 30%.

In a large case-control study, three factors were associated with preterm PROM in a multifactorial analysis. These were previous preterm delivery (odds ratio [OR] = 2.5; 95% confidence interval [CI] = 1.4-2.5), cigarette smoking (stopped during pregnancy, OR = 1.6; 95% CI = 0.8–3.3; continued during pregnancy, OR = 2.1; 95% CI = 1.4–3.1), and bleeding (first trimester, OR = 2.4; 95% CI = 1.5–3.9; third trimester, OR = 6.5; 95% CI = 1.9–23; more than one trimester, OR = 7.4; 95% CI = 2.2–26). This study enrolled controls at the same gestational age as cases (thus correcting for the decreasing frequency of coitus closer to term) and found no association between coitus and PROM. However, other large studies have not confirmed smoking or vaginal bleeding as risk factors. Recent coitus is probably not a cause of PROM.

Investigations into the placental histology have provided correlates with clinical outcomes in cases of preterm premature rupture of the membranes. Overall, acute inflammation was seen in 43%, vascular lesions were seen in 20%, inflammation plus vascular lesions in 20%, normal findings in 14%, and “other” findings in 3% (Fig. 11.1). When acute inflammation was seen in the placenta (either by itself or mixed with vascular lesions), birth less than 26 weeks was more common, and delivery for suspected or proved clinical infection was also more common.

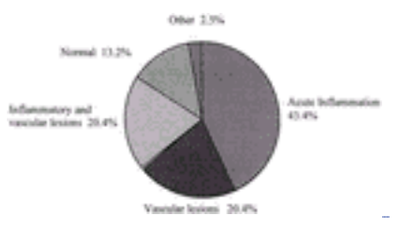


FIG. 11.1. Placental histology in 235 cases of premature PROM. (From Sweet RL, Gibbs RS. *Infectious diseases of the female genital tract*, fourth ed. Philadelphia: Lippincott Williams & Wilkins, 2002; with permission.)

COMPLICATIONS AND CONSEQUENCES OF PROM

Onset of Labor

At term, the onset of labor occurs within 24 hours after membrane rupture in 80% to 90% of patients. Among patients with PROM prior to term, latent periods occur longer. Latent periods of more than 24 hours occur in 57% to 83%, of more than 72 hours in 15% to 26%, and of 7 days or more in 19% to 41%. There is an inverse relationship between gestational age and the proportion of patients with latent periods longer than 3 days. For pregnancies between 25 and 32 weeks, 33% had latent periods longer than 3 days, whereas for pregnancies of 33 to 34 and 35 to 36 weeks, the corresponding values were 16% and 4.5%, respectively.

Effect of Tocolytic Drugs

The value of tocolytics in PPROM remains controversial. None of eight prospective trials showed a decrease in neonatal morbidity, whether tocolysis was used prophylactically (for all patients in admission regardless of uterine activity) or therapeutically (for patients who developed uterine contractions). Only three of the eight showed a prolongation of the latency period; an additional study showed a prolongation for gestation less than 28 weeks. In three studies steroids were used; in another three studies antibiotics were used.

A comparison of short-term versus long-term tocolysis in preterm PROM at 26 to 35 weeks showed adverse effect of “long-term tocolysis.” Patients with preterm PROM at 26 to 35 weeks were randomized to receive either an intravenous ß-mimetic drug for less than 48 hours versus until delivery. All patients received corticosteroids, and group B streptococci (GBS) and gonococci were treated. There was no significant difference in the latent period or in neonatal infection, but there was a significant increase in both chorioamnionitis and endometritis with long-term tocolysis. Accordingly, use of tocolytics in patients with preterm PROM remains controversial, but the bulk of the evidence shows no benefit. However, if tocolytics are used, such as during transfer to a tertiary care center or obtaining benefits of corticosteroids, the course of tocolytics should be limited to less than 48 hours.

Respiratory Distress Syndrome, Infections, and Other Complications

The risks of PROM have generally been viewed as those of infection versus those of prematurity. The most common clinically evident complication among pregnancies with PROM before 37 weeks is respiratory distress syndrome (RDS), which, in general, is found in 10% to 40% of neonates. Bona fide neonatal sepsis is documented in less than 10%, and amnionitis (based always on clinical criteria) occurs in approximately 3% to 31%. Subclinical infection, based upon positive amniotic fluid culture or histologic inflammation of the cord or membranes, is seen much more often, in up to 80% at very early gestational ages with PPROM. Endometritis develops in 0% to 29%. Abruption after PROM is reported in 4.0% to 6.3% of cases, higher than the usually quoted rate of 0.5% to 1.0%. Pulmonary hypoplasia is a serious fetal complication occurring in preterm PROM. Pulmonary hypoplasia is more common when there is very early preterm PROM, especially when this occurs in the presence of prolonged PROM and with severe oligohydramnios. There is nearly a 100% probability of lethal pulmonary hypoplasia when PROM occurs before 23 weeks and when there is severe oligohydramnios. With later gestational age at the onset of preterm PROM, the likelihood of pulmonary hypoplasia decreases. Notably with preterm PROM more than 28 to 29 weeks, even with oligohydramnios, pulmonary hypoplasia is rare. When preterm PROM occurs less than 25 weeks with severe oligohydramnios lasting more than 14 days, the likelihood of lethal pulmonary hypoplasia is estimated to be 80%. At the other extreme, when preterm PROM occurs at more than 25 weeks and when there is either no severe oligohydramnios or severe oligohydramnios for less than 5 days, then the predicted probability of lethal pulmonary hypoplasia is only 2%. These data provide important information for counseling patients with mid-trimester PROM.

RECURRENCE

The reported recurrence rate for PPROM is 32% for patients who had PPROM in an index pregnancy. Based on these data, the risk of recurrence is considerable, prompting patient education and close follow-up in subsequent pregnancies.

EVALUATION

Diagnosis

The initial evaluation may reveal amniotic fluid egressing from the vagina. The differential diagnosis of rupture of membranes includes loss of mucus plug, vaginal discharge associated with infection, and urinary incontinence. If the patient is not going to be delivered immediately, then a digital examination should be deferred as examination may introduce bacteria into the uterus and shorten the latent phase. A sterile speculum exam may demonstrate pooling of fluid in the posterior vaginal vault. Direct observation of fluid leaking from the cervical os is proof of ruptured membranes. The normal pH of the vagina is between 4.0 and 4.7 in pregnancy, whereas the pH of the amniotic fluid is 7.1 to 7.3. Nitrazine paper changes to a dark blue from yellow with a pH above 6.5. Nitrazine paper to diagnose amniotic fluid in the vagina has an overall accuracy of approximately 93%, but false-positive results can result from blood, semen, alkaline urine, bacterial vaginosis, and trichomoniasis.

The diagnosis of PROM may also be confirmed by observing arborization or “fern” of dried amniotic fluid on a slide. This method has an overall accuracy of diagnosis of PROM of approximately 96%. False positives occur with contamination by semen or cervical mucus. False negatives can result from a dry swab, contamination with blood at a 1:1 dilution, or not allowing sufficient time for the fluid to dry on the slide. Amniotic fluid arborization is unaffected by meconium at any concentration and is unaffected by pH alteration.

Ultrasound examination has been used widely, since oligohydramnios suggests PROM, but there have been no evaluations of its sensitivity and specificity. A multicenter clinical trial compared fetal fibronectin detection with standard tests for detection of rupture of membranes at term. Fetal fibronectin showed an excellent sensitivity (98.2%) but a low specificity, leading to speculation that fetal fibronectin in cervicovaginal secretions may be a marker for impending labor, even without frank rupture of the membranes.

When the diagnosis of ruptured membranes is unclear by these tests, a transabdominal dye injection is sometimes performed. A dye such as indigo carmine blue is injected into the amniotic fluid, and a sponge is placed into the vagina and later inspected for the dye. Methylene blue should not be used because of reported methemoglobinemia in the fetus. This test is invasive, and the accuracy of diagnosis is not established. After dye injection, an observation period of 30 minutes is sufficient to detect passage of dye from the vagina.

Fetal Maturity

Determination of the fetal age and maturity status is useful in developing a treatment plan. The patient's history and early milestones of the pregnancy should be used. Ultrasound examination of the fetus can be limited because of the decreased fluid surrounding the fetus, and some measurements, especially of the abdomen and head, may be altered with oligohydramnios after PROM. As part of the overall decision process as to delivery, assessment of fetal lung status may be incorporated, for example, if gestational age is 32 to 34 weeks or if there is uncertainty regarding growth restriction versus prematurity. Amniotic fluid may be collected by amniocentesis or by collection from the vaginal pool. Vaginal pool collection is less accurate for lecithin/sphingomyelin ratio (L/S R) determination. Whereas phosphatidylglycerol (PG) production by vaginal bacteria has been described, there has been an excellent correlation between PG detection in amniotic fluid obtained vaginally and transabdominally.

Cervical Status

In addition to documentation of ruptured membranes, the sterile speculum exam can evaluate the degree of cervical dilation and can exclude the possibility of a fetal extremity or umbilical cord prolapsing through the cervix. Endovaginal ultrasound may be used in patients with preterm PROM without increasing the risk of infection or shortening the latent period.

Infection

When the diagnosis of PROM is made, a rectovaginal culture should be taken for GBS and appropriate antibiotics for prevention of GBS infection should be given

pending culture results.

All patients with preterm PROM should be evaluated for possible evidence of chorioamnionitis. Physical exam includes maternal or fetal tachycardia, uterine tenderness, and detection of a purulent, foul-smelling discharge. Temperature elevation is often a late sign of chorioamnionitis, especially in preterm PROM. In Table 11.1, we show the positive and negative predictive values of several tests for intrauterine infection in PPROM. Amniocentesis may be performed to evaluate for an intrauterine infection, for example, if there are equivocal clinical signs of infection. Because of the high likelihood of subclinical infection and the association of intrauterine infection with cerebral palsy, there is a growing enthusiasm for early detection of subclinical infection. Accordingly, amniocentesis may become more widely used. Analyses of amniotic fluid for possible infection include Gram stain, glucose concentration, and culture. Gram stain does not identify colonization with genital mycoplasmas. A low amniotic fluid glucose predicts a positive amniotic fluid culture. When the glucose is greater than 20 mg per dL, the likelihood of a positive culture is less than 5%; when glucose is less than 5 mg per dL, the likelihood of a positive culture approaches 90%. Although not widely available, an elevated interleukin 6 (IL-6) in amniotic fluid may be the most sensitive predictor of intrauterine infection. A biophysical profile of 6 or less has been shown in several studies to correlate with intrauterine infection. Most newborns who are delivered after clinical chorioamnionitis do not show clinical infection.

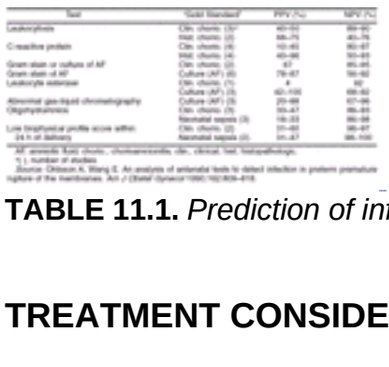


TABLE 11.1. *Prediction of infection in PROM*

TREATMENT CONSIDERATIONS

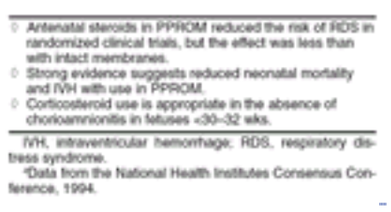
The overall approach to management of PROM takes into consideration neonatal survival at the gestational age when rupture occurs. Management may be divided into four different phases of pregnancy. During the second trimester, neonatal survival is nil, leading numerous investigators to adopt a policy of expectant management or induction. Early in the third trimester, neonatal survival rises markedly, but there is still considerable morbidity associated with delivery at this gestational age. In the mid-third trimester, neonatal survival is high, but there is still considerable morbidity, whereas in the late third trimester (at or near term) neonatal mortality and morbidity are low. Neonatal outcome is one of the driving features in determining clinical management.

Diagnosis of Infection After PROM

Both invasive and noninvasive tests have been assessed. As shown in Table 11.1, none of these tests is ideal, particularly because of their low positive predictive values.

Use of Steroids

Clinicians remain unable to agree on the risks and benefits of steroids in preterm PROM. The first meta-analysis in 1989 concluded that the use of steroids “increases the incidence of endometritis and may increase neonatal infections.” The 1994 National Institutes of Health (NIH) Consensus Conference concluded that the risk of maternal and infant infection may be increased with corticosteroid use after PROM but that the magnitude of this risk was small. The NIH recommendations are summarized in Table 11.2. The benefits of steroids with PPROM before 28 weeks, however, have not been firmly established.



- Antenatal steroids in PPROM reduced the risk of RDS in randomized clinical trials, but the effect was less than with intact membranes.
- Strong evidence suggests reduced neonatal mortality and IVH with use in PPROM.
- Corticosteroid use is appropriate in the absence of chorioamnionitis in fetuses <30–32 wks.

IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome.
[a]Data from the National Health Institutes Consensus Conference, 1994.

TABLE 11.2. *Corticosteroid use in PPROM* [a]

Effect of Latent Period and Vaginal Examination upon Incidence of Amnionitis

In earlier studies, the incidence of amnionitis rose with increasing length of the latent period, but other investigators have found no increase in the incidence of amnionitis among preterm pregnancies with increasing latent periods. In a comparison of outcomes, women with digital examination after PROM had a significantly shorter latent period (2.1 ± 4.0 vs. 11.3 ± 13.4 days; $P < .001$), more maternal infection (44% vs. 33%; $P = .09$), and more positive amniotic fluid cultures (11/25 [44%] vs. 10/63 [16%]; $P < .05$). Thus, routine vaginal examination should be avoided until labor develops in patients with preterm PROM.

Use of Prophylactic Antibiotics

In patients with PROM prior to term, there are two rationales for prophylactic antibiotics. The first is a clear one; namely, for prevention of perinatal GBS infection.

A second rationale for antibiotic prophylaxis has been based upon the hypothesis that infection is either the triggering cause of preterm PROM or that infection ensuing after preterm PROM triggers the labor. Accordingly, this rationale for prophylactic antibiotics has been to delay delivery after preterm PROM rather than to prevent clinically evident infection. We believe that good evidence has been provided to favor use of broad-spectrum antibiotics in selected cases of preterm PROM. This support was provided in a meta-analysis and in prospective randomized trials. In the meta-analysis, 24 trials were identified and 13 were included, containing 1,594 women. However, only 6 of the trials were placebo-controlled, and the trials were heterogeneous with regard to antibiotics used. In addition, there was no standard use of steroids, tocolytics, or prophylaxis for GBS. Nevertheless, benefits were demonstrated in favor of women receiving antibiotics. These benefits included a significant delay in delivery within 7 days, a reduction in chorioamnionitis, and a reduction in neonatal sepsis. There were also reductions (that did not achieve statistical significance) in postpartum infection, neonatal death, neonatal pneumonia, and neonatal bacteremia.

In the large MFM trial, patients were enrolled if they had preterm PROM for less than 72 hours at 24 to 32 weeks gestation. Patients were excluded if there was chorioamnionitis, labor, or fetal distress. Patients were then randomized to a course of ampicillin plus erythromycin (each for 2 days i.v. followed by up to 7 days orally) vs. placebo. Patients with GBS were given treatment during the latent period and no tocolytics were used. However, at the time the study was designed, it was decided not to use corticosteroids in any patients. The primary end point was a prospectively defined composite of neonatal death, neonatal RDS, grade III or IV intraventricular hemorrhage, grade II or III necrotizing enterocolitis, or neonatal sepsis. Patients randomized to antibiotic therapy had a significantly greater likelihood of remaining undelivered when assessed at 2 days, 7 days, 14 days, and 21 days (Fig. 11.2). In addition, the primary composite outcome was significantly reduced in the total population and in the GBS-negative cohort. Individual adverse outcomes significantly reduced in the antibiotic group included RDS, chorioamnionitis, neonatal sepsis, and neonatal pneumonia. Table 11.3 summarizes the benefits of antibiotics in patients with preterm PROM and stratifies the results by total population versus the GBS-negative cohort.

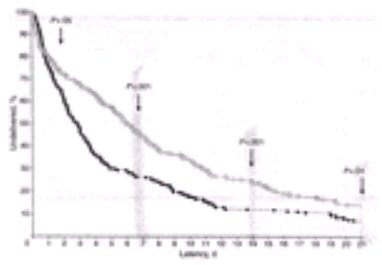


FIG. 11.2. Prolongation of pregnancy in group B streptococci-negative cohort. Antibiotic group shown in *open circles*; placebo in *solid circles*. (From Sweet RL, Gibbs RS. *Infectious diseases of the female genital tract*, fourth ed. Philadelphia: Lippincott Williams & Wilkins, 2002; with permission.)

	Total population	GBS-negative cohort
Primary outcome	↓ (*P* = .04)	↓ (*P* = .03)
RDS	↓ (*P* = .04)	↓ (*P* = .03)
NEC	↓ (*P* = .03)	
Amnionitis	↓ (*P* = .01)	↓ (*P* = .01)
Neonatal sepsis		↓ (*P* = .01)
Neonatal pneumonia		↓ (*P* = .04)

GBS, group B streptococci; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome.
Source: Mercer BM, et al. (19).

TABLE 11.3. *Maternal–Fetal Medicine network trial of antibiotics after PPROM: summary of benefits*

Subsequent to this trial, others have appeared assessing antibiotics in conjunction with antenatal corticosteroid therapy for patients with preterm premature rupture of the membranes. One study assessed 112 women with PROM from 25 to 35 weeks and randomized them to ampicillin sulbactam/amoxicillin clavulanate versus ampicillin/amoxicillin versus placebo. Tocolytics were used in this trial and betamethasone was used weekly up to 32 weeks. Patients receiving the antibiotics had less serious neonatal complications including neonatal death, RDS, and neonatal sepsis ($P < .05$) and they also had significantly higher mean birth weight ($P = .03$). Lewis and colleagues reported a randomized clinical trial of corticosteroids in patients with preterm PROM after treating these patients for a minimum of 12 hours with ampicillin/sulbactam. Antibiotics were continued for 7 days and steroids were repeated weekly. No tocolytics were used. The authors defined the primary outcome as the incidence of RDS, whereas secondary outcome measures included latency and neonatal or maternal infections. In this study of 77 patients, no statistically significant difference in latency was noted comparing the steroid versus no steroid group, and both neonatal and maternal infections were similar. However, there was a significant reduction in the incidence of RDS, 18.4% in the steroid group compared with 43.6% in the no steroid group. The authors concluded that treating preterm PROM with a broad-spectrum antibiotic before corticosteroids decreased RDS without apparent adverse effect. In 1998, a meta-analysis of five trials on antibiotic and glucocorticoid treatment reportedly did not show a significant effect on outcomes including maternal infection, neonatal sepsis, RDS, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal morbidity. In contrast, the authors note “antibiotic therapy without concomitant use of glucocorticoids significantly reduced the odds of maternal infection, neonatal sepsis, and intraventricular hemorrhage substantially.” However, this meta-analysis did not include some of the more recent studies noted immediately above.

In a very large (nearly 5,000 patients) international trial (ORACLE I), patients with PPROM were randomized to one of four courses: oral erythromycin, oral amoxicillin-clavulanic acid, both antibiotics, or oral placebo. Each regimen was taken four times a day for 10 days or until delivery. The primary outcome measure used was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasound. Erythromycin was associated with several benefits to the neonate (fewer cases with the composite outcome, prolongation of pregnancy, and fewer positive blood cultures). Amoxicillin-clavulanic acid—with or without erythromycin—was associated with prolongation of pregnancy, but it was also associated with a significant increase in neonatal necrotizing enterocolitis. The applicability of this study to contemporary U.S. practice is limited, however, because the authors made no provision for GBS prophylaxis. Other features of the study to emphasize are that antibiotics were used orally, enrollment was permitted up to 37 weeks (only 50% of cases were less than 32 weeks), and there was no standard approach for use of steroids or tocolytics. (Steroids were used in 75% of cases and tocolytics in <15%.)

Widespread use of antibiotics in this situation has raised concern about selection pressure toward resistant organisms, but in the MFM trial, there was no significant increase in maternal yeast infection or neonatal Candida sepsis, nor were there any cases of pseudomembranous colitis, maternal sepsis, or maternal death.

Determination of Fetal Lung Maturity

Because RDS is the single greatest threat to infants with PROM, some investigators have determined the status of fetal pulmonary maturity and proceeded with delivery when there was lung maturity. One study used amniocentesis and obtained fluid in about half of the cases. Others have attempted to collect amniotic fluid from the vagina and have had success rates of 80% to 94%. Presence of either PG or an L/S R of more than two in amniotic fluid collected vaginally has been reported to be a good predictor of pulmonary maturity.

In a larger series of patients with PROM before 36 weeks, investigators determined whether PG was present in the vaginal pool and delivered patients when there was presence of PG, spontaneous labor, or evidence of sepsis. PG in amniotic fluid from the vagina reliably predicted fetal lung maturity. However, absence of PG did not necessarily mean that RDS would develop. Of the 131 patients who did not show PG in the vaginal pool in any sample, 82 (62%) were delivered of infants who had no RDS. Thus, even with PROM, delivery of a premature infant simply because its lungs showed biochemical maturity may be questioned in view of other potential hazards of prematurity and the difficulty of the induction. Of note, some genital tract bacteria have been found to yield a false-positive test for PG.

MANAGEMENT

PROM at or Near Term (Table 11.4)

- Induction usually preferred, with oxytocin or prostaglandin preparations (especially with unripe cervix), either upon admission or after a finite period of observation (up to 12 or even 24 h).
- Prophylaxis for group B streptococci with a positive screening culture at 35–37 wks, or with rupture of membranes >18 h in patients with unknown culture status.

TABLE 11.4. *Summary of management: PROM at or near term (= 35 wks)*

In the last few years, new studies have influenced changes in management of PROM at term. Previously, induction of labor (with oxytocin) within 12 to 24 hours after PROM at term was a practice followed by most U.S. obstetricians. Studies in the United States and in Scandinavia supported the safety of this approach and reported shorter maternal hospital stays with less clinically evident neonatal infection. Although expectant management with inpatient observation had been shown to be safe in most patient populations, this approach has become less popular because of the inconvenience and expense of the hospitalizations. Several studies have reported the safety and benefits of prostaglandins and have supported the increased popularity of induction with these preparations. In comparison to patients managed expectantly, those given intravaginal prostaglandin E_2 (PGE_2) shortly after admission had significantly less likelihood of a need for oxytocin and a significantly shorter time to delivery. There was no significant difference in cesarean section rate or in maternal or neonatal infection rates. In the largest trial of management of PROM at term, patients were studied in a four-arm trial with approximately 1,250 patients in each arm. These arms were as follows: Expectant management plus oxytocin for induction as needed; induction with i.v. oxytocin shortly after admission; induction with PGE_2 gel in a dose of only 1 to 2 mg shortly after admission; and expectant management followed by PGE_2 induction as needed. One methodological concern regarding this study is the low dose of PGE_2 gel used vaginally. With most patients receiving less than 2 mg, the dose was smaller than used in most U.S. trials. As shown in Figure 11.3, patients randomized to expectant management initially had significantly longer times to delivery than patients randomized to either of the induction arms ($P < .001$). In addition, the rate of clinically diagnosed chorioamnionitis was less in the patients randomized to induction initially (with significance achieved at $P < .01$ comparing arms *1 vs. 2*). The distribution of postpartum infection was similar to that of chorioamnionitis. In addition, there was no significant difference in rates of neonatal infection or cesarean section. Of note, patient satisfaction was significantly higher in the induction arms.

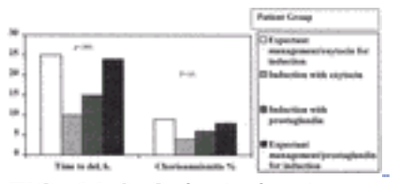


FIG. 11.3. Selected outcomes in an international term PROM trial. (From Sweet RL, Gibbs RS. *Infectious diseases of the female genital tract*, fourth ed. Philadelphia: Lippincott Williams & Wilkins, 2002; with permission.)

A large meta-analysis involving 23 studies and including nearly 7,500 patients concluded that conservative management may result in more maternal infections than immediate induction with either oxytocin or prostaglandins. This meta-analysis also showed that the rate of chorioamnionitis was higher in patients induced with prostaglandin versus those induced with oxytocin. However, this meta-analysis was heavily influenced by the large international trial, and as noted previously, this trial used a very low dose of prostaglandin.

Within the last few years, intravaginal misoprostol (a PGE_1 analog) has assumed marked popularity for induction because of its efficacy and low cost. Intravaginal misoprostol (50 µg every 4 hours for a maximum of 12 tablets) was compared with oxytocin in women with single pregnancies and an unfavorable cervix (<2 cm dilated and <80% effaced). The results of this trial are presented in Table 11.5. Overall, patients randomized to misoprostol had a shorter induction time, by approximately 2 hours, but they had significantly more uterine tachysystole. Of note, over 85% of patients required only one dose of misoprostol. Compared to other trials evaluating misoprostol in patients at term with intact membranes, the dose used in this trial is relatively high.

	Misoprostol (n = 70)	P	Oxytocin (n = 71)
Induction time (min)	416.0	0.04	539
One dose, %	85.7		
Uterine tachysystole*, %	28.6	<.04	14.0

*≥6 contractions/10 min. × 20 min. No difference in mode of delivery or any other complications.

Source: Sanchez-Ramos L, Chen AH, Kaunitz AM, et al. Labor induction with intravaginal misoprostol in term premature rupture of membranes: a randomized study. *Obstet Gynecol* 1997;89:909–912.

TABLE 11.5. *Misoprostol vs. oxytocin in PROM*

A 1998 American College of Obstetricians and Gynecologists' (ACOG) Practice Bulletin concluded that with term PROM, labor may be induced at the time of admission or that patients may be observed for up to 24 to 72 hours after PROM. In sum, while a range of practices is available and supported in the literature, the decision regarding delivery after PROM at term must take into account fetal presentation, fetal status, cervical ripeness, presence of infection, and patient desires. For patients with a breech (or other malpresentation) infant or an infant with evidence of intolerance of labor, prompt cesarean delivery is most appropriate. If there is clinically evident infection and no contradiction to vaginal delivery, then immediate induction and antibiotic therapy are indicated. If the cervix is ripe, then a short period of observation is reasonable, but induction with oxytocin resolves the situation. When the cervix is unripe, induction with either prostaglandins or oxytocin shortens the time to delivery, decreases risk of infection, and does not appear to increase cesarean section rate. The epidemiologic data linking chorioamnionitis with cerebral palsy provide additional impetus to move toward delivery after PROM at term.

PROM at 32 to 34 Weeks (Table 11.6)

◊ Expectancy vs. induction, especially if there is evidence of fetal lung maturity based upon analysis of amniotic fluid collected by amniocentesis or from vaginal pool.
◊ Prophylaxis for group B streptococci.
◊ Although broad-spectrum antibiotics have been used in some studies to prolong pregnancy in the gestational age bracket, there are concerns about selection pressure for resistant organisms and about masking fetal infection. Therefore, the author limits such broad-spectrum antibiotic use to earlier gestational ages.
◊ Do not use tocolytics.
◊ Do not give corticosteroids.

TABLE 11.6. *Summary of management: PROM at 32–34 wks*

Management in this gestational age category remains controversial. When there is evidence of fetal lung maturity, two trials have reported benefits to induction versus continued expectancy. In one trial, induction had several benefits, including a shorter time to delivery (14 vs. 36 hours; P < .001), shorter maternal hospital stay (2.3 vs. 3.5 days; P < .001), and less chorioamnionitis (11 vs. 28%; P = .06). Neonatal hospital stay was also shorter (6.3 vs. 7.3 days), but this difference was not significant. Although the authors found less clinically diagnosed neonatal sepsis in the induction group (28 vs. 60%; P < .003), there was no difference in confirmed sepsis (7 cases in induction group vs. 4 in expectant). There were no significant differences in the rates for cesarean delivery, postpartum infection, or neonatal survival. The other trial also found advantages to induction versus expectancy. Despite the reasons advanced by these authors, there is not yet compelling evidence to induce all pregnancies with PROM at 32 to 34 weeks simply because there is evidence of lung maturity. There is no improvement in perinatal mortality (PNM), and in other populations, induction in the presence of an unripe cervix at 32 to 34 weeks might result in higher infection rates or cesarean delivery rates. However, the evolving concern of intrauterine infection causing cerebral palsy adds strength to arguments for induction in the presence of lung maturity.

For pregnancies with PROM at 32 to 34 weeks, we have generally used expectant management. We do not routinely perform amniocentesis, but use this selectively when we suspect infection or growth restriction. We assess fetal status during expectant management with usual testing, mainly daily nonstress tests with biophysical profiles as needed for backup. In selected pregnancies at 32 to 34 weeks, we induce labor in the presence of lung maturity. Such situations include development of a favorable cervix (noted on a speculum examination) or poor patient compliance. We, of course, proceed with delivery when there are maternal or fetal indications including evidence of infection. For pregnancies with PROM at 32 to 34 weeks, we give intrapartum prophylaxis per the Centers for Disease Control and Prevention (CDC)/ACOG guidelines. We also obtain an appropriate rectovaginal culture for GBS at the time of admission, unless delivery is imminent. We then begin empirical intravenous prophylaxis until the culture result is available and is negative. If at 33 to 34 weeks the culture is positive, we will continue intravenous penicillin for 48 hours, then stop and re-culture.

PROM at 25 to 31 Weeks (Table 11.7)

◊ Expectancy.
◊ Prophylaxis for group B streptococci.
◊ Antibiotics for 7 d. No standard regimen has been established. (ampicillin + erythromycin or erythromycin), or alternative regimens.
◊ Corticosteroids.
◊ Use of tocolytics remains controversial. If used, they should be limited to 48 h.

TABLE 11.7. *Summary of management: PROM at 25–32 wks*

Management in the gestational age category also remains especially controversial. For management of PROM after viability but before 32 weeks, our practice is to generally follow expectant management and proceed with delivery where there is spontaneous onset of labor or clinical evidence of infection. We follow national guidelines for intrapartum prophylaxis for prevention of GBS neonatal sepsis. For patients in whom delivery is not imminent, we also obtain an appropriate culture for GBS from the rectovaginal area. We do administer corticosteroids in a standard regimen. We also apply broad-spectrum antibiotic therapy, usually following the ampicillin/amoxicillin plus erythromycin regimen of the MFM trial. This regimen is limited to 7 days. When the patient goes into labor, we begin GBS prophylaxis unless the GBS culture was negative on admission, as recommended by the CDC. Use of tocolytics during this gestational age in patients with preterm premature rupture of the membranes remains controversial.

PROM at Less Than 25 Weeks (Table 11.8)

◊ Induction vs. expectancy, depending upon gestational age and patient desires. ◊ No data on steroids, tocolytics, or antibiotics (prophylaxis for group B streptococci or prolonging pregnancy). ◊ It is unlikely that tocolytics achieve any significant prolongation of pregnancy and may mask early evidence of infection. Therefore, they are not recommended. ◊ It is unlikely that corticosteroids provide any fetal benefit at this gestational age, and corticosteroids may also increase the risk of intrauterine infection. Therefore, corticosteroids should be reserved for gestational ages where benefit is more likely. ◊ A course of antibiotics for 7 d may prolong pregnancy and decrease complications as in pregnancies with PPROM at 25–32 wks. ◊ After a period of inpatient hospitalization, home management may be used for uncomplicated, selected patients.

TABLE 11.8. *Summary of management: PROM <25 wks*

For PROM before viability (approximately 24 weeks), several descriptive reports have demonstrated a highly variable latent period, high maternal infection rates (but with little serious morbidity), and an appreciable survival rate, especially when delivery occurs after week 24 (Table 11.9). Outcome data with expectant management of PROM in the second trimester showed perinatal survival and "intact" neurologic survival stratified by the gestational age at the time of PROM (Fig. 11.4). In sum, when gestational age occurred from weeks 14 to 19, overall survival was only 40% whereas when PROM occurred at 20 to 25 weeks, overall survival was nearly 90%. The alternative to expectant management is induction. In the patient with PROM this early in pregnancy, we individualize the decision, involving the family fully. In the proper setting, we offer expectant management.

Outcome measure	Result
Gestational age at rupture of membranes (median [range])	23.5 wks (17–26)
Latent period (median [range])	7.6 d (1–161)
Amnionitis (mean [range])	39% (22–63)
Survival (mean [range])	38% (25–46)
Normal development at 1 y (mean [range])	59% (20–68)

From: Sweet RL, Gibbs RS. *Infectious diseases of the female genital tract*, fourth edition. Philadelphia: Lippincott Williams & Wilkins, 2002.

TABLE 11.9. *Summary of management: PROM at =24 wks*

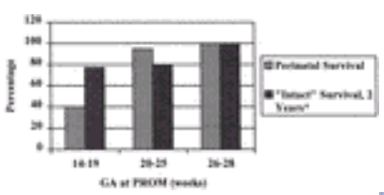


FIG. 11.4. Outcome with expected management of second trimester PROM. (From Sweet RL, Gibbs RS. *Infectious diseases of the female genital tract*, fourth ed. Philadelphia: Lippincott Williams & Wilkins, 2002; with permission.)

Chorioamnionitis Complicating PROM at Any Gestational Age (Table 11.10)

◊ Begin intravenous, broad-spectrum antibiotics, based upon the array of aerobic and anaerobic organisms isolated in amniotic fluid of cases of clinical chorioamnionitis. ◊ There is no place for expectant management in clinically overt chorioamnionitis. ◊ The route of delivery should be determined by standard obstetric considerations. Immediate cesarean delivery increases maternal morbidity and does not improve neonatal outcome. However, the cesarean delivery rate is high in pregnancies complicated by clinical chorioamnionitis because of poor progress in labor, nonreassuring fetal heart rate patterns, and malpresentation.

TABLE 11.10. *Management of clinically evident chorioamnionitis*

When clinically evident chorioamnionitis is diagnosed at any gestational age, broad-spectrum antibiotics, appropriate for the array of suspected aerobes and anaerobes, should be initiated intravenously. There is no place for expectancy when intrauterine infection becomes clinically overt and preparation should be made for delivery.

SUMMARY POINTS

Management of PROM

- At or near term (35 weeks) induction is usually preferred; GBS prophylaxis is given with a positive screening culture at 35 to 37 weeks or with rupture of membranes greater than 18 hours plus an unknown culture status.
- At 32 to 34 weeks, manage by either expectancy or by induction (especially with evidence of lung maturity). Give GBS prophylaxis. Do not use tocolytics or corticosteroids.
- At 25 to 32 weeks, manage by expectancy. Give GBS prophylaxis and give corticosteroids. We give antibiotics for 7 days to prolong pregnancy. No standard regimen is established. We use ampicillin plus erythromycin most often. Use of tocolytics is controversial.
- At less than 25 weeks, manage by induction or expectancy, depending upon gestational age and patient desires. We do not use tocolytics or corticosteroids in this situation. A course of antibiotics for 7 days may prolong pregnancy as at 25 to 32 weeks.

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Chapter 12

Henry L. Galan and John C. Hobbins

Intrauterine Growth Restriction

DETERMINANTS OF NORMAL AND ABERRANT PLACENTAL GROWTH
Normal Placental Development
Abnormal Placental Development
DETERMINANTS OF NORMAL AND ABERRANT FETAL GROWTH
Normal Fetal Growth
Abnormal Fetal Growth
DEFINITION OF IUGR
ETIOLOGY OF IUGR
DIAGNOSIS OF IUGR
Dating the Pregnancy
Ultrasound
DOPPLER VELOCIMETRY IN THE ASSESSMENT OF IUGR
Doppler Ultrasound
Normal Fetal Circulation
Circulation of the IUGR Fetus
Umbilical Artery Doppler
Middle Cerebral Artery (MCA)
Precordial and Cardiac Flows
Temporal Doppler Changes in the IUGR Fetus
MANAGEMENT OF THE IUGR FETUS
QUANTIFICATION OF FLOW
Doppler Prediction of IUGR and Preeclampsia
SUMMARY POINTS

SUGGESTED READINGS

Approximately 10% of the almost 4 million infants born each year in the United States are classified as low birth weight (LBW). Terminology used to describe the small fetus/newborn can be confusing. The term LBW is used clinically by pediatricians postnatally and is defined strictly as a birth weight less than 2500g with no regard for gestational age. The term “small for gestational age” (SGA) was originally defined by pediatricians as a newborn with a birth weight less than expected given gestational age and which can occur in a term or a preterm neonate. However, use of the term SGA subsequently expanded from the postnatal period to the antenatal period and is currently used interchangeably with intrauterine growth restriction (IUGR). For the purposes of this chapter, the use of the term SGA will be reserved for the newborn and IUGR, as implied by the name, will be restricted to the fetus. IUGR is more specifically defined later in the chapter. The fetus or newborn classified as IUGR or SGA, respectively, encompasses a group of fetuses-newborns that are small for a variety of reasons with varying prognoses, including congenital infections, congenital malformations, aneuploidy, uteroplacental insufficiency, and constitutionally small. It is important to recognize that not all fetuses or newborns that are classified as IUGR or SGA are small due to pathologic reasons (i.e., constitutionally small), but simply represent the smaller fetuses/newborns at the lower end of the bell-shaped distribution of the normal poulation. The prognosis for a given IUGR fetus is dependent on the etiology. Placental insufficiency accounts for the majority of IUGR fetuses. The scope of the problem with IUGR is quite broad, not just because it increases morbidity and mortality of the fetus, but also because it does so for the newborn and adult the fetus is destined to become. IUGR places the fetus at risk for hypoxemia, acidemia, antepartum death, and intrapartum distress. It places the neonate at risk for a number of metabolic disturbances, polycythemia, pulmonary transition difficulties, intraventricular hemorrhage, impaired cognitive function, and cerebral palsy. Several epidemiologic studies and animal studies in the early 1990s began to report on long-term sequelae of IUGR including adult hypertension, heart disease, stroke, and diabetes. The theory of fetal programming as the origin of adult disease was introduced by Barker and colleagues and is commonly referred to as the “Barker hypothesis.” The challenge in management of the IUGR fetus is to identify the condition and manage it such that adverse sequelae are minimized. The use of real-time ultrasound and Doppler velocimetry play pivotal roles in the diagnosis and management of IUGR. This chapter reviews normal placental–fetal growth, etiologies of the IUGR fetus, and practical uses of ultrasound and Doppler velocimetry in the diagnosis and management of the IUGR fetus.

DETERMINANTS OF NORMAL AND ABERRANT PLACENTAL GROWTH

Normal Placental Development

In most mammalian species, the placental and fetal mass increase exponentially for at least a portion of pregnancy. Normal growth of the fetus is in turn dependent on normal placentation and growth of the placenta. The placenta is a dynamic and multifaceted organ that serves as an interface between mother and fetus with the critical role of meeting the metabolic and circulatory demands of the growing fetus. The roles of the placenta include:

Nutritional: Provides oxygen, glucose, amino acid, and volume (fluid) transfer.
Immunologic: Protects the fetus from pathogens and the maternal immune system.
Endocrinologic: Produces numerous hormones, growth factors, cytokines, and other vasoactive mediators.
Metabolic: Serves as the respiratory and the kidney organ for the fetus and is responsible for elimination of carbon dioxide, metabolic acids, and other waste products from the fetus to maintain acid–base balance.

Placentation must be normal in order for these functions to be met.

Research has begun to provide an understanding of the complexity of the implantation and placentation processes, which requires production and coordination of numerous angiogenic growth factors (fibroblast growth factor, hepatocyte growth factor, placental growth factor, vascular endothelial growth factor), cell-adhesion molecules, cytokines, nitric oxide, extracellular matrix metalloproteinases, hormones, and transcription factors (hypoxia inducible factor). This process of coordination begins very early in pregnancy and can dictate whether the pregnancy grows in a normal or abnormal direction. During the luteal phase of the menstrual cycle, the endometrium becomes decidualized in preparation for acceptance of the products of conception. Shortly after entering the uterine cavity on day 4 postconception, the morula becomes a blastocyst with an inner cell mass at one pole that is called the *embryoblast* and an outer cell mass that is called the *trophoblast.* On day 7 postconception, the trophoblast differentiates into the cytotrophoblast, which envelops the blastocyst circumferentially. Simultaneously, the newly developed cytotrophoblast cells further differentiate into a sheet of syncytiotrophoblast cells. The syncytiotrophoblast produces proteins and steroid hormones. The cytotrophoblast, made up of nucleated cells, continues to produce the anucleate syncytiotrophoblast throughout gestation primarily by mitotic activity and loss of cytotrophoblastic cell walls. By day 13, the cytotrophoblast layer has differentiated into invasive and noninvasive cytotrophoblast. The invasive cytotrophoblast forms invasive cell columns that invade the uterine epithelium to anchor the fetus and establish blood flow to the placenta and fetus. During this process, the invasive cytotrophoblast cells (extravillous trophoblast):

- *migrate* through the syncytiotrophoblast and into the decidualized endometrium and myometrium
- *invade* the vessel walls of the maternal-based spiral arteries in these areas
- *transform* the spiral arteries from a high-resistance to a low-resistance vessel.

As the invasive cell columns of the cytotrophoblast penetrate the syncytiotrophoblast, spaces called *lacunae* are created, which subsequently fuse to form the intervillous space with intervening syncytiotrophoblast columns called *trabeculae.* The process of intervillous space formation and spiral artery transformation directs an increasing maternal cardiac output into the intervillous space. Loss of spiral artery vessel media is the mechanism by which the spiral arteries drop their resistance to blood flow. The syncytiotrophoblast-based trabeculae branch laterally to initiate placental villi formation on approximately day 13. The extent of vascularization of the villus architecture defines the villus as stem or primary villus, secondary villus. or tertiary villus. The stem villus is without vessels and only has trophoblast cells. The secondary villus is formed by central invasion of the primary villous core by the allantoic mesenchyme of the embryoblast. The tertiary villus forms during vasculogenesis, which is the development of de novo blood vessels from mesenchymal cells differentiating into hemangioblasts. Hemangioblasts are precursors of endothelial cells. This process begins in the 5th week of gestation.

Each cotyledon, labeled by some as a fetal unit, is characterized by a villous tree that contains three basic types of villi:

1. stem villi

2. intermediate villi
3. terminal villi.

These three villous types represent progressively smaller generations of villous branching with the terminal villi serving as the end point. The stem villi extend from the chorionic plate to the basal plate. The stem villi contain a single truncus that progressively branches into the rami chorii, which in turn branches into the ramuli chorii. It is from the ramuli chorii that the intermediate villi appear of which there are two types: The immature and mature intermediate villi. The terminal villi are the primary gas exchanging villi, which have actually been identified at all levels of branching. They account for 55% of the total number of cross-sectional villi in the peripheral villous tree. Smooth muscle staining shows that vessels coursing through the villi contain smooth muscle media down to the level of the immature villi. This distinguishes the stem and immature villi from the gas-exchanging mature and terminal villi. It has been noted that the intermediate villi, because of the smaller arterioles, venules, pre- and postcapillaries contained within, may serve a hemodynamic regulatory function (i.e., control of blood pressure and flow). The concept of blood flow control at this level is further supported by previously described sphincterlike precapillary structures.

In contrast to vasculogenesis, angiogenesis represents the formation of new blood vessels from endothelial cells and is classified into branching and nonbranching angiogenesis. *Branching* angiogenesis occurs primarily in the first and second trimesters and leads to the formation of the immature villous tree. Branching angiogenesis continues until the end of the second trimester when there is a transition to *nonbranching* angiogenesis. During this process there is a dramatic increase in mature intermediate and terminal villi. The nonbranching angiogenesis forms terminal capillary loops with minimal branching and provides the network of capillaries for the intermediate and terminal villi. A dramatic decrease in vascular resistance and an increase in blood flow through the placenta are coincident with this process. The progressive decline in vascular resistance is depicted by increased end-diastolic velocities in Doppler flow velocity waveforms of the umbilical artery (Fig. 12.1).

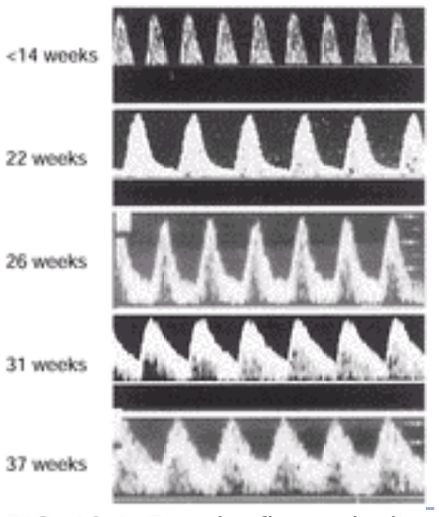

FIG. 12.1. Doppler flow velocity waveform profiles in the umbilical artery across normal gestation. Note the progressive increase in end-diastolic flow.

Abnormal Placental Development

In pregnancies complicated by preeclampsia and IUGR, trophoblast invasion is limited to the decidualized endometrium, which results in failure of the spiral arteries to become low resistance vessels. The inability of spiral arteries to transition from high to low blood flow resistance can be detected by Doppler velocimetry of the uterine artery which supplies blood to the spiral arteries. The blood flow velocity waveforms in the uterine artery obtained with pulsed-wave Doppler velocimetry are reflective of the waveforms downstream at the spiral arteries. These abnormalities are identified on a Doppler flow velocity waveform (FVW) profile by a high resistance pattern (low velocity of flow at end-diastole relative to that at systole) and by a protodiastolic (early diastolic) notch. Failure of this process to occur on the maternal side of the circulation may lead to adverse effects on both the mother and the fetus. Maternal vascular endothelial dysfunction may lead to production of a variety of vasoactive mediators, which could subsequently lead to the development of preeclampsia. Poor growth of the placental–fetal unit may also result from poor invasion and remodeling of the spiral arteries by the cytotrophoblast.

A variety of villous and vascular abnormalities have been described in the placenta of the IUGR fetus. Placentas from IUGR pregnancies have fewer gas-exchanging villi. The gas-exchanging villi are also slender, elongated, poorly branched, and poorly capillarized. Vascular abnormalities include reduced branching of stem arteries and disorganized vascular patterns including less coiling as depicted by placental vascular cast studies. There are also fewer terminal villi with smaller lumens. The reduced branching seen in the villous vasculature creates abnormal blood flow and an increase in vascular resistance to flow that can be likened to that of an electric circuit—the fewer downstream tributaries that exist from the main supply line, the higher the resistance.

DETERMINANTS OF NORMAL AND ABERRANT FETAL GROWTH

Normal Fetal Growth

In order for a fetus to grow normally, the placental developmental activities described earlier must proceed undisturbed. At 37 weeks gestation, the placenta has reached maximal surface area (11 m^2) and weighs approximately 500 g. Coincident with this is maximal amniotic fluid volume and maximal human placental lactogen levels, suggesting peak placental function. Fetal growth velocity also curtails at this juncture in pregnancy. Interestingly, although the fetus grows less quickly, calorie acquisition by the fetus continues to be quite high. At this time in pregnancy, the fetus is rapidly accumulating fat which provides thermal stability for the immediate postnatal period. Fat has a high caloric content (9 calories/g) compared to carbohydrates and proteins (4 calories/g). The high metabolic demands of the fetus result in a fetal temperature that is 0.5°C above that of the mother. This difference in temperature is seen in the maternal immediate postpartum shivering, which reflects a compensatory response to the loss of fetal-derived heat.

For the fetus to achieve maximal growth potential, the uterine–placental–fetal circulation must be normal in order for the fetus to receive a variety of necessary substrates. A key feature of the uterine vascular bed in pregnancy is the lack of responsiveness to changes in blood gas tensions (PO_2, PCO_2). Thus, oxygen therapy for either maternal disease or for fetal benefit will not cause vasoconstriction. In contrast, the lack of responsiveness and lack of autoregulation in the uterine vascular bed renders these vessels incapable of compensating for maternal hypotension. Animal studies have shown that the volume blood flows (mL/min) in the uterine and umbilical circulations are unaffected by maternal hyperoxygenation. This is important clinically since the improvement in fetal PO_2 by maternal oxygen therapy does not appear to have an adverse affect on fetal blood flow.

Glucose, oxygen, and amino acids are the major substrates needed for normal fetal growth. Glucose freely crosses the placenta by facilitated diffusion into the fetus. The maternal–fetal glucose concentration gradient that exists widens with advancing gestational age in order to accommodate the increasing metabolic demands of the fetus. Under normal circumstances, glucose is metabolized by the fetus to produce energy in the form of adenosine triphosphate (ATP) in the presence of oxygen. Oxygen passes across the placenta to the fetus by simple diffusion and is regulated by concentration gradients and uterine blood flow as described by the Fick principle. Transplacental transport of all essential and nonessential amino acids occurs by active transport. Animal and human studies have confirmed that amino acid carrier systems are present on both the maternal and fetal sides of the placenta. The placenta is quite active in amino acid metabolism contributing significantly to net umbilical–fetus uptake of certain amino acids.

Abnormal Fetal Growth

Failure of the placenta to deliver these primary substrates to the fetus will result in diminished protein production by the fetus, reduced glucose metabolism, and reduced glycogen deposition in the liver. If oxygen supply is markedly reduced either from an acute or chronic insult, the fetus will convert from an aerobic to an anaerobic metabolic state in order to meet energy (ATP) requirements. Anaerobic metabolism is far less efficient at producing ATP from a given unit of glucose compared to aerobic metabolism. Furthermore, anaerobic activity will produce “fixed” acids (lactate, urate, etc.), which diffuse slowly across the placenta thus accumulating in the fetal system. If the anaerobic process is not reversed, the accumulation of acids will consume available buffers, and the fetal blood pH will fall, leading to an acidemic and acidotic fetus.

The IUGR fetus attempts to compensate for reduced substrate delivery by different mechanisms. From a metabolic standpoint, the fetus changes the maternal–fetal glucose gradient. The normally wide glucose gradient that exists between the mother and fetus, which is needed for movement of glucose to the fetus, widens further. This compensatory mechanism enhances glucose movement across the placenta to the fetus. The smaller abdominal circumference noted in the IUGR fetus is a result

of less hepatic glycogen formation in order to maximize glucose availability. In a similar fashion to the liver, fat stores, which are normally an important depot site for fat-soluble vitamins and fatty acids, are reduced. This change in body composition is reflected in the ponderal index, which neonatologists use as an index of "scrawniness." The fetus also adjusts to reduced nutrient delivery by redistributing systemic blood flow to vital organs. The fetus will reduce flow to nonvital organs by reducing vascular resistance and increasing blood flow to the brain which normally has a relatively high vascular resistance pattern compared to other organ systems. This can be demonstrated with pulsed-wave Doppler velocimetry of the middle cerebral artery (MCA) in which the flow velocity profile shows an increase in end-diastolic velocity. Other organs being "spared" through vascular redistribution include the heart and adrenal glands. Redistribution of blood flow to vital organs in experimental animal models of hypoxemia or infusion of angiotensin II into the sheep fetus mimic the hemodynamic alterations observed in the human IUGR fetus.

DEFINITION OF IUGR

A number of definitions of IUGR have been proposed based on percentile, standard deviation, or growth rate. The most commonly used clinical definition of IUGR is an estimated fetal weight (EFW) less than the tenth percentile as determined by ultrasound. This mirrors the definition of SGA, which was originally described by Battaglia and Lubchenco in 1967 as a birth weight less than the 10th percentile for gestational age. They noted that SGA infants were at increased risk for neonatal death. The problem with the tenth percentile as a cutoff for the diagnosis of IUGR is that a number of fetuses with an EFW below that value will be normally small, otherwise referred to as "constitutionally" small and not at risk. Studies have demonstrated that if determinants of birth weight, such as maternal ethnicity, parity, maternal weight and height are considered, up to 50% of fetuses less than the tenth percentile will be constitutionally small. This has been the basis for using other definitions including less than the third or fifth percentile or less than 2 SDs from the mean. Some authors have suggested using an abdominal circumference (AC) of less than 2 SDs for gestational age. The AC measurement represents a single objective ultrasound measurement rather than combining several fetal biometric ultrasound parameters into a formula where each parameter is weighted differently.

While it seems that an EFW less than the tenth percentile is not a sufficiently strict definition of IUGR, there is also a significant problem associated with the use of more strict criteria. If a definition of less than the third percentile is used, there is a reasonable chance that one could miss some fetuses that do not meet their growth potential and could be at risk for adverse events. We believe that the fetus genetically programmed to be born at the 90th percentile that is born at the 20th percentile may be in more trouble than the baby born to a jockey and a gymnast who is at the 8th percentile. The bottom line is that no receiver operator curves have been established to assess sensitivity and specificity in order to establish a "cutoff" for the diagnosis of IUGR. This has been quite difficult to do, in part because of a wide biologic variation between patients and because of a wide variation of parameters used to diagnose IUGR (EFW, AC < 2SD, etc.). Customized growth curves, such as those envisioned and created by Gardosi that include variables that impact fetal size, may be the answer to establishing a better cutoff value for IUGR. Until such standards become published and available, the use of tools such as pulsed-Doppler velocimetry to investigate the status of the fetal circulation will help identify an IUGR pregnancy that is secondary to uteroplacental insufficiency and potentially at risk of perinatal morbidity and mortality. Doppler velocimetry is discussed in detail later in the chapter.

ETIOLOGY OF IUGR

The type and timing of insult during fetal development will dictate the subsequent development and morphology of the fetus. Fetal growth in the first trimester is characterized primarily by an increase in cell number or hyperplasia. In the second trimester, growth is a combination of hyperplasia and hypertrophy of preexisting cells. The third trimester is characterized primarily by hypertrophy. If an insult occurs in the first half of pregnancy where hyperplasia predominates, all fetal cell numbers can be reduced and lead to a small fetus that is *symmetrically* proportioned. That is, somatic and cerebral growth will both be similarly reduced. The underlying etiology of symmetric IUGR varies widely and includes: Karyotypic abnormalities, congenital anomalies, or congenital infections. Maternal medical illness, obstetric conditions, or primary placental pathology place the fetus at risk for uteroplacental insufficiency that may lead to a small fetus, which is asymmetrically proportioned. If these types of insults occur sufficiently early enough in pregnancy, there can be an impact on hyperplasia of cells and a symmetric growth pattern. More commonly, there is an impact upon hypertrophy that occurs late in pregnancy and primarily affects fat and hepatic glycogen deposition. The reduction in hepatic glycogen stores reduces liver size and results in an increase in the head-to-liver ratio, which defines asymmetric growth. Asymmetric growth is also characterized by a redistribution of fetal cardiac output to vital organs including the brain, heart, and adrenal glands. The redistribution of blood flow to the head allows the fetal head and brain to be preserved and maintain a normal growth velocity compared to parameters of somatic growth (abdomen and extremities). This is the basis for the common phrase, "brain-sparing". Thus, the relative proportions of fetal dimensions can provide some insight to the etiology of IUGR based on the symmetric or asymmetric nature of the ultrasound parameters.

DIAGNOSIS OF IUGR

Dating the Pregnancy

Studies in the past decade have clarified the associations of IUGR and long-term health hazards by confirming good gestational age dating. The use of actual gestational dating rather than birth weight alone is critical since it more clearly establishes that the link of cardiovascular disease and diabetes with IUGR status at birth is not due to prematurity, but to true intrauterine growth restriction. Establishing the most accurate gestational age is probably the single most important service we provide the pregnant patient since every test or intervention performed during pregnancy is dictated by the gestational age of the patient.

The diagnosis of IUGR begins with accurate dating of the pregnancy, which in turn begins with the establishment of the estimated date of confinement (EDC) based on information gathered on the last menstrual period (LMP). Normal human gestation lasts 280 days from the LMP, and it is this time frame that "pregnancy wheels," commonly used to determine estimated gestational age and date of confinement, are based upon. The 280-day gestation is, in turn, based upon a normal menstrual cycle length of 28 days. However, a portion of patients will have menstrual cycle lengths that vary from 21 to 35 days, which will shorten or lengthen the gestational dating, respectively. Therefore, the EDC should be adjusted accordingly. Other important questions regarding the LMP include regularity, certainty (calendar recorded, etc.), date of conception, and oral contraceptive use at the time of the LMP. It has been previously reported that the LMP is unreliable up to one-third of the time, and it is in these circumstances that ultrasound becomes a valuable resource.

After establishment of gestational age by LMP and/or ultrasound, clinical acumen can lead to a presumptive diagnosis of IUGR. The most commonly used clinical tool for assessing growth of the pregnancy is serial measurement of uterine fundal height during regular clinic visits. Measurement of uterine fundal height (cm) from the symphysis across the uterus to the top of the fundus provides an index of growth for which a nomogram has been reported (Fig. 12.2). In general, the uterine fundus will be within 2 cm of the gestational age in weeks. This simple screening technique has been reported to be 75% accurate in diagnosing IUGR. However, the measurement may be erroneous because of several variables that impact uterine size, including interobserver variation, obesity, uterine fibroids, multiple gestation, polyhydramnios, and so forth.

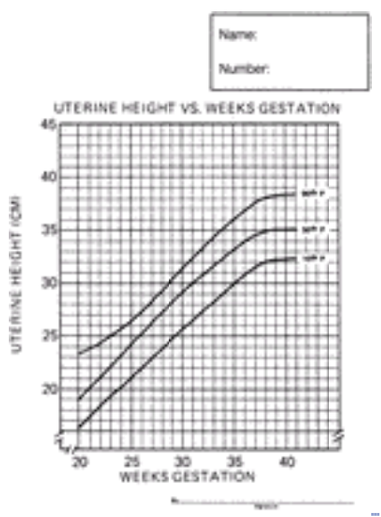

FIG. 12.2. Uterine fundal height chart for the diagnosis of fetal growth restriction.

Ultrasound

While LMP dating and clinical acumen are important in screening for IUGR, ultrasound remains the cornerstone for the diagnosis and management of this condition. The diagnosis of IUGR is made by combining ultrasound biometric measurements of the fetus into a formula that calculates the estimated fetal weight (EFW). The most

commonly measured fetal biometric parameters include the biparietal diameter (BPD), the head circumference (HC), the abdominal circumference (AC), and the femur length (FL). As described earlier, IUGR is diagnosed when the EFW falls below the tenth percentile for gestational age. If available, it is important to use local standards for the diagnosis since it has been previously shown that tenth percentile for EFW can vary depending on the population studied. Goldenberg and colleagues have shown that growth charts can differ dramatically among different patient populations. For example, a fetal weight nomogram constructed by ultrasound in Colorado suggests that consistently, across gestational ages, fetuses in Denver are lighter than fetuses at sea level. The Shepard and Hadlock formulas are the most commonly used formulas for calculating EFW. Table 12.1 shows the estimated fetal weight using Hadlock's formula plotted across gestation. In general, the more parameters included, the more accurate the EFW (Hadlock: 4 parameters; Shepard: 3 parameters). However, as you increase the number of parameters in the formula above, EFW begins to lose accuracy because of the standard error of the method associated with the measuring of each parameter. Using the Shepard formula, a practitioner will obtain an EFW that will fall within 5% of the true weight 50% of the time and within 10% of the weight 80% of the time.

Menstrual week	Percentiles (g)				
	3rd	10th	50th	90th	97th
10	26	29	35	41	44
11	34	37	45	53	56
12	43	48	58	68	73
13	55	61	73	85	91
14	70	77	93	109	116
15	88	97	117	137	146
16	110	121	146	171	183
17	136	150	181	212	226
18	167	185	223	261	279
19	205	227	273	319	341
20	248	275	331	387	414
21	299	331	399	467	499
22	359	398	478	559	598
23	426	471	568	665	710
24	503	556	670	784	838
25	589	652	785	918	981
26	685	758	913	1,068	1,141
27	791	876	1,055	1,234	1,319
28	908	1,004	1,210	1,416	1,513
29	1,034	1,145	1,379	1,613	1,724
30	1,169	1,294	1,559	1,824	1,949
31	1,313	1,453	1,751	2,049	2,189
32	1,465	1,621	1,953	2,285	2,441
33	1,622	1,794	2,162	2,530	2,703
34	1,783	1,973	2,377	2,781	2,971
35	1,946	2,154	2,595	3,036	3,244
36	2,110	2,335	2,813	3,291	3,516
37	2,271	2,513	3,028	3,543	3,785
38	2,427	2,686	3,236	3,786	4,045
39	2,576	2,851	3,435	4,019	4,294
40	2,714	3,004	3,619	4,234	4,524

Source: Adapted from Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991;181:129–133; with permission.

TABLE 12.1. *In utero fetal weight standards at ultrasound*

A commonly encountered clinical scenario is the patient who is sent for evaluation of suspected IUGR in whom the clinical dating criteria are poor and gestational age unknown. For example, a fetus measuring 3 to 4 weeks less than expected may be the result of any of the following three possibilities:

1. The patient is 3 to 4 weeks off on clinical dating.
2. The fetus is truly 3 to 4 weeks less than clinical dating, but is genetically predisposed to be small.
3. The fetus is small, growth-restricted, and at risk.

Several ultrasound strategies are available to address this problem and to categorize the fetus into one of the categories. The ultrasound biometric parameters can be used to calculate ratios and provide some insight into the severity of the IUGR. In the 1970s, Campbell and Thoms first described the HC/AC ratio. In approximately 60% of cases with IUGR, the HC/AC ratio is in the 90th percentile for gestational age, which suggests a “brain-sparing” process. The FL/AC ratio provides information on the amount of muscle and fat mass present on the fetus providing a picture of the “scrawniness” of the fetus. This is analogous to the ponderal index used by neonatologists. Unlike the HC/AC ratio, the FL/AC ratio is gestational-age independent and may be useful when the gestational age is unknown. Other aspects of the fetus that appear to be relatively independent of the IUGR process and that remain consistent throughout gestation include the transcerebellar diameter (TCD), foot length, and epiphyseal centers. These are other strategic tools to help approximate the gestational age when dating criteria are poor.

The TCD measured in centimeters mirrors the gestational age until about 22 weeks and then accelerates. Cerebellar measurements are shown in Table 12.2. While original studies by Reece and co-workers showed that the TCD is “spared” in IUGR, one study suggests that only 40% of IUGR fetuses demonstrated the sparing effect. However, the etiologies for IUGR in this study were not clearly identified. If the gestational age by TCD is greater than that suggested by other biometric parameters and is consistent with the unsure LMP dating criteria, it may be that the fetus is indeed further along and possibly growth restricted. In a similar fashion, Hadlock and colleagues showed that the foot length is gestational-age independent and may be useful in IUGR. Although not useful for estimating gestational age in the second and early third trimester, the appearance of epiphyseal centers of the long bones on ultrasound provides reassurance that the fetus is in the second half of the third trimester of gestation. In a nondiabetic population, the presence of a distal femoral epiphysis of greater than 3 mm and the presence of any proximal tibial epiphysis indicated a mature lung profile in almost all cases. The proximal tibial epiphysis is not typically present prior to 36 weeks gestation. Additionally, the proximal humeral epiphysis rarely appears prior to 38 weeks gestation. Unpublished information suggests that appearance of the epiphyseal centers in IUGR fetuses may be delayed. This should be taken in the context that it is the presence of the tibial and humeral epiphyseal centers that are useful markers of pulmonic maturity, while the absence of these centers may suggest a more immature fetus.

Gestational age (wk)	Percentile		
	10th	50th	90th
15	13	14	16
16	14	16	17
17	16	17	18
18	17	18	19
19	18	19	20
20	19	20	21
21	20	21	23
22	22	23	24
23	23	24	26
24	23	26	28
25	25	27	30
26	26	28	32
27	27	30	33
28	28	31	35
29	29	33	38
30	31	35	40
31	33	38	42
32	34	39	43
33	35	40	44
34	38	41	44
35	41	42	45
36	42	43	45
37	43	45	48
38	45	48	50
39	48	52	55
40	52	55	58

Source: Adapted from Goldstein I, Reece EA, Pilu G, et al. Cerebellar measurements with ultrasonography in the evaluation of fetal growth and development. *Am J Obstet Gynecol* 1987;156:1065–1069; with permission.

TABLE 12.2. *A nomogram of the transverse cerebellar diameter (mm)*

Serial ultrasound measurements of fetal biometry and estimated fetal weight are also useful in assessing the growth-restricted fetus. The fetus that demonstrates appropriate growth, that is, continued growth along nomograms, probably represents a fetus genetically predisposed to being small and one that is likely not at immediate risk. A couple of problems of relying on growth potential alone is that it does not tell you where in gestation the fetus is or how the fetus is doing at the first evaluation. As with all these biometric tools, it is best to look at the big picture and formulate an opinion based on all information that one can obtain with the ultrasound. Another tool that can be used to categorize a small fetus is pulsed-wave Doppler velocimetry. This ultrasound modality, which has revolutionized the management of the IUGR fetus, can also be used to help delineate whether a fetus is “normal” small or “abnormal” small based on the umbilical FVW.

DOPPLER VELOCIMETRY IN THE ASSESSMENT OF IUGR

Doppler Ultrasound

The concept of Doppler, which is used in ultrasound, is named after Johann Christian Doppler. The Doppler concept refers to energy that is reflected from a moving boundary, and how the frequency of the reflected energy varies in relation to the moving boundary. In ultrasound terms, Doppler depends on the ability of an ultrasound beam to be changed in frequency when encountering a moving object (red blood cells). After cosmetic manipulation, a waveform is generated that has a clear systolic and diastolic component. Although resistance to blood flow in a given interrogated vessel in the fetus cannot be directly measured, it is possible from the waveform to obtain an index of resistance. Figure 12.3 shows a FVW in the umbilical artery with clear systolic and diastolic cardiac components. Using the peak systolic and peak diastolic values, it is possible to generate Doppler indices of resistances. These include the systolic-to-diastolic (S/D) ratio, pulsatility index, and resistance index. Because these three indices are functions of the same variables, they are correlated highly with one another. The characteristics of these indices are also shown in

Figure 12.3. The original continuous-wave Doppler technology has been replaced by pulsed-wave Doppler technology. Doppler velocimetry is useful in cases where the fetus is asymmetrically grown due to a uteroplacental etiology.

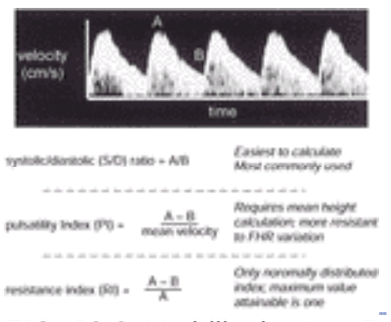

FIG. 12.3. Umbilical artery Doppler flow velocity waveform demonstrating peak systolic (**A**) and peak end-diastolic (**B**) velocities. Doppler indices are defined below.

Over the past decade, numerous centers across the United States and in Europe have shed light on circulatory physiology in the normal and growth-restricted fetus. This has been approached by assessing FVWs in a number of different vessels in the fetus. While these reports provide useful information on any given vessel, reports on one or two vessels alone are not practical from the clinical standpoint since these were primarily cross-sectional studies and did not provide any information on the temporal nature of Doppler changes. After the turn of the 21st century, three reports appeared in the literature that combined longitudinal information on several different vessels with biophysical data obtained from the IUGR fetus. These studies showed that there are sequential changes in Doppler FVW-resistance measurements in different vessels of the severely growth-restricted fetus that is progressively deteriorating.

Normal Fetal Circulation

The umbilical vein leaves the placenta and enters the umbilicus with oxygen and nutrient-rich blood and volume, which are necessary for normal development of the fetus. The venous vasculature of the liver consists of the umbilical and portal veins, hepatic veins, and the ductus venosus. The umbilical vein turns acutely cephalad as it passes through the umbilicus and in the inferior portion of the falciform ligament. The hepatic portion of the umbilical vein then travels horizontally and posteriorly, and bends to the right where it joins the transverse part of the left portal vein. These then join the right portal vein, which branches anteriorly and posteriorly. As the hepatic portion of the umbilical vein bends to the right, the ductus venosus emanates, heading in a posterior and cephalad direction and joins the inferior vena cava (IVC) just below the diaphragm. The three hepatic veins (right, middle, and left) fuse and join at the juncture of the ductus venosus and IVC confluence. The ductus can be visualized easily on both axial and midline sagittal views of the fetus with the use of color velocimetry. Its detection can be enhanced by adjusting the velocity scale and looking for aliasing of the color that indicates the area of highest flow velocity. The ductus venosus plays a critical role in shunting the most oxygenated and nutrient-rich blood from the hepatic portion of the umbilical vein to the right atrium. More than half of the umbilical vein blood enters the ductus venosus. Portal blood primarily travels to the right lobe of the liver and, as a result, 98% of the blood passing through the ductus venosus comes from the umbilical vein. Some of the blood supply to the left lobe of the liver comes from branches of the umbilical vein, which increases blood oxygen levels in the left hepatic vein compared to the right. Preferential streaming is a phenomenon that occurs within precordial venous structures and the heart to ensure delivery of the most nutrient-rich blood to the left side of the heart. Briefly, nutrient-rich blood within the ductus and left hepatic vein course preferentially through the posterior and left portions of the column of blood in the thoracic IVC. Blood that is deoxygenated and contains waste products from the abdominal IVC and the right hepatic vein streams, preferentially, along the anterior and right portions of the column of blood in the thoracic IVC. Blood from the superior vena cava joins the blood traveling anteriorly and rightward, enters the right atrium across the tricuspid valve, and exits via the pulmonary artery. Only 10% of the blood from the pulmonary artery enters the pulmonary circulation with the majority crossing the ductus arteriosus into the aorta and the systemic circulation. The posterior and leftward nutrient-rich blood passes across the right atrium through the foramen ovale into the left atrium and out the left ventricle. This ensures that the heart and brain see the most oxygenated blood.

The precordial veins (ductus venosus, hepatic veins, IVC, umbilical and portal veins) have characteristic FVWs as shown by pulsed-wave Doppler velocimetry. The umbilical and portal veins have FVWs that are steady and without pulsations, while the other precordial “systemic” veins have FVWs that reflect the central venous pressures. The following information on the precordial venous FVWs is in reference to the hepatic vein, ductus venosus, and IVC, which have three characteristic phases during a single cardiac cycle. Ventricular systole induces the greatest pressure gradient between the right atrium and the precordial veins during the cardiac cycle. Thus, the blood traveling within these vessels to the heart will have the highest velocity during systole. This is referred to as the “S” component of the FVW. During early diastolic filling, the second highest velocity of blood through these venous conduits will occur and is referred to as either “D” or “e”. The lowest velocity of blood traveling through these vessels is in late diastole when the atria are contracting; this phase of the FVW is referred to as the “a”-wave. The a-wave in the ductus venosus remains in a positive direction (i.e., blood continues to move toward the heart even during the phase of lowest pressure gradient during atrial contraction). In contrast, the a-wave in the IVC and hepatic veins is in a negative direction indicating that blood is moving away from the heart. The difference in the a-waves between these vessels is important clinically because one can easily confuse reverse flow in the ductus venosus due to the close proximity of these vessels. However, the use of color Doppler and the identification of aliasing should easily distinguish the vessels.

The vast majority of fetal Doppler studies have adopted qualitative indices to describe FVW indices both for arterial flow and venous flow (i.e., S/a ratio of the venous flow of the ductus venosus). For some selected areas of investigation, quantitative parameters are calculated (i.e., peak velocity of the outflow tract of the great vessels). The arterial pipelines to almost all organs have been investigated, including the kidneys, the adrenal glands, the spleen, the lower limbs, the lungs, and the coronary arteries. While these reports provide a piece of the big picture, they do not add to information on fetal status and management gained from cardiac and precordial Doppler studies. As such they are not discussed, but are referenced at the end of the chapter (see “ Suggested Readings”).

Circulation of the IUGR Fetus

A convenient way to clinically approach the variety of fetal vessels that lend themselves to Doppler investigation is to conceptualize the progressive nature of the IUGR disease process and categorize them into three compartments related to the fetal heart:

1. Postcardiac (arterial) Dopplers
2. Cardiac Dopplers
3. Precardiac (precordial or venous) Dopplers.

The three general categories and vessels for each category are shown in Table 12.3. This organization follows the physiologic adaptations by the fetal circulation to progressive abnormalities in the placental vascular tree. Changes in the circulatory architecture of the IUGR placenta create a high-resistance vascular bed, which can be detected by Doppler velocimetry of the umbilical artery and the MCA. These represent the earliest Doppler changes in the IUGR fetus. As the IUGR fetus deteriorates, one can detect changes in peak velocities of the cardiac outflow tracts and abnormal valvular flow. Precordial or venous Dopplers also change in the IUGR fetus that is decompensating and these vessels include the ductus venosus, hepatic veins, IVC, and intrahepatic and intraamniotic umbilical veins.

1. **Postcardiac (arterial)**
Umbilical artery
Middle cerebral artery
2. **Cardiac**
Outflow tract peak velocities
Mitral and tricuspid valve E/A ratios
Tricuspid regurgitation
3. **Precardiac (precordial or venous)**
Ductus venosus
Hepatic veins
Inferior vena cava
Hepatic and amniotic cavity umbilical vein

TABLE 12.3. *Categorization of fetal vessels for Doppler study*

Umbilical Artery Doppler

The first fetal vessel to be assessed by Doppler velocimetry FVW analysis was the umbilical artery in the mid-1970s. During the late 1970s and early 1980s, Gill and colleagues and Trudinger and co-workers described the umbilical artery FVW in normal and IUGR pregnancies. In 43 infants with birth weight less than the 10th percentile, Trudinger and colleagues found that the umbilical artery S/D ratio was elevated above the 95th percentile in 85% of cases. This was determined to be related to a decrease in diastolic velocity, which was in turn due to an increase in resistance to blood flow within the placenta. This was supported by work from Giles

and colleagues who correlated the pathologic FVW in IUGR pregnancies with placental lesions. The key concept was that a poorly developed placental vascular bed and progressively abnormal vascularization in the face of increased fetal metabolic demands lead to an increase in placental vascular resistance. This is further supported by research work on hemodynamic bases of waveform changes as affected by increased impedance, changes in the viscosity of the blood, loss of vessel wall compliance, and decreasing inotropic function of the myocardium, all of which contribute to the increased resistance seen in abnormal arterial flow. The umbilical artery was chosen because it was the vessel that extended from the fetus to the placenta and because it reflects resistance patterns downstream within the placenta. This, in turn, could be identified clinically simply by switching a Doppler beam on the umbilical arteries and looking for an increased S/D ratio (low diastolic velocity) of the arterial waveform. During the 1990s, multiple studies on umbilical artery Doppler velocimetry in the IUGR fetus were followed by three major meta-analyses that showed a reduction in perinatal mortality by approximately one-third when umbilical artery Doppler velocimetry was used as an adjunct to other means of antenatal biophysical testing. In 1993, a European multicentered, prospective, observational trial reported by Karlsdorp and colleagues provided strong evidence suggesting that growth restricted fetuses with abnormal umbilical pulsatility index, with absent diastolic flow and with reverse diastolic flow, had progressively more severe perinatal outcomes.

Middle Cerebral Artery (MCA)

As mentioned earlier in this chapter, prolonged fetal hypoxia as a result of uteroplacental insufficiency will result in a redistribution of blood flow within the fetus in an attempt to deliver more oxygen by increasing volume blood flow to vital organs. This has been shown to be the case in some classic animal studies where prolonged hypoxia leads to blood flow redistribution that is favorable to the heart, brain, and adrenal glands. This redistribution has also been shown by pulsed-wave Doppler velocimetry to occur in human IUGR fetuses. The fetal brain normally has a high-resistance blood flow pattern, which is depicted by low flow velocity at end-diastole, relative to other organs and large vessels. During hypoxia, cerebral vascular autoregulation adjusts blood flow within the brain by decreasing the resistance to flow. The decrease in resistance can be easily detected by pulsed-wave Doppler, which provides an FVW profile that depicts an increase in end-diastolic flow velocity. This will in turn result in a calculated Doppler index of resistance that is low compared to the normally high resistance seen in the cerebral circulation. The most common cerebral artery used for Doppler assessment of the fetal brain-sparing effect is the MCA. The anatomic site and direction of the MCA is perpendicular to the cerebral midline (Fig. 12.4). This allows for the Doppler beam to be easily positioned along the midportion of the vessel with a minimal angle of insonation, thereby optimizing FVW acquisition. Incidentally, another advantage of the MCA position is that acquisition of a direct measurement of the absolute velocity in cases of fetal anemia (i.e., Rh isoimmunization and parvovirus) is easily obtained at this location.

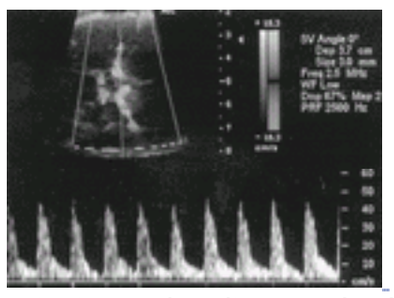

FIG. 12.4. The ultrasound color Doppler image shows the circle of Willis and the middle cerebral artery branches. Also shown is the near 0-degree angle of insonation and the middle cerebral artery flow velocity waveform. See color figure 12.4.

Both direct and indirect evidence acknowledge that hypoxia is a plausible mechanism for the decrease in MCA pulsatility index (PI) in IUGR. Direct evidence supporting this mechanism was reported by Capponi and associates in a group of IUGR fetuses with an abnormal umbilical PI. They showed that the best predictor of hypoxia at cordocentesis was the MCA PI. Baschat and co-workers provided good indirect evidence in support of hypoxia as a mechanism for the decreased MCA PI. In this study of IUGR fetuses with an abnormal umbilical artery PI, those with a decreased MCA PI had significantly higher nucleated red blood cell counts compared with those who had no Doppler evidence of MCA dilation.

The reduction in abdominal circumference typically precedes Doppler abnormalities in the umbilical artery and the MCA. Doppler studies have shown that the decrease in resistance by the fetal brain and the increase in resistance in the umbilical artery are the earliest arterial changes in Doppler flow velocities in the IUGR fetus. In our experience, they begin more than 3 weeks prior to non-reassuring fetal heart rate recordings. The primary message conveyed by Doppler investigation of the MCA vessel in IUGR fetuses is that the fetus is adapting appropriately to intrauterine hypoxia by “brain-sparing.” Loss of the “brain-sparing” adaptation is thought to be due to loss of cerebral autoregulation, and is considered to be a very late or terminal sign in the decompensating fetus. Before a *loss* of the “brain-sparing” is acted upon, one must be sure to avoid excessive transducer pressure because this will artificially lower the end-diastolic velocity. Furthermore, one will not see a loss of “brain-sparing” in the face of otherwise normal Doppler waveforms elsewhere, especially on the venous (precordial) side.

Precordial and Cardiac Flows

Cardiac Doppler studies in the IUGR fetus primarily include assessment of peak velocities of the outflow tracts, left and right ventricular cardiac output, and flow ratios across the valves. Variables that influence these measurements include preload, afterload, and intrinsic contractility of the left and right ventricles, as well as the valve dimensions. Significant contributions have been published on the changes in the atrioventricular filling waveform, and on the flow velocities of the outflow tract of the great vessels. Cross-sectional and longitudinal studies of IUGR fetuses with increased umbilical artery vascular resistance and decreased MCA vascular resistance show a progressive decrease in outflow tract velocity and cardiac output with advancing gestation. Valvular abnormalities tend to occur late in the course of an IUGR fetus that is rapidly decompensating. In one study of 31 IUGR fetuses and 289 normally grown fetuses, tricuspid valve regurgitation (TR) was a frequent, but in most cases, transient finding. Only 2 of the 31 IUGR fetuses showed TR. In one fetus it was only part-systolic, while the other fetus it was severely compromised with abnormal flows in both the arterial and venous system. That TR is a late sign in the course of IUGR has been confirmed elsewhere.

As mentioned earlier, Doppler velocimetry has been used to assess blood flow through the venous circulation of the IUGR fetus including the umbilical vein, ductus venosus, hepatic veins, and IVC. The IVC and the ductus venosus essentially represent the preload profile of the cardiovascular system. Interesting information conveyed by research on these vessels is the significant correlation between abnormal changes in the vessels and acid-base changes of the fetus. Others have correlated these Doppler indices with fetal heart monitoring patterns. Abnormalities in the ductus venosus are characterized by a decrease in velocity of the a-wave, and if the fetus continues to deteriorate, the ductus venosus may show absent or reversed flow velocity of the a-wave. The ductus venosus waveform in a severely growth restricted fetus from 20 to 22 weeks gestation of a mother with severe renal disease and hypertension is shown in Figure 12.5. The a-wave at 20 weeks showed reasonable flow velocity, but progressively deteriorated to intermittent absent and reverse flow velocity.

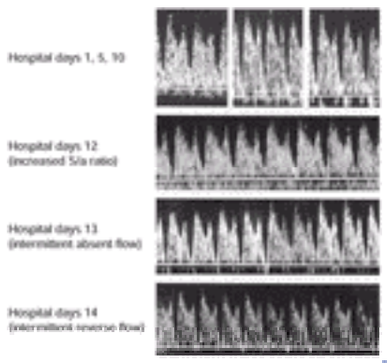

FIG. 12.5. Ductus venosus flow velocity waveform with abnormal a-waves in a severely growth restricted fetus admitted at 20 weeks gestation. Note the progressive decrease in velocity of flow in the a-wave.

The umbilical vein normally has a steady FVW. The presence of pulsations or nicking in the umbilical vein FVW is a very late sign of the decompensating fetus and likely due to ventricular failure. These pulsations have been shown through animal studies to be initiated from atrial pressure changes and transmitted in a retrograde fashion. In early pregnancy, umbilical venous pulsations can be a normal finding. While assessing the umbilical vein with pulsed-wave Doppler, it is important to be cognizant that fetal breathing can mimic the nicking or pulsations of cardiac origin and these obviously have largely differing implications. Pulsations due to fetal breathing and due to cardiac failure can easily be distinguished by looking for fetal breathing motions or determining the rate of the pulsations seen on the FVW. A

normal umbilical waveform, pulsations due to breathing, and pulsations due to cardiac failure are shown in Figure 12.6.

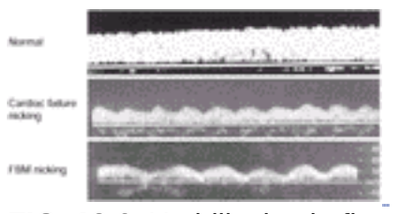

FIG. 12.6. Umbilical vein flow velocity waveform profiles demonstrating pulsations due to fetal breathing motions and cardiac failure compared to normal.

Temporal Doppler Changes in the IUGR Fetus

While umbilical artery Doppler is useful as an adjunct in antenatal testing, it alone is not capable of distinguishing a decompensating fetus to the extent that morbidity can be reduced. Waiting until there is reverse flow nearly always results in an acidotic fetus with adverse long-term sequelae. It is here where venous Doppler studies will likely play a role in identifying earlier signs of deterioration in the IUGR. Since the late 1990s, more than 100 papers have been published both on the pathophysiology and clinical correlation of Doppler studies with traditional monitoring and with neonatal outcome. Advances in digital ultrasound technology have had a tremendous impact on the basic knowledge of fetal circulatory adaptation to placental supply deprivation. Clinically, this technology has allowed us to collect information and take a snapshot of fetal adaptation to placental dysfunction, which in turn can be interpreted as appropriate or inappropriate (i.e., decompensating) based upon the pattern of Doppler findings. The considerable knowledge gained through Doppler studies on isolated vessels or organs subsequently lead to two basic study questions regarding the “big picture”:

Is there a consistent temporally related sequence of Doppler changes within the circulation of the IUGR fetus?

If there is a progressive sequence of changes, is there a parallel increase in fetal morbidity and mortality?

These questions are just now being addressed.

In 2001 and 2002, three studies introduced the idea that a deteriorating fetus follows a sequence of Doppler abnormalities prior to having a markedly abnormal biophysical test (nonstress test [NST], biophysical profile [BPP]) that would normally dictate delivery. It is important to understand that these studies were conducted on very preterm and severely growth-restricted fetuses. Baschat and colleagues reported that sequential deterioration of arterial and venous flows precedes BPP score abnormalities, and that perhaps adding Doppler to the BPP may enhance the performance of the BPP. Hecher and others reported that short-term variability and ductus venosus abnormalities are the important indicators for optimal timing of delivery. More recently, Ferrazzi and colleagues reported on fetal–neonatal injury and the sequential changes in Doppler velocimetry. Briefly, increased pulsatility in the umbilical artery, decreased pulsatility in the MCA (i.e., brain-sparing), and absent flow in the umbilical artery are considered “early” changes and alone were not associated with fetal injury. The next vessel to become abnormal was the ductus venosus, which was subsequently followed by other venous and cardiac Doppler abnormalities. These were considered “late” changes, frequently preceded by NST abnormalities, and were associated with a significant increase in fetal and neonatal morbidity and mortality. These “early” and “late” Doppler changes are shown in Figure 12.7. Thus, these studies suggest that waiting until the NST or the BPP become abnormal before delivery might be too late to prevent serious sequelae to the newborn and the child or adult that newborn is destined to become. They also suggest that the vessel that best determines the optimal timing for delivery is the ductus venosus.

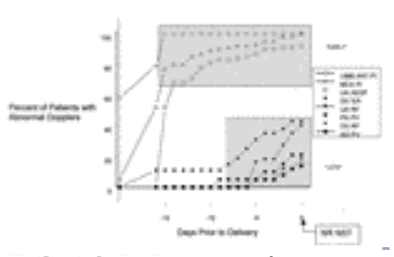

FIG. 12.7. Temporal sequence of Doppler velocimetry changes in intrauterine growth restricted fetuses. (Modified from Ferrazzi E, Bozzo M, Rigano S, et al. The temporal sequence of changes in fetal velocimetry indices for growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2002;19:140–146.)

MANAGEMENT OF THE IUGR FETUS

Historically, the management of the IUGR fetus was based on the fetus reaching fetal lung maturity, flattening of the growth curve, or awaiting a fetal heart rate change. In the mid-1990s, several meta-analyses demonstrated that perinatal mortality could be reduced by including umbilical artery Doppler velocimetry as part of the fetal biophysical assessment. While this was clearly a major advancement in management of the IUGR fetus, it still fell short of the goal of not only reducing perinatal mortality, but also reducing perinatal morbidity. In 1993, investigators in Milan, Italy reported a useful classification for IUGR severity. Table 12.4 shows the classification scheme that is based on fetal heart rate monitoring and umbilical artery Doppler velocimetry and the risk of fetal hypoxemia and acidemia. The study showed that waiting for the fetal heart rate to become non-reassuring would result in a hypoxic–acidemic fetus more than 60% of the time. Studies on Doppler changes in the IUGR fetus suggest that the fetus experiencing progressive compromise tends to follow a sequence of Doppler changes that may allow for better timing of delivery. These Doppler studies will likely be most useful in the management of the very preterm and severely IUGR fetus. Figure 12.8 is an algorithm for management guidelines of the IUGR fetus, which includes workup considerations for symmetric and asymmetric growth, daily routines, fetal monitoring, and gestational age based timing of delivery. Since amniotic fluid volume is a function of urine output and renal perfusion, the presence of oligohydramnios in an IUGR fetus should serve as a red flag. Oligohydramnios is not included in the algorithm. However, if it is present, delivery should be considered. If the fetus is extremely premature, hospitalization should be considered for in-house fetal monitoring.

Group	FHR tracing	UmA Doppler	Hypoxemia/acidemia
I	Normal	Normal	0%
II	Normal	Abnormal	5%
III	Abnormal	Abnormal	60%

FHR, fetal heart rate; IUGR, intrauterine growth rate.

TABLE 12.4. *Fetal heart tracings, umbilical artery doppler, and the IUGR fetus*

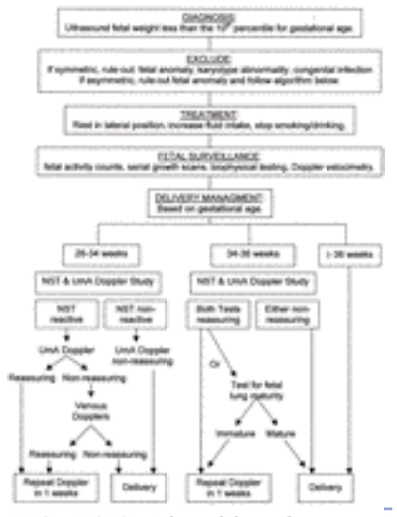

FIG. 12.8. Algorithm for management guideline of the intrauterine growth restricted fetus.

QUANTIFICATION OF FLOW

Until recent advancements in high-resolution digital imaging with simultaneous imaging and Doppler methodologies, the reproducibility and clinical feasibility of flow quantification have been limited. Studies show that umbilical venous flow can be measured accurately (inter- and intra-observer variability <7%) and in a timely fashion (<5 min). These flow measurements have been validated by invasive physiologic preparations in fetal lambs. Ultrasound images and formula for calculation of umbilical venous flow is shown in Figure 12.9. In a longitudinal study, not only was volume flow found to be reduced in the IUGR fetus compared to controls, but the variable responsible for this reduction was a low velocity of blood flow and not the umbilical vein diameter. Interestingly, the low umbilical flow in IUGR fetuses was identified very early in the course of IUGR before Doppler changes in other vessels became apparent. Quantitative flow measurements can even be obtained in very small vessels such as the ductus venous. Quantitative flow measurements are a potentially new-tool approach for the assessment of the growth-restricted fetus since quantification of placental flow to the fetus and its redistribution to the liver and heart is now possible.

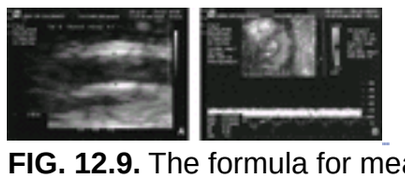

FIG. 12.9. The formula for measurement of umbilical venous flow is shown. **A:** On ultrasound, how to obtain umbilical vein diameter (note that the calipers are placed just inside the specular reflections). **B:** On ultrasound, how color is used to ensure an angle of insonation at nearly 0 degrees and how Doppler velocimetry is used to obtain a steady umbilical vein waveform velocity. See color figure 12.9.

Doppler Prediction of IUGR and Preeclampsia

The maternal side of the uteroplacental circulation has also been investigated by Doppler ultrasound and FVW analysis in hopes of identifying those pregnancies at increased risk for developing preeclampsia, abruption, and IUGR. Since the original reports on uterine artery Doppler waveform analyses, several important methodological issues have been established that include proper technology (color Doppler-guided, pulsed-wave Doppler sampling, and site of sampling), and normal reference values (S/D ratio >2.6, or resistance index >0.58). The pathophysiologic basis for abnormal uterine artery resistance is that resistance of the smaller spiral artery branches that lie downstream fail to become low-resistance vessels as a result of poor trophoblastic invasion early in pregnancy.

This test has gained a popular role in screening for preeclampsia and IUGR at 20 to 24 weeks of gestation. Scoring systems based on FVW abnormalities (increased resistance and notching) have been developed. For the most part, the highest risk for encountering an adverse pregnancy outcome goes up by having both early diastolic notching and high resistance, and if these occur bilaterally. The problem with the uterine artery Doppler test is that reported positive values vary considerably and there is a reasonably high false-positive rate. The false-positive rate can be reduced by repeating the test at 24 weeks gestation.

SUMMARY POINTS

- Proper establishment of the uterine–placental–fetal circulation early in gestation is critical to appropriate placental and fetal growth.
- Abnormal uterine artery Doppler waveforms reflect abnormal placentation and may be predictive of adverse pregnancy outcome.
- Establishment of accurate dating in pregnancy is necessary for assessment of appropriate growth and management of the pregnancy.
- Ultrasound dating of the pregnancy is most accurate in the first trimester.
- The transcerebellar diameter remains relatively unaffected in asymmetrically growth restricted fetuses.
- A distal femoral epiphysis of more than 3 mm is consistent with a pregnancy greater than 36 weeks gestation.
- In IUGR, it is important to remember to consider the possibility of a constitutionally small baby.
- In IUGR, use of umbilical artery Doppler velocimetry reduces perinatal mortality when used as an adjunct to other tests of fetal well-being.
- Doppler velocimetry studies of the venous circulation may be the best way to optimally assess the timing of delivery in the very preterm and growth-restricted fetus.

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Chapter 13

Lisa Moore and James N. Martin, Jr.

Prolonged Pregnancy

ETIOLOGY
AMNIOTIC FLUID
ANTENATAL TESTING
THE FETUS
MANAGEMENT
PREVENTION
INDUCTION OF LABOR
SUMMARY POINTS

REFERENCES

A prolonged pregnancy, also commonly called postterm pregnancy, is one that has lasted longer than 42 weeks or 294 days beyond the first day of the last menstrual period ([1]). Postdatism implies pregnancy lasting beyond the estimated due date at 40 weeks. The term “postmature” is reserved for the pathologic syndrome in which the fetus experiences placental insufficiency and resultant intrauterine growth restriction. Prolonged pregnancies have been recognized since antiquity. Hadrian, emperor of Rome from 117 to 138 A.D., decreed that a child born 11 months after the death of a husband was illegitimate. French law recognizes as legitimate a child born 300 days after the husband's death ([2]). Postdatism as a risk factor for adverse fetal outcome has been recognized since the early part of the 20th century. Whether prolongation of a low-risk pregnancy results in increased perinatal morbidity and mortality is a matter of debate.

Postdatism occurs in 3% to 12% of all pregnancies ([1]). The definition of prolonged pregnancy is, however, somewhat arbitrary and was formulated before ultrasound dating of gestation became routine. Divon and colleagues ([3]) have suggested that the definition should be changed so that pregnancies =41 weeks are considered post-term. This recommendation is based on a study of over 180,000 pregnancies at 40 weeks or more in which a significant increase in perinatal mortality was seen after 41 weeks. This same finding was noted by Browne ([4]), who described perinatal mortality after 41 weeks as 10.5 per 1,000 pregnancies, doubling that at 43 weeks, and tripling that amount at 44 weeks.

Prolonged pregnancies are at risk for macrosomia resulting in shoulder dystocia and fetal injury, oligohydramnios, meconium aspiration, intrapartum fetal distress, and stillbirth. Maternal risks include trauma, hemorrhage, and labor abnormalities (Table 13.1). Interventions for preventing or improving outcomes in low-risk, prolonged pregnancies have proven to be of minimal benefit.

Fetal/neonatal	Maternal
Shoulder dystocia	Trauma
Fetal injury	Hemorrhage
Oligohydramnios	Labor abnormalities
Meconium aspiration	
Intrapartum fetal heart rate abnormalities	
Stillbirth	

TABLE 13.1. *Complications of prolonged pregnancy*

ETIOLOGY

The most common cause of a prolonged pregnancy is inaccurate dating. Early ultrasound dating of pregnancies has been shown to reduce the number of women who are induced for apparently prolonged pregnancies ([5]).

The physiology underlying the spontaneous onset of labor remains enigmatic. Several animal models have been studied, and a great deal of information on the process has been gathered. Parturition in the human female, however, is very different from other species. In humans, the role of the fetal hypothalamic–pituitary–adrenal (HPA) axis appears to be permissive rather than essential as in other species ([6]). Consistent with this, the average gestational age at delivery was 39.6 weeks for a group of anencephalic pregnancies, the same as for normal gestations. This number is questionable because there was a high incidence of extremely preterm (25–30 weeks) and extremely postterm (48–52 weeks) gestations in this series. This seems to demonstrate a loss of precision in timing the onset of labor in anencephalic fetuses.

The synthesis of estrogen and progesterone is controlled differently in humans than nonhumans. In humans the fetal adrenal is deficient in 3ß-hydroxysteroid dehydrogenase that converts pregnenolone to progesterone and dehydroepiandrosterone to androstenedione. The placenta is deficient in 17a-hydroxylase and C17-20 lyase but has high sulfatase and aromatase activity. The fetal adrenal secretes dehydroepiandrosterone sulfate (DHEA-S) which the placenta converts to estrogen. Placental sulfatase deficiency is an X-linked disorder that affects male fetuses. The sulfatase-deficient placenta is unable to use DHEA-S and other fetal adrenal precursors to synthesize estrogens ([7]). These pregnancies are associated with poor response to cervical ripening and induction as well as postdatism.

Postulated maternal risk factors for prolonged pregnancy include primiparity, previous prolonged pregnancy, and young maternal age.

AMNIOTIC FLUID

Reduced amniotic fluid (i.e., oligohydramnios) is a frequent finding in prolonged pregnancies. It presents a problem because it can be a marker for fetal compromise and because it puts the fetus at risk for cord accidents. Oligohydramnios has been attributed to placental insufficiency causing the fetus to redistribute blood flow to protect the brain. This, in turn, is considered to cause renal hypoperfusion with reduced glomerular filtration and urine production leading to decreased amniotic fluid. However, a study of 57 women at gestations greater than 41 weeks in which the resistance index of the fetal middle cerebral, renal, and umbilical arteries was evaluated, found no evidence that oligohydramnios was associated with redistribution of blood flow ([8]).

It is commonly accepted that amniotic fluid volume decreases as gestational age advances beyond term. In at least one study, this was not found to be the case. Among 511 women at 41 weeks or more, only 11.5% had oligohydramnios defined as a four-quadrant amniotic fluid index (AFI) of 5 or less. The average AFI at 41 weeks was 12.4 cm ± 4.2 cm ([9]).

The best method to accurately estimate the amount of amniotic fluid is also a matter of debate. Commonly used ultrasound techniques include the four-quadrant AFI and the largest vertical pocket. In a study of 190 women at 40 weeks or more in which four ultrasound methodologies were studied for amniotic fluid volume estimation (the four-quadrant AFI, the largest vertical pocket, the largest transverse pocket, and the sums of all pockets), the only technique which demonstrated diagnostic value was use of the largest vertical pocket. A cutoff of 2.7 cm correlated well with favorable outcomes ([10]). The traditional cutoff of 2 cm in largest vertical diameter was also found to be an indicator of favorable outcome, but the authors thought that sensitivity could be increased by raising the cutoff to 2.7 cm.

ANTENATAL TESTING

Any pregnancy at risk for uteroplacental insufficiency is a candidate for antenatal fetal monitoring. It is most likely that the morbidity and mortality associated with prolonged gestation is due to placental insufficiency in which fetal requirements for oxygen and nutrients can no longer be met. The goal of antenatal testing is to identify those fetuses that should be delivered. It is useful to remember that no form of antenatal testing will predict random unfortunate events such as sudden significant umbilical cord compression.

Some form of antenatal testing is usually initiated between 41 and 42 weeks in otherwise healthy pregnancies. The frequency and the type of antenatal testing is based mostly on physician preference and experience since no testing modality has been shown to improve outcomes in uncomplicated post-term pregnancies whether

initiated before or after 42 weeks ([1]).

Grubb and colleagues ([11]) reviewed 8,038 postterm gestations that were followed with twice-weekly nonstress tests (NSTs) and determination of the AFI. Prior to 42 weeks patients received one assessment. There were 9 antepartum deaths giving a stillbirth rate of 1.12 per 1,000. Two of those deaths occurred before 42 weeks. Using twice-weekly biophysical profiles (BPPs), an older study reported a stillbirth rate of 0.44 per 1,000.

Ratios of the middle cerebral artery (MCA) blood flow to the umbilical artery (UA) blood flow have been studied as indicators of fetal compromise. Two common ratios are the UA/MCA pulsatility index ratio and the MCA/UA systolic/diastolic (S/D) ratio. Normally, the UA should have low impedance flow with a relatively low S/D ratio and low pulsatility index. The MCA should have high impedance flow with a high S/D ratio and a high pulsatility index. With brain-sparing redistribution of blood flow, we would expect impedance in the UA to increase resulting in decreased or absent end-diastolic flow. Impedance in the MCA should decrease, with lowering of the S/D ratio and the pulsatility index and an increase in the peak velocity of the blood flow. With redistribution of blood flow, the MCA/UA S/D ratio should be low as the values approach each other. A study of women at 41 weeks or more, by Devine and colleagues ([12]) found that an MCA/UA S/D ratio less than 1.05 had an 80% sensitivity and 95% specificity with 80% positive predictive value of an adverse perinatal outcome.

The contraction stress test (CST) was the first test used for antepartum fetal monitoring. The underlying premise is that the fetus with uteroplacental insufficiency would experience late decelerations with contractions in response to hypoxia generated by decreased blood flow to the intervillous space. The NST is the first-line screening test at many medical centers. It is quickly and easily performed in an outpatient setting. The NST is based on the knowledge that fetal hypoxia interrupts the pathway between the fetal heart and an intact central nervous system (CNS). The fetus with an intact CNS will have heart rate accelerations with movement or stimulation. The CST has a high false-positive rate and the NST has a false-negative rate of 2.7 per 1,000 in a high-risk population ([13]). The BPP score predicts the presence or absence of asphyxia. The loss of the components of the BPP reflects sequential adaptive deletions to reduce fetal oxygen requirements. A normal BPP has a false-negative rate of 0.7 to 0.8 per 1,000.

The CST, NST, and BPP were compared in 583 women who had completed 42 weeks gestation ([14]). There were three protocols:

1. Weekly NST with CST for nonreactive NST.
2. Twice weekly NST with BPP for nonreactive NST with induction for a 4/10 BPP.
3. Twice weekly NST with BPP for nonreactive NST and a weekly determination of the amniotic fluid volume.

Patients were induced for low fluid or decelerations on the NST. In protocol 1, patients were reevaluated in 24 hours for a suspicious CST and induced for a positive CST. Protocol 3 had the highest intervention rate and the least perinatal morbidity. Protocol 1 had no interventions and the highest perinatal morbidity rate. Cesarean delivery was more common in protocols 2 and 3. Of note, the best outcomes were achieved with a low threshold for intervention.

THE FETUS

In 1954 Clifford ([15]) described the fetal postmaturity syndrome in which the postmature infant was characterized by peeling, parchmentlike skin, wasted appearance and meconium staining of skin, membranes, and the cord. The syndrome progressed in three stages from placental insufficiency with minimal associated morbidity and mortality to chronic insufficiency with an associated anoxic event.

The postmaturity syndrome described by Clifford is seen in only a small percentage of prolonged pregnancies. By far the most common complication is macrosomia resulting in dystocia with associated brachial plexus injuries and fractures.

Seven thousand infants were studied to determine the rate of growth after 39 weeks ([16]). Mean birth weight increased from 39 to 42 completed weeks. A similar increase was seen in head circumference and crown-to-heel length. In a study of 519 pregnancies beyond 41 weeks, 23% weighed more than 4,000 g and 4% were larger than 4,500 g ([17]).

To assess the risk to the fetus in a prolonged uncomplicated gestation, 1,408 infants delivered at 41 weeks and 340 delivered at 42 weeks were compared to 5,915 delivered at 39 or 40 weeks ([18]). Fetal distress and meconium release were twice as common at or after 42 weeks than at term. There was an eight-fold increase in meconium aspiration, which occurred 1 per 455 at term, 1 per 175 at 41 weeks, and 1 per 57 at 42 weeks. There was no increase in the incidence of birth asphyxia measured by the need for mechanical ventilation at birth.

MANAGEMENT

The management of uncomplicated prolonged pregnancies is controversial. An adverse event in a pregnancy that has carried beyond 40 weeks seems especially difficult because it might have been avoided by simply delivering the patient. Although rare, the risk of stillbirth increases as gestational age increases. Nonetheless, available data indicate that induction and expectant management have similar outcomes, and either is suitable for managing the uncomplicated prolonged gestation.

The National Institutes of Health (NIH) ([19]) sponsored a clinical trial to compare induction at 41 weeks (n = 265) to expectant management (n = 175) consisting of twice weekly NST and AFI. There were no differences in outcome between the two groups. The trial concluded that either approach was acceptable.

Active management of the prolonged pregnancy, defined as induction at 42 weeks was studied in 707 patients ([20]). Sixty-two percent of the patients labored spontaneously and 38% were induced. Perinatal mortality was 12 per 1,000. All deaths were in the spontaneously laboring group. Cesarean sections and indications for cesarean sections were similar in both groups. Meconium was present in 23% of inductions and 34% of the spontaneously laboring group. The authors concluded that routine induction at 42 weeks was justified to prevent perinatal deaths in this population.

The Parkland Group studied 56,317 pregnancies at 40, 41, and 42 weeks ([21]). Labor was induced at 42 weeks. Neonatal outcomes were similar in all groups. Sepsis and neonatal intensive care unit admission were more common in the 42-week group. Labor complications increased between 40 and 42 weeks, including length of labor and operative delivery. Their data suggest that routine induction at 41 weeks would increase labor complications with little or no neonatal benefit.

The Canadian Multicenter Post-term Pregnancy Trial was conducted at 22 hospitals, over a 5-year period ([22]). Singleton pregnancies at 41 weeks or more were assigned to induction or monitoring. In the monitored group, women were asked to perform kick counts each day. In addition, the fetuses received NSTs three times a week and AFI determinations two or three times weekly. Patients in the monitored group were delivered at 44 weeks or for maternal–fetal indication(s). Perinatal morbidity and mortality were the same for both groups.

PREVENTION

Separation of the membranes from the lower uterine segment (membrane sweeping) is a safe and inexpensive method of inducing labor, although its effectiveness is most likely operator-dependent. Membrane sweeping works by causing prostaglandin release from the chorionic membranes. One hundred eighty women at 38 weeks were randomized to either weekly membrane sweeping or a gentle cervical exam to determine Bishop score. The treatment group had a significant reduction in prolonged gestation, 3.3% compared to 15.6% in the control group ([23]). In another investigation, women with a Bishop score =4 and negative fetal fibronectin at 39 weeks received either membrane sweeping every 3 days or gentle cervical exams. The mean gestational age for onset of labor in the treatment group was 39.9 ± 0.3 compared to 41.5 ± 0.6 in the control group. Eighteen of 32 women in the control group were induced at 42 weeks versus none in the treatment group ([24]). In summary, membrane sweeping prior to 40 weeks appears to be an effective method for reducing postdate inductions.

INDUCTION OF LABOR

In the presence of a favorable cervix, induction after 41 weeks is reasonable.

Because induction of an unfavorable cervix may be unsuccessful and lead to cesarean delivery, the course of action in an otherwise uncomplicated prolonged gestation with an unfavorable cervix is less clear. Patients at 41 weeks of an uncomplicated gestation with Bishop scores of 4 or less were randomized to daily cervical exams, daily membrane sweeping, or daily prostaglandin gel for 1 week ([25]). Sixty-nine percent of the control group required induction at 42 weeks compared to only 20% (prostaglandin gel) and 17% (membrane sweeping) in the treatment groups. Wing and colleagues gave women who were at 41 weeks or more with unfavorable cervixes either 200 mg of mifepristone or placebo 24 hours before induction. They found only a modest effect on cervical ripening ([26]). Sequential application of

prostaglandin E_2 (PGE_2) gel for cervical ripening was tested in 50 women at or beyond 41 weeks. All had Bishop scores less than 9 and received 2 mg of PGE_2 gel twice a week as outpatients. PGE_2 gel failed to improve cervical ripening over placebo ([27]). Alexander and colleagues ([28]) scheduled 1,325 women at 41 weeks for induction at $41^6/_7$ weeks. Six hundred eighty-seven women entered spontaneous labor before their scheduled inductions and served as controls. Labor was longer in the women who were induced and there was an increase in cesarean sections for failure to progress in the induced group but not for fetal distress. Associated risk factors for cesarean delivery in this study were undilated cervix, analgesia, and nulliparity.

SUMMARY POINTS

- Solid evidence from several randomized controlled trials indicates that uncomplicated prolonged gestations can be managed expectantly or by induction of labor and that outcomes are similar for either method.
- Accurate dating of the pregnancy is important and an early dating ultrasound can prevent unnecessary interventions.
- Perinatal morbidity and mortality increase significantly beyond 41 weeks gestation.
- Membrane sweeping can help to reduce the number of pregnancies that continue beyond 40 weeks.
- Antenatal testing is initiated to identify the fetus in need of delivery. No testing modality has been shown to improve outcomes in prolonged gestations.
- The uncomplicated post-term pregnancy with an unfavorable cervix can be watched expectantly with twice weekly fetal assessments or labor induction can be undertaken. Induction at 41 weeks reduces the risk of stillbirth.
- It remains unclear which method of induction is most effective for prolonged pregnancy.

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Chapter 14

Roger B. Newman

Multiple Gestation

ETIOLOGY AND EPIDEMIOLOGY
PLACENTATION
MATERNAL COMPLICATIONS
- Cardiovascular Risks
- Hematologic Abnormalities
- Metabolic Disorders
- Premature Birth
- Pregnancy-Induced Hypertension/Preeclampsia
- Placental Abruption
- Hydramnios
- Urinary Tract Infection
- Postpartum Hemorrhage

COMPLICATIONS UNIQUE TO MULTIPLES
- Vanishing Twin Syndrome
- Fetal Death in Utero (Acute Intertwin Transfusion Syndrome)
- Monoamniotic Twins
- Discordant Twin Growth
- Twin-to-Twin Transfusion Syndrome: Chronic Intertwin Transfusion

FETAL AND NEWBORN COMPLICATIONS
- Prematurity
- Intrauterine Growth Restriction
- Congenital Anomalies

ANTEPARTUM CARE
- Beneficial Interventions
- Controversial Interventions
- Nonbeneficial Interventions

INTRAPARTUM MANAGEMENT
- Timing of Delivery
- Route of Delivery
- Interval Between Deliveries

POSTPARTUM MANAGEMENT
SUMMARY POINTS

SUGGESTED READINGS

Multiple gestations have become one of the most common high-risk conditions encountered by the practicing obstetrician/gynecologist. In 1998, there were 118,295 multiples born in the United States, the highest number ever recorded. Since 1980, the number of twins delivered in the United States has risen 62% and twins now represent approximately one out of every 40 deliveries. Triplets and higher order births, formerly statistical improbabilities according to the Hellin hypothesis, have increased 470% over the same time period and triplets now occur with a frequency approaching one in every 500 deliveries.

Although multiples account for only a small percentage of all live births, they are responsible for a disproportionate share of all the perinatal morbidity and mortality suffered in the United States. Multiples result in 13% of all preterm births less than 37 weeks; 15% of all preterm births less than 32 weeks; 21% of all low–birth-weight (LBW) (<2,500 g); and 25% of all very low–birth-weight (VLBW) (<1,500 g) infants. As a consequence of these high rates of both prematurity and LBW, twins are at an approximate five-fold greater risk of dying before their first birthday compared to singletons, while triplets are at an almost 14-fold greater risk. Multiples account for 16% of all neonatal deaths in the United States.

Among survivors, there is an increased risk of long-term mental and physical handicaps. Twin pregnancies result in a child with cerebral palsy 12 times more often than do singleton births. One-fifth of all triplet pregnancies and one-half of all quadruplet pregnancies result in at least one child with a major long-term disability. While many cases of cerebral palsy are related to extreme prematurity, not all are the result of premature birth. Even when matched for gestational age, multiples have a nearly three-fold greater risk of developing cerebral palsy than do singletons.

Multiples also experience a significantly increased risk of growth restriction, which can compound the problems associated with prematurity. Growth-retarded, premature infants, regardless of plurality, experience greater morbidity and mortality than do appropriately grown infants of the same gestational age. Twins and triplets with intrauterine growth restriction have been shown to experience an excess of neurodevelopmental abnormalities compared to appropriately grown, gestational age-matched multiples. Multiples are at risk for numerous other complications that contribute to adverse outcomes. These complications include higher rates of congenital anomaly, twin-to-twin transfusion, monoamnionicity, cord prolapse, placental abruption, placenta previa, intrapartum asphyxia, and birth trauma.

Not unexpectedly, multiples are also associated with significantly higher health care costs. Neonatal intensive care unit (NICU) admission is required by one-fourth of twins, three-fourths of triplets, and virtually all quadruplets with average NICU stays of 18 days, 30 days, and 58 days, respectively. Women pregnant with multiples are almost six times more likely to be hospitalized with antepartum complications—most frequently preterm labor, preterm premature rupture of the membranes (PPROM), and preeclampsia. In addition to higher rates of antepartum admission, hospital costs for the birth admission average 40% higher than for gestational age-matched singletons due to longer lengths of stay and increased intrapartum complications with multiples.

ETIOLOGY AND EPIDEMIOLOGY

Monozygotic twins are those gestations where both fetuses arise from single fertilized ova and are genetically identical. Monozygotic twinning is considered to be a random event, independent of modifying influences such as age, race, parity, or heredity. The incidence of monozygotic twinning is 3 to 4 per 1,000 live births in virtually all populations. One of the few known influences on the rate of monozygotic twinning is the use of assisted reproductive technologies such as in vitro fertilization. The increased frequency of monozygotic twinning with infertility treatment has been attributed to a defective zona pellucida, which allows premature and partial hatching of the blastomeres.

The incidence of dizygotic twinning, on the other hand, is extremely variable and accounts for most of the increase in multiple births seen over the past few decades. Dizygotic, or fraternal twins, result from multiple ovulation with fertilization by separate sperm. Multiple factors are known to affect the incidence of dizygotic twinning including personal or family history. If a woman has already had one set of dizygotic twins, her chance of having a second set is increased two-fold and a first-degree relative with twins will increase a woman's risk as well. The father's side of the family contributes little or no hereditary risk.

It is estimated that approximately one-fourth of the increase in the number of multiple births is due to delayed childbearing and the fact that dizygotic twinning occurs more frequently among older women. The trend toward delayed childbirth has been a dramatic sociologic phenomenon of the past quarter century. Since 1975, the proportion of first births among women 30 years and older has increased from 5.3% to 22.8% and the proportion of all births to women =30 years of age rose from 16.5% to 35.5%. In women younger than 20 years, the multiple birth rate is only 1.5% compared to 4.1% among women between the ages of 30 to 39 years and up to 17.8% for women 45 years or older.

The majority of the increase in dizygotic twinning has been a result of ovulation induction therapy and newly developed assisted reproductive technologies (ART). An annual summary of ART programs in the United States reported on 14,702 deliveries of 21,196 neonates. Of these ART cycles resulting in clinical pregnancies, 39% of in vitro fertilization, 34% of gamete intrafallopian transfers, and 36% of zygote intrafallopian transfers resulted in multiples. Approximately 40% of all triplets and more than 90% of all quadruplet pregnancies in the United States are secondary to either ovulation induction or ART. Women contemplating assisted reproduction should receive preconceptional advisories regarding the risk of multiple birth and the risks associated with those births. Among pregnancies resulting from ART, approximately 25% to 30% will be twins, 5% will be triplets, and 0.5% to 1% will be higher order multiples. Efforts are being made to reduce the number of oocytes, zygotes, or embryos that are being transferred back in order to minimize the risk of multiple pregnancy. However, three or more oocytes, zygotes, or embryos are still being

transferred in many cases, especially among older women where the rate of successful implantation is reduced.

Maternal race also affects the frequency of dizygotic twinning. Dizygotic twinning occurs approximately 7 to 10 times per 1,000 live births among Caucasians, 10 to 40 times per 1,000 live births for persons of African descent, and only 3 times per 1,000 live births among Asians. Interestingly, white women are more than twice as likely as black women and three times as likely as Hispanic women to have a triplet or higher order multiple, which almost certainly reflects a greater use of ART in the white population. Increased maternal parity, higher body mass index (BMI), and recent discontinuation of hormonal birth control agents have also been associated with higher rates of dizygotic twinning.

PLACENTATION

The placentation of dizygotic twins will always be diamniotic, dichorionic. Two complete placental units are produced, each composed of an amnion and a chorion. As a result, the membrane separating dizygotic twins will consist of four layers; an amnion and a chorion from each fetus. The placentas themselves may be separate or fused in dizygotic twins but the central membrane will always consist of four layers. In monozygotic twins, the placentation depends on the time at which twin division occurs. If division of the zygote occurs in the first three days, two complete placental units will be formed and the central membrane will contain two amnion and two chorion layers, just as with dizygotic twins. The syncytiotrophoblast cells, which will give rise to the chorion, begin to differentiate about day 3 from the periphery of the blastocyst. If division occurs between days 3 and 8, the placental unit will consist of a single chorion which has already differentiated and two amnions which have not yet begun to form. As a result, the central membrane will be thin and wispy because it consists of only two opposed amniotic membranes without the intervening chorionic layers. This placentation is referred to as diamniotic, monochorionic. The amnion begins to differentiate by about day 8 and if embryonic division occurs between days 8 and 13, the twins will share a single amnion and chorion; a monoamnionicity, monochorionic placentation. This situation, with no central membrane separating the fetuses, allows for potentially lethal entanglement of the umbilical cords. Different types of placental development in dizygotic and monozygotic twins are illustrated in Figure 14.1. Division, which occurs after day 13, results in a physical attachment producing conjoined twins.

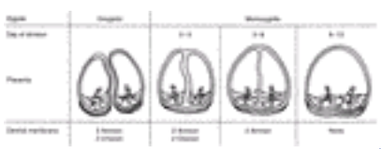

FIG. 14.1. Types of placentation in monozygotic and dizygotic twinning.

Examination of the placenta(s) and a detailed description of its central membrane are critical for determining zygosity of the infants. The microscopic appearance of the central membrane consisting of either two or four layers is seen in Figure 14.2. Diamniotic, dichorionic twins are dizygotic if the twins are of opposite sex. If the central membrane contains only amnionic layers and a monochorionic placenta, the infants are monozygotic. If the central membrane has two amnion and two chorion layers (i.e., diamniotic, dichorionic) and the infants are the same sex, the twins may be either dizygotic or monozygotic. Despite this limitation, the obstetrician can still accurately determine zygosity in the delivery room in over 50% of cases by simply observing the fetal sex and grossly inspecting the placenta. In those cases that remain uncertain, a more specific diagnosis can be made by blood or HLA antigen typing or more sophisticated DNA analyses.

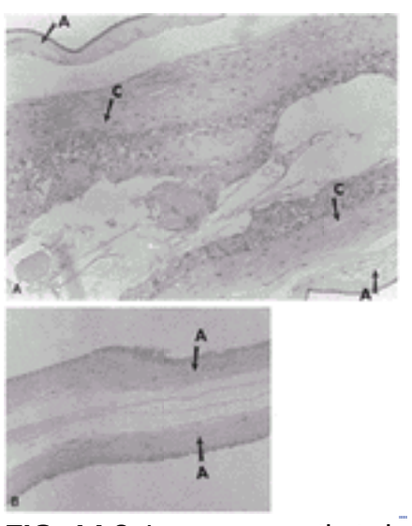

FIG. 14.2. In monozygotic twinning, the central membrane contains **(A)** four layers or **(B)** two layers (*A*, amnion; *C*, chorion).

MATERNAL COMPLICATIONS

Women pregnant with multiples are more likely to be hospitalized antenatally for both an increased frequency and severity of pregnancy-related complications. Some of these increased risks are associated with maternal characteristics that predate the pregnancy such as older maternal age, nulliparity, increased pregravid BMI, and conception by ART. However, the majority of these complications are directly related to higher plurality and the more extreme maternal adaptation required.

Cardiovascular Risks

One of the major physiologic changes occurring with a multiple pregnancy is significant expansion of the plasma volume and cardiac output above that seen in singleton pregnancies. This increased plasma volume has obvious adaptational value as the maternal host tries to meet the demands of a multiple conception. Increased cardiac demand is reasonably well tolerated in the absence of underlying cardiac disease such as undiagnosed mitral valve stenosis. However, the common use of tocolytic therapy, the not uncommon iatrogenic fluid overload, and the occasional infection will all generate significant additional cardiovascular stress. Although infrequent, tocolytic therapy (especially ß-adrenergic agonists) has been associated with pulmonary edema, myocardial ischemia, and potentially lethal maternal tachyarrhythmias in multiples. An increased risk of postpartum cardiomyopathy has also been reported, especially among older gravidas with higher order multiples. A case-controlled study of pregnant women found that multiple pregnancy was an independent and significant risk factor (odds ratio [OR] = 2.3; confidence interval [CI] 95% = 1.2–4.5) for admission to an intensive care unit.

Hematologic Abnormalities

Increased red blood cell volume expansion is unable to keep pace with plasma volume expansion in either singleton or multiple gestations. This results in a physiologic hemodilution. The average hemoglobin concentration for women pregnant with twins is 10 g per dL at 20 weeks gestation. Hemoglobin and hematocrit values decline beginning in the first trimester, reaching a nadir in the second trimester before gradually rising again in the third trimester. Hemoglobin levels below 11 g per dL in either the first or third trimester accompanied by a serum ferritin less than 12 µg per dL represents iron deficiency anemia, which complicates some 21% to 36% of multiple gestations. This rate is two- to three-fold higher than in singletons. Multiples generate a great demand for elemental iron, which might not be available in the average diet. This need should be addressed through the consumption of heme-rich animal protein and supplementation with 60 mg per day of elemental iron and 1 mg per day of folic acid when the woman has low or absent stores of these nutrients.

Metabolic Disorders

Women pregnant with multiples have lower fasting and postprandial glucose levels, exaggerated insulin responses to eating, and higher levels of ß-hydroxybutyrate than women pregnant with singletons. These differences suggest more rapid depletion of glycogen stores and resultant metabolism of fat between meals and during an overnight fast.

Gestational diabetes represents a disorder of relative insulin deficiency exposed as a consequence of the antiinsulin effects of several placental hormones, most notably human placental lactogen. Multiple gestations are at increased risk for gestational diabetes due to the elevated levels of these placental hormones associated with the increased placental mass. Gestational diabetes appears to be increased two- to three-fold among multiples (7% among twins, 9% among triplets, and 11%

among quadruplets) compared to the 3% to 4% incidence among singletons. Given the high rate of premature labor among multiples, it should be remembered that both ß-adrenergic agents and corticosteroids can induce both insulin resistance and hyperglycemia.

Premature Birth

The risk of preterm birth increases with the number of fetuses in utero and is the single greatest threat to the health of the newborns. Premature labor and PPROM are responsible for more than 70% of these premature deliveries. The incidence of preterm birth less than 37 weeks gestation in the United States is between 30% to 55% for twins, between 66% to 80% for triplets, and is virtually 100% for quadruplets. The mean gestational age at delivery is inversely proportional to fetal number: 39 weeks for singletons, 35 to 36 weeks for twins, and 32 to 33 weeks for triplets. Of all infants born in Australia and New Zealand prior to 32 weeks gestation in 1995, more than one-fourth were the products of a multiple gestation.

Pregnancy-Induced Hypertension/Preeclampsia

Pregnancy-induced hypertension or preeclampsia is frequently encountered in multiple gestations. Reported frequencies increase from approximately 7% in singletons to 14% for twins, 21% for triplets, and 40% for quadruplets. A population-based study of singleton and twin births in the state of Washington found twins to have a four-fold higher risk of preeclampsia and a 14-fold higher risk if the woman is primigravid. Pregnancy-induced hypertension or preeclampsia frequently occurs earlier, is more severe, and is more often atypical in multifetal gestations. Hypertension is not always the presenting sign, nor is proteinuria universally present, especially in higher order multiples. Only 3 of 16 triplets and quadruplets reported in one study met the traditional criteria for preeclampsia. The most common presentation among these higher order multiples was maternal symptoms typical of severe preeclampsia associated with laboratory abnormalities consistent with the HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome.

Placental Abruption

Antepartum maternal hemorrhage is also increased in multiple gestations. Twin pregnancies have an approximately three-fold increased frequency of abruption, even when controlling for maternal hypertension. Abruption occurs most frequently in the third trimester, and is also a significant risk immediately after vaginal delivery of the first infant. Conformational changes in the uterine shape that occur between deliveries can predispose to sheering off of the attached placenta.

Hydramnios

Hydramnios occurs in 2% to 5% of twin gestations, and twins account for approximately 8% to 10% of all cases of hydramnios. Polyhydramnios may develop as a consequence of twin-to-twin transfusion syndrome with the co-twin experiencing both growth restriction and oligohydramnios. The development of idiopathic acute hydramnios with respiratory embarrassment has also been reported in multiples.

Urinary Tract Infection

Women with multiples have a 1.4-fold increased risk of developing urinary tract infection during pregnancy. These infections usually involve only the lower urinary tract because the incidence of pyelonephritis is not significantly increased. This complication is thought to be a consequence of increased urinary stasis due to the gravid uterus.

Postpartum Hemorrhage

Overdistention of the uterus in a multifetal gestation predisposes to postpartum hemorrhage caused by uterine atony. In addition, women carrying multiples are at increased risk for retention of placental tissue, surgical or mechanical trauma to the genital tract, pharmacologic effects of medications such as magnesium sulfate which is frequently used to manage both preeclampsia and preterm labor, as well as other maternal characteristics such as advanced age, obesity, or higher parity. In a British population-based study of postpartum hemorrhage, multiple pregnancy was associated with a significantly increased risk ratio (RR = 4.46; 99% CI = 3.01–6.61). In the British study, the risk of postpartum hemorrhage among singletons was 1.2% compared to 6% for twins, 12% for triplets, and 21% for quadruplets. Compared to the twins, the risk of postpartum hemorrhage was two-fold higher for triplets and four-fold higher for quadruplets.

While the above scenarios represent several of the more significant maternal complications associated with multiples (Fig. 14.3), others are encountered with increasing frequency. These include cholestatic jaundice, pruritic urticarial plaques and papules of pregnancy (PUPP), hyperemesis, and deep venous thrombosis. Women with multiple gestations also experience an increased number of somatic complaints such as shortness of breath, loss of balance, varicose veins, significant dependant edema, constipation, and hemorrhoids. Thankfully, multiples are less often asked to carry their pregnancy postdates.

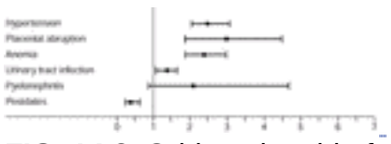

FIG. 14.3. Odds ratio table for maternal antepartum complications among 1,253 twin and 5,119 singleton pregnancies between 1982 and 1987. (Adapted from Spellacy WN, et al. A case-controlled study of 1,253 twin pregnancies from a 1982–1987 perinatal database. *Obstet Gynecol* 1990;75:168–171.)

COMPLICATIONS UNIQUE TO MULTIPLES

Vanishing Twin Syndrome

The loss of one or more fetuses can complicate a multiple gestation at any point during pregnancy but is most common in the first trimester. Between 20% to 50% of multiple gestations identified by ultrasound in early pregnancy are lost either as a spontaneous abortion of all fetuses or by the spontaneous loss and reabsorption of at least one of the multiples. This latter occurrence is referred to as the “vanishing twin phenomenon” and its exact frequency is difficult to ascertain for obvious reasons.

The published experience of the Norfolk in vitro fertilization program allows an estimation of the frequency of this occurrence. Spontaneous loss of all fetuses with previously documented cardiac activity occurred in 17 of 165 twin (10.3%), 2 of 26 triplet (7.7%), and 1 of 5 quadruplet (20%) pregnancies. In addition, 33 twins spontaneously reduced to a singleton and nine triplets spontaneously reduced to twins. Considering both the spontaneous abortion rate and the “vanishing twin phenomenon”, the overall first trimester pregnancy loss rate was 50 of 165 twins (30.3%), 11 of 26 triplets (42.3%), and 1 of 5 quadruplets (20%). Although these data are limited by the fact that all pregnancies were the result of in vitro fertilization, similar loss rates have been reported in spontaneously conceived multiples.

When a “vanishing twin phenomenon” does occur, it is usually silently reabsorbed. However, in some cases, the reabsorption may be associated with a modest amount of vaginal bleeding. Some have estimated that up to 5% of all patients with first trimester bleeding may be experiencing a vanishing twin. Maternal reassurance should be offered as the prognosis for the surviving twin is excellent when silent reabsorption occurs in the first trimester. Following delivery, the placenta will frequently show a whitish plaque on the membranes representing the remnant of the other gestational sac.

While the “vanishing twin phenomenon” occurs with a greater frequency than previously appreciated, it is important not to overdiagnose this event. The diagnosis of a vanishing twin should be preceded by identification of specific embryonic parts in each sac as opposed to an anembryonic cavity. Numerous sonographic findings can mimic a second anembryonic cavity including subchorionic blood clots, chorioamnionic separations, a decidual pseudosac in the contralateral horn of a bicornuate or didelphic uterus, a cystic uterine fibroid, or even excessive transducer pressure on a thin woman. The emotional impact of a vanishing twin should not be underestimated. Parents will perceive the situation as the loss of a child and perinatal grief counseling may even be appropriate in some situations.

Fetal Death in Utero (Acute Intertwin Transfusion Syndrome)

After the first trimester, single fetal demise occurs in 2% to 5% of twin gestations and 10% to 15% of triplet gestations. The risk of a single fetal death in utero is increased three- to four-fold by monochorionicity. When death of one fetus occurs in a dichorionic gestation, the risk to the surviving co-twin is minimal although higher rates of preterm labor or PPROM have been reported. Virtually all the adverse sequelae for the surviving co-twin occur in monochorionic gestations. Antenatal demise

of a monochorionic co-twin is associated with an approximate 25% mortality rate and a similar high rate of morbidity for the second fetus.

Injury to the surviving co-twin was previously thought to be a result of intervascular coagulation and embolism of tissue thromboplastins through ubiquitous placental anastomoses from the fetal demise. The passage of these tissue thromboplastins result in embolic ischemic organ injury or development of disseminated intervascular coagulopathy in the survivor. A more recent theory suggests that following fetal demise, there is an acute transfusion into the dead fetus through the shared placenta. This hemorrhage into the dead fetus may cause severe fetal hypotension, hypoxic end-organ injury, and potentially lethal fetal exsanguination. This is often referred to as acute intertwin transfusion syndrome. In prospective studies, 5% to 25% of surviving monochorionic twins have ischemic end-organ injury, most notably neurologic. Neurologic abnormalities reported among surviving twins include necrosis and cavitation of the cerebral white matter, cerebellar necrosis, multicystic encephalomalacia, hydranencephaly, hydrocephalus, porencephaly, microcephaly, and hemorrhagic infarction. In addition to neurologic injuries, other abnormalities seen among surviving co-twins include ischemic bowel lesions, intestinal atresia, renal cortical necrosis, and cystic renal dysplasia.

Most reported cases of demise or neurologic injury occurring in a monochorionic co-twin following death of its sibling have occurred in the third trimester. However, neurologic deficit has been reported in a surviving monochorionic twin following loss of its co-twin as early as 18 weeks gestation.

Following a fetal demise in utero, continuing pregnancy management will depend upon gestational age, chorionicity, and maternal and fetal status. If the pregnancy is known to be dichorionic, then no intervention is required unless a term gestation has already been achieved or there is a specific maternal or fetal indication for delivery. A single fetal demise in a monochorionic gestation is an indication for immediate delivery if fetal maturity can be inferred based on gestational age or documented by amniocentesis. Decisions regarding delivery at earlier gestations should be based on an assessment of the neonatal complications likely to result from delivery as opposed to the potential risk of remaining in utero. Since it is possible, if not probable, that hypoxic/ischemic end-organ injury occurs almost immediately after demise of the monochorionic co-twin, it is unclear if these injuries can be prevented by prompt delivery. With expectant management, increased fetal surveillance of the surviving twin should be performed and any evidence of fetal compromise would also necessitate immediate delivery.

Monoamniotic Twins

Monoamniotic twins are rare, complicating fewer than 1% of monozygotic gestations. Their importance is that they carry a fetal mortality rate that approaches 40%, primarily as a consequence of cord entanglement and subsequent occlusion. Cord entanglement is present in virtually every case of monoamniotic twins. Monoamniotic twins are also at greater risk for other complications such as congenital anomaly and twin-to-twin transfusion syndrome.

Some reviews have suggested that spontaneous intrauterine fetal demise due to cord entanglement is unlikely after 32 weeks gestation as intrauterine crowding limits the ability of the fetuses to make major moves in relationship to each other. However, a review of over 200 non-conjoined, monoamniotic twins demonstrated that fetal deaths occur throughout pregnancy, with a large percentage occurring after 32 weeks. In this large review, those monoamniotic twins that were prenatally diagnosed and subjected to intensive antepartum surveillance enjoyed a much higher perinatal survival rate than has been historically reported. Prenatal diagnosis allows for institution of an aggressive management protocol designed to identify fetal compromise, enhance fetal lung maturity, and electively deliver once neonatal survival can be anticipated (Table 14.1).

Confirm monoamnionicity (exclude stuck twin syndrome)
Ultrasonographic evaluation at 18–20 wks to exclude congenital anomalies and conjoining
Parental education regarding unique risks
Serial ultrasonographic assessment of fetal growth (twin–twin transfusion syndrome common)
Daily fetal kick counts beginning at 26 wks
Nonstress testing 3×/wk beginning at 26 wks
Antenatal glucocorticoid administration
Amniocentesis for fetal lung maturity at 32 wks
Elective delivery at 34–35 wks if fetal lung maturity not previously confirmed
Cesarean delivery usually recommended

TABLE 14.1. *Management recommendations for monoamniotic/monochorionic twin gestations*

Cesarean delivery is usually recommended due to concerns over intrapartum fetal distress related to tightening of the umbilical cord entanglement. If vaginal delivery is planned, continuous fetal monitoring is essential along with capability for immediate cesarean birth.

Discordant Twin Growth

In addition to the concordant intrauterine growth restriction (IUGR), ultrasound is useful for the detection of significantly discordant fetal growth, which is unique to multiple gestations. In terms of actual birth weight, a large review found that twin birth weight differed by 500 to 999 g in 18% of sets and the difference was greater than 1,000 g in 3%. Some 15% to 30% of twins exhibit birth weight differences of 20%. Discordance between the largest and smallest triplet is 20% in more than 40% of triplet gestations with 7% being as much as 40%.

Evidence suggests that the smaller infant may be at risk for both increased perinatal morbidity and mortality when birth-weight discordance is excessive. Another concern is that significant diversions in twin growth may predispose the smaller twin to disadvantages in long-term physical and intellectual development.

Much of the discordance in birth weight will be due to constitutional factors such as the genetic dissimilarity of dizygotic twins. The more severe the discordancy, the more likely the possibility that pathologic conditions exist such as twin-to-twin transfusion syndrome, an anomalous fetus with a normal co-twin, congenital infection, or growth restriction affecting a single fetus due to local placental implantation factors. Percent discordance is calculated by dividing the actual or estimated weight difference by the actual or estimated weight of the larger twin.

It is also important to appreciate that birth-weight discordance and intrauterine growth restriction are interrelated. When birth-weight discordance of 20% is present, one of the fetuses will be IUGR in more than 50% of the cases. When discordant fetuses are both appropriately grown for gestational age, differences in perinatal outcome have not been identified. Both prematurity and intrauterine growth restriction are much greater threats to the fetus than is the degree of discordancy.

Evaluation of discordant growth should be undertaken simultaneously with consideration of gestational age, individual fetal growth, and fetal well-being. In the absence of fetal anomalies or intrauterine growth restriction, and in the presence of reassuring fetal testing, birth-weight discordance among preterm twins should be managed expectantly in anticipation of achieving more advanced gestation or enhanced fetal maturity. Some caution is appropriate given that the ultrasound diagnosis of both intrauterine growth restriction and in utero growth discordance is limited. The sensitivity of ultrasonography for substantial intertwin discordance is, at best, only 60%. Alternatively, ultrasound evidence suggesting 20% to 25% growth discordance or intrauterine growth restriction of either twin at 35 weeks gestation would be appropriate indications for delivery.

Twin-to-Twin Transfusion Syndrome: Chronic Intertwin Transfusion

Twin-to-twin transfusion is a serious complication affecting multiple pregnancies and is sometimes referred to as chronic intertwin transfusion syndrome. Chronic intertwin transfusion syndrome is a complication of monozygotic/monochorionic twins in which intraplacental arterial venous shunts are uncompensated and preferential blood flow exists. Vascular communications are present in virtually all monochorionic placentas and approximately one third will demonstrate at least some clinical evidence of the syndrome. Severely affected pregnancies are much less common, occurring in fewer than 5% of monochorionic gestations. Contrary to what might be expected, severe twin-to-twin transfusion syndrome is associated with fewer, or even a single arterial venous malformation within the placenta rather than multiple vascular anastomoses. Multiple anastomoses function to restore a balance of bi-directional flow within the monochorionic placenta while a limited number predispose to preferential flow. Severe chronic intertwin transfusion syndrome identified in the second trimester is associated with loss rates approaching 100% if untreated. Chronic intertwin transfusion syndrome accounts for 15% to 17% of all perinatal mortality in twin gestations.

In chronic intertwin transfusion, the arterial donor twin may be growth retarded, anemic, hypotensive, and oligohydramniotic. If there is little or no amniotic fluid surrounding the smaller fetus, the amniotic membrane may lay in close apposition to the smaller fetus restricting it to the uterine wall. This is referred to as the “stuck twin”. The “stuck twin” can sometimes be misidentified as monoamniotic. The arterial donor twin may also experience ischemic organ damage involving the brain, kidneys, or bowel. The venous recipient twin can be hypervolemic, hyperviscous, hypertensive, and polyhydramniotic due to increased renal blood flow. Either twin may be hydropic due to volume overload in the recipient or high output failure in the donor. Polyhydramnios, which is common in the venous recipient, also contributes to a high incidence of premature labor or PPROM.

The diagnosis of chronic intertwin transfusion syndrome has become controversial. Older diagnostic criteria, focused primarily on neonatal measures (i.e., cord blood

hemoglobin differences of 5 g per dL or birth-weight differences of 20%). These parameters have generally been discarded since they did not efficiently identify those gestations thought to be affected by this disorder. Chronic intertwin transfusion syndrome is now diagnosed using ultrasonographic criteria including:

- marked size disparity in fetuses of the same sex
- disparity in size between the two amniotic sacs
- disparity in size of the umbilical cords
- a single placenta
- evidence of hydrops in either fetus
- findings of congestive heart failure in the recipient.

Doppler ultrasound has also been proposed as a tool that may help improve diagnostic accuracy and assess fetal well-being. The normal placenta in chronic intertwin transfusion syndrome results in normal, non-discordant systolic/diastolic (S/D) ratios. Abnormal SD ratios are more likely to reflect placental abnormalities associated with fetal growth restriction. The absence of underlying placental vascular lesions in chronic intertwin transfusion syndrome results in concordant uterine artery waveforms helping differentiate chronic intertwin transfusion syndrome from fetal growth restriction.

Management of chronic intertwin transfusion syndrome will be individualized depending on the stage of pregnancy at which it is encountered. The option of delivery will depend on fetal maturity and the potential morbidity to be encountered. At earlier gestational ages, serial decompression amniocentesis and tocolytic therapy have been successful in prolonging pregnancy. With the development of fetoscopy, direct laser occlusion of the placental vascular anomaly has become an option. For those patients not delivered, fetal health should be frequently evaluated with biophysical profile scoring or fetal heart rate monitoring. Of all available management options, large volume-reduction amniocentesis is an efficacious and minimally invasive therapy that is probably the treatment of choice after attainment of viability. For the previable patient, the prognosis is extremely poor and consideration might be given to intrauterine laser ablation of placental surface vascular anastomoses, fetoscopic cord clamping, or termination.

FETAL AND NEWBORN COMPLICATIONS

Prematurity

The contribution of multiple gestations to national rates of both perinatal morbidity and mortality has been delineated earlier in this chapter. Multiples contribute disproportionately to virtually every measure of perinatal health as well as longer-term measures of infant mortality and long-term mental and physical handicap. Infants of multiple gestations account for approximately 20% of all NICU admissions. An admission to an NICU can be expected in approximately 25% of all twins, 75% of all triplets, and in more than 90% of quadruplets. Respiratory distress syndrome, one particularly costly measure of neonatal morbidity, occurs in approximately 14% of twins, more than 40% of triplets, and more than 60% of quadruplets. The average length of NICU stay is 18 days for twins, approximately 1 month for triplets, and almost 2 months for quadruplets. Birth weight and gestational age account for the vast majority of increased use of NICU services among multiple gestations.

While the consequences of prematurity are easily calculable in terms of fetal and neonatal adversity, it must not be forgotten that prematurity also contributes significantly to the long-term health and well-being of these infants. Compared to singletons, the risk of dying before the first birthday is 5 times greater for twins and 14 times greater for triplets. Among survivors, the relative risk of severe handicap, controlling for both birth weight and gestational age is 1.7 (95% CI = 1.6–2.0) for twins and 2.9 (95% CI = 1.5–5.5) for triplets compared to singleton gestations.

Intrauterine Growth Restriction

Although intrauterine growth restriction is not unique to multiple gestations, it is certainly more common. During the third trimester, the average growth of multiples begins to diverge from average singleton rates. Healthy twin gestations demonstrate growth velocities similar to that of singletons until approximately 30 to 32 weeks gestation while triplet and quadruplet growth velocity begins to slow at 27 to 28 and 25 to 26 weeks, respectively. The mean estimated fetal weight for twins falls below the singleton 50th percentile at about 32 weeks but typically remains between the 10th and 50th percentile until approximately 36 weeks. Beyond 36 weeks, twins frequently fall below the 10th percentile compared to singleton norms. Between 36 to 38 weeks gestation, approximately one-third of all twins will demonstrate intrauterine growth restriction. In comparison, approximately 12% of triplets will have a birth weight less than the 10th percentile based on singleton standards by 32 to 34 weeks, and the rate of IUGR increases to more than 60% by 35 to 36 weeks. Evaluation of the individual parameters of fetal biometry suggests that the reduced growth velocity seen in multiples is most consistent with an asymmetric intrauterine growth restriction. Relative placental insufficiency magnified by the inherent competition for nutrients presented by the multiple fetuses is the most likely cause of this constrained pattern of growth. Other potential contributors to the intrauterine growth restriction identified in multiples include a higher incidence of abnormal placental implantation, umbilical cord abnormalities including a two-vessel cord, velamentous or marginal insertions, chromosomal or structural abnormalities, and intertwin transfusion syndrome.

Intrauterine growth restriction in multiples is best predicted using an estimated fetal weight calculated from multiple biometric parameters including the abdominal circumference. The detection of IUGR is also aided by early diagnosis and accurate dating of the pregnancy. Beyond 20 weeks gestation, fetal growth in multiple gestations should be periodically evaluated by detailed ultrasonographic studies. In general, these scans can be performed on a monthly basis although little data exist that define the optimal interval. That interval can likely be extended if results of the previous scan were reassuring, especially in a dichorionic gestation. Shorter intervals of every 2 to 3 weeks may be required once IUGR has been identified or is suspected. The diagnosis of IUGR in one or both twins should lead to the institution of antenatal fetal surveillance, nonstress testing, assessment of amniotic fluid volume, umbilical artery Doppler velocimetry, and consideration given to the safety of early delivery just as it would be in a singleton gestation. If amniocentesis is used to assess fetal lung maturity, results obtained from the amniotic fluid of either twin will usually reflect the lung maturity status of both making only a single puncture necessary. If intrauterine growth restriction is suspected in only one of the twins, it is likely that the smaller twin will have accelerated lung maturity and therefore the amniotic fluid of the larger twin should be sampled.

Congenital Anomalies

Congenital malformations occur approximately twice as often in multiples as compared to singletons. The majority of malformations occur in monozygotic twins. However, twins are concordant for fetal anomaly in only a minority of cases. Even higher rates of congenital malformation have been reported in triplet gestations.

Identification of congenital malformations represents a major use of ultrasonography in multiples. Transabdominal evaluation of fetal anatomy is best performed between 18 to 22 weeks. However, transvaginal sonography may allow an opportunity to detect certain malformations even earlier. In a single center series of 245 consecutive twin gestations (490 infants), the use of antepartum ultrasound for the detection of congenital anomalies (4.4% anomaly rate) was excellent with a sensitivity of 88% (21 of 24 anomalous fetuses detected), a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 99%. An accurate diagnosis of congenital anomaly is an obvious prerequisite for antepartum or intrapartum interventions. These interventions may include increased fetal surveillance, a change in the timing, location or mode of delivery, consultation with various neonatal and pediatric subspecialists, and in some cases, interventions such as fetal therapy, selective reduction, or pregnancy termination.

ANTEPARTUM CARE

Beneficial Interventions

Maternal Nutrition Alterations in fetal growth described in multiple gestations have been attributed, in part, to the intensified fetal competition for maternal nutrients. This inherent competition results in a drain on maternal resources and an accelerated depletion of maternal reserves. Placental transfer of an adequate nutrient supply is diminished after a combined fetal weight of 3,000 g is exceeded. Unfortunately, most of the investigations that have evaluated the impact of nutrition on perinatal outcome have involved singleton gestations, overlooking the prenatal care of multiples. This is unfortunate because there is accumulating evidence that nutrition is an important and modifiable variable which can improve intrauterine fetal growth and potentially lengthen gestation. The constrained pattern of fetal growth experienced by multiples makes environmental factors, such as nutrition, a greater influence on ultimate fetal growth than in singleton gestations. This allows a proportionately greater opportunity to positively influence birth weight and pregnancy outcome in multiple gestations by modifying maternal nutrition and monitoring the rate of maternal weight gain. Studies have identified maternal weight gains of 24 lbs by 24 weeks and overall weight gains of 40 to 45 lbs as being associated with optimal pregnancy outcomes defined as an average twin birth weight of 2,500 g. A 35- to 45-lb weight gain has been recommended in normal weight women with twins. Investigators have noted the importance of adequate early weight gain (<24 weeks gestation). A ripple effect of maternal weight gain on fetal growth has been demonstrated with gains before 20 weeks and between 20 to 28 weeks influencing subsequent twin growth from 20 to 28 weeks and 28 weeks to delivery, respectively. Poor weight gain prior to 24 weeks (<0.85 lbs per week), regardless of the rate of gain after 24 weeks, has been associated with both reduced intrauterine growth and higher perinatal morbidity. Studies among large cohorts of multiples have demonstrated that maternal weight gain prior to 20 weeks and between 20 to 28 weeks had a greater effect on birth weight in both twin and triplet pregnancies than did weight gain in the third trimester. These findings were particularly notable among underweight women. Patterns of higher maternal weight gain throughout pregnancy results in a favorable combined twin birth-weight difference of more than 1 lb at term compared to low patterns of maternal weight gain. Almost certainly, weight gain recommendations for twins need to be modified based on the maternal body mass index just as they are for

singletons. Analyzing patterns of both intrauterine fetal growth and twin birth weights, Luke and colleagues have proposed BMI-specific weight gain guidelines for twin pregnancies. These guidelines were modeled using multiple regression analysis for the gestational periods of 0 to 20 weeks (early), 20 to 28 weeks (middle), and 28 weeks to delivery (late). As might be expected, excellent twin growth was achieved with lesser maternal weight gains among overweight and obese women compared to underweight or normal weight women. Optimal rates of fetal growth and optimal birth weights were associated with BMI-specific rates of maternal weight gain (lb per wk) as described in Table 14.2.

TABLE 14.2. *Body mass index: specific weight gain recommendations for women pregnant with twins*

In an analysis of over 1,000 triplet pregnancies, Elster and colleagues identified male gender, older maternal age, increased parity, maternal height, pregravid weight, and maternal weight gain as factors associated with improved intrauterine fetal growth. They noted that a longer length of gestation was associated with higher maternal age, parity, and weight gain. Maternal weight gain was also associated with higher birth weight, improved birth weight for gestational age, and a longer length of gestation in a study of 144 triplets reported by Luke. Regression analyses again indicated that periods of maternal weight gain with the greatest impact on triplet birth weight were from conception to 20 weeks and between 20 and 28 weeks gestation. Maternal nutrient requirements are all increased in multiples. Due to the greater expansion of blood volume, increases in maternal tissues (body fat, muscle, breast, uterine) and fetal mass, caloric requirements are estimated to increase by about 40% in twins and by 80% in triplets. Although there are no national guidelines, an estimate of individual nutrient needs in multiples is provided in Table 14.3 based on the recommended daily allowances for nonpregnant and singleton pregnancies published by the National Research Council, Food and Nutrition Board, and extrapolations for twin and triplet pregnancies published by Luke.

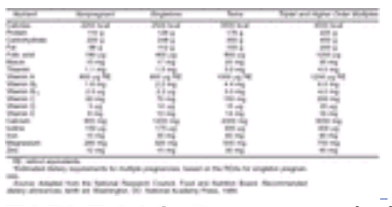

TABLE 14.3. *Recommended dietary allowances (RDAs) for nonpregnant women and women pregnant with singletons and estimated dietary requirements for women with twins, triplets, and higher order multiples* [a]

Maternal anemia, both the iron and folate deficiency types, are common in multiples. Many have recommended supplementation of the standard prenatal vitamin with iron (60 mg per day) and folic acid (1 mg per day) when a multiple pregnancy is diagnosed. The frequency of maternal anemia is related to the overall nutritional status of the woman, which reemphasizes the need for adequate nutrition with a focus on heme-rich protein intake and an emphasis on folate-containing green leafy vegetables. Other nutrients often lacking in women's diets include calcium, magnesium, and zinc, and their specific supplementation has been recommended by some to both prevent their depletion and to reduce pregnancy complications. There is good evidence that intensive patient education, aggressive nutritional counseling, and an emphasis on early and appropriate maternal weight gain can all contribute to improved intrauterine growth and perinatal outcomes in multiple gestations.

Ultrasound Ultrasound plays numerous critical roles in the antepartum care of multiples. These include their diagnosis, determination of amnionicity and chorionicity, identification of fetal or placental anomalies, evaluation of fetal growth and amniotic fluid volume, evaluation of fetal biophysical parameters, and determination of presentation. Accurate determination of chorionicity and amnionicity is important in antepartum management. Monochorionic pregnancies are at substantially higher risk for intrauterine growth restriction, growth discordance, congenital anomalies, and intrauterine fetal death. Although rare, monoamniotic placentation represents an extreme risk with high rates of twin-to-twin transfusion, cord entanglement, and fetal demise. Dichorionic twins are at lower risk as this placentation does not carry the potential for vascular communication and is associated with a lower risk of congenital anomaly. The value of antepartum ultrasound for the identification of fetal congenital malformations has already been described. If two separate placentas are identified or if the fetuses are of different sex, the placentation is dichorionic. A thin, wispy membrane along with a single placenta and same sex fetuses suggest monochorionicity. There are several membrane characteristics that can help differentiate a monochorionic placenta from a fused dichorionic placenta. A “thick” dividing membrane composed of four layers suggests dichorionicity. Another helpful characteristic is the “twin peak” or “lambda sign”. The “twin peak” represents a wedge-shaped projection of placental tissue extending above the fused chorionic surface and separating the diamniotic/dichorionic intertwin membrane. Using these criteria, chorionicity can be predicted accurately in more than 80% to 90% of twin gestations. Determination of chorionicity is most accurate in the first trimester; as pregnancy progresses, the dividing membrane progressively thins and the likelihood of placental fusion increases. Few studies have specifically addressed either the value of serial ultrasound assessment of fetal growth or the appropriate interval for screening. It can be easily inferred, however, that ultrasound has an important role. Intrauterine growth restriction is three times more common among twins compared to singletons and ultrasound is the only modality capable of assessing individual fetal growth. In twin gestations, asymmetric growth restriction becomes increasingly more common as gestational age advances. The presumption is that ultrasound will allow identification of multiples with growth restriction resulting in antenatal surveillance or delivery which may improve perinatal outcome. Evidence of improved outcomes in multiples through the use of ultrasound is limited. In the routine antenatal diagnostic imaging with ultrasound (RADIUS) trial, twins were diagnosed both more consistently and at earlier gestational ages than in the control group receiving selective ultrasound. More than a one third of the triplets in the control group were not diagnosed until after 26 weeks gestation and approximately 10% were not diagnosed until the onset of labor. The RADIUS trial demonstrated a 50% reduction in the incidence of composite adverse perinatal outcomes among the multiple gestations in the routinely screened group. While this reduction was dramatic, it was not statistically significant since the trial was not powered to identify differences in the multiple gestation subgroup. A 10-year study of routine ultrasonography in Europe involving over 22,000 women and 249 multiple gestations also revealed improved perinatal outcomes associated with routine earlier detection by ultrasound. Ultrasound is critical to the management of both twin and triplet gestations. In the second half of gestation, fetal growth should be assessed periodically by serial ultrasound examinations. Most clinicians repeat these ultrasounds on a monthly basis although the appropriate interval between scans has not been determined. This interval can likely be extended if previous examinations suggest appropriate fetal growth, especially in dichorionic gestations.

Selective Multifetal Pregnancy Reduction Gestational age and birth weight at delivery are the two most important factors determining perinatal morbidity and mortality and both are inversely proportional to the number of fetuses present. According to the U.S. Vital Statistics, the average birth weight and gestational age for singletons is 3,358 g at 39.3 weeks, compared to 2,500 g at 36.2 weeks for twins and 1,698 g at 32.2 weeks for triplets. Data from smaller reviews suggest that the average birth weight and gestational age is about 1,455 g at 30.5 weeks for quadruplets and 980 g at 29 weeks for quintuplets. These higher order multiples are at significant risk of delivery prior to viability and for those who reach viability, an appreciable risk of serious long-term morbidity. Expectantly managed triplets and quadruplets have a 20% to 30% risk of delivery prior to 24 weeks and an 8% to 12% risk of delivery between 24 to 28 weeks. Multifetal pregnancy reduction has emerged as a procedure meant to improve the chances of survival and health in higher order multiple gestations. The overall pregnancy loss rate prior to 24 weeks gestation following multifetal pregnancy reduction has dropped from initially reported rates of 15% to 20% to approximately 5% to 8% as experience with the procedure has increased. The risks of pregnancy loss and early preterm birth following multifetal pregnancy reduction have also been described based on the accumulated experience of a consortium of national and international centers. The loss rate prior to 24 weeks is related to both the starting and finishing number of fetuses. A higher starting number is associated with a greater pregnancy loss rate. The loss rate under 24 weeks gestation fell from 15.4% to 11.4%, 7.3%, 4.5%, and 6.2% with six or more, five, four, three, and two fetuses present, respectively, at the start of the procedure. The optimal finishing number of fetuses appears to be twins with loss rates at =24 weeks of 10.9%, compared with 13.7% and 18.0%, respectively, for singletons and triplets. The preferred technique is the transabdominal, ultrasound-guided, fetal intracardiac injection of potassium chloride. It was initially believed that women with quadruplets or more would be ideal candidates for multifetal pregnancy reduction. A meta-analysis of the effect of multifetal pregnancy reduction on pregnancy outcome demonstrated that reduction to twins is associated with longer gestations, higher birth weights, and lower NICU admission rates. The incidence of maternal antenatal hospitalization, preterm labor, and cesarean birth are also reduced although incidences of preeclampsia, gestational diabetes, and other pregnancy complications are not. Somewhat more controversial has been the value of multifetal pregnancy reduction in triplets. Smaller series have not identified an improvement in perinatal mortality in reduced versus nonreduced triplets. Several investigators have reported a significant reduction in early preterm births (24–32 weeks) among triplets reduced to twins compared to nonreduced triplets. Because early preterm birth is a known risk factor for disability, reduction of triplets to twins may reduce the rate of serious morbidity and improve the quality of life for those remaining. Two relatively large databases that have specifically addressed the issue of reduction of triplets to twins have identified better outcomes for the reduced triplets including decreased fetal loss prior to 24 weeks, decreased severe prematurity, increased gestational age at delivery, increased birth weights, decreased perinatal mortality, decreased neonatal respiratory morbidity, and decreased interventricular hemorrhage. It is also important to be aware of the psychological implications for mothers undergoing multifetal pregnancy reduction. Follow-up studies of the emotional responses of women undergoing this procedure revealed that 70% mourned for the reduced fetus(es), but most of the depressive symptoms were mild and lasted only 1 month. For a few however, moderately severe sadness and guilt continued for a longer period. Ultimately, over 90% of the women concluded they would make the same decision again. In addition to multifetal pregnancy reduction, selective fetal termination can sometimes be offered in order to allow a pregnancy to continue following identification of a serious or life-threatening malformation in one twin. The most common indications for selective fetal termination include dizygotic twins discordant for fetal chromosome abnormality, serious fetal structural malformation, or one twin affected by a single gene disorder. Multifetal pregnancy reduction of triplet and higher order multiple gestations is associated with longer gestations, higher birth weights, and lower rates of perinatal morbidity. Multifetal pregnancy reduction of quadruplets or quintuplets would also be associated with significant reductions in perinatal mortality. Multifetal pregnancy reduction should be included in the counseling of all women with triplets and higher order multiples.

Serial Digital Cervical Examination The value of antepartum digital cervical examination lies in its ability to provide ongoing risk assessment. One cervical score is

calculated as follows: cervical length (cm) minus cervical dilation at the internal os (cm). A cervix that is 2 cm long with a closed internal os gives a score at +2. A cervix that is 1 cm long, dilated 1 cm at the internal os gives a score of zero. A cervix that is 1 cm long with an internal os dilated 3 cm gives a score of -2. A cervical score =0 on any single examination predicted preterm labor within 14 days in 69% of those women. When only multiparous women were considered, the predictive value rose to 80%. Newman and Ellings performed weekly digital cervical examinations on 86 twin and 7 triplet gestations as part of routine antepartum surveillance. There was a progressive fall in cervical score throughout the latter half of gestation, most notable after 30 weeks gestation. A cervical score =0 on or before 34 weeks gestation had a positive predictive value of 75% and a four-fold increase relative risk of delivery =37 weeks. The earlier in gestation that a cervical score =0 is detected, the greater the positive predictive value ascribed to it. Only two (2.6%) women experienced spontaneous preterm labor or PPROM within 1 week of having a cervical score greater than 0. A cervical score =0 is a marker of abnormal cervical status and increased preterm delivery risk. Conversely, women who maintain a cervical score greater than 0 are good candidates for continued observation without obstetric intervention. Ideally, these examinations should be done by a consistent examiner on an every 1- to 2-week basis between 24 to 36 weeks gestation. There are no prospective studies or cohort series that demonstrate that antepartum digital cervical examination is associated with obstetric complications or adverse perinatal outcomes.

Corticosteroid Administration Corticosteroids should be administered to women with multiples experiencing preterm labor prior to 34 weeks gestation. The National Institutes of Health also recommends corticosteroid therapy for women with PPROM at less than 30 to 32 weeks gestation. Corticosteroids have been shown to induce fetal lung maturity and reduce perinatal complications in twin gestations as well as singletons. Evaluation of the clinical characteristics and outcomes of twin gestations complicated by PPROM reveals that the nonpresenting twin was more likely to develop hyaline membrane disease, respiratory complications, and require more oxygen therapy than the presenting infant. As a consequence, the nonpresenting twin was at greater risk for infant mortality.

Fetal Surveillance Although no prospective trials exist, all retrospective reviews indicate that the nonstress test has equivalent efficacy in multiples to that seen in singletons. Both the nonstress test and the biophysical profile have been shown to be effective in identifying the growth-retarded multiple, the multiple at risk for hypoxic/asphyxic injury, and the multiple at risk for perinatal mortality. One retrospective cohort study compared 230 twins who received third trimester nonstress tests to 435 twins who did not. Although the differences did not achieve statistical significance, there was only a single intrauterine fetal demise in the nonstress test group compared to nine in the control group. Similar findings have been reported in smaller retrospective studies involving triplet and higher order gestations. While the routine use of antepartum fetal surveillance in uncomplicated multiples has not been shown to be of benefit, surveillance is certainly indicated in those gestations identified as being at higher risk. These would include those with intrauterine growth restriction, abnormal fluid volumes, growth discordance, pregnancy induced hypertension, fetal anomalies, monoamnionicity, or any other pregnancy complications placing one or more of the fetuses at increased risk. Other recommended methods of fetal surveillance include fetal kick counting, although some patients may find it difficult to distinguish the movements of one fetus from those of another. Umbilical cord Doppler velocimetry may be of help in evaluating growth-retarded fetuses. Ultrasonography obviously contributes to both the risk assessment and surveillance of multiple gestations. The limitations of ultrasound for both the diagnosis of intrauterine fetal growth restriction as well as for fetal growth discordance would be the major indication for some clinicians to recommend routine surveillance of all multiples. At present, antepartum fetal surveillance in multiples is recommended in all situations for which one would perform similar surveillance in a singleton pregnancy. Further studies are needed to determine if routine antepartum fetal surveillance provides objective benefit in either twin or triplet gestations.

Controversial Interventions

Reduced Activities/Rest Activity restriction and increased rest at home is commonly recommended for women with multiples although there are no prospective randomized data evaluating this intervention. Existing data are both dated and limited by study design. Studies evaluating the role of prescribed rest in both twin and triplet gestations compared to similar pluralities with unrestricted activities typically date from time periods when the unrestricted multiples were in reality undiagnosed. Maternal rest has been associated with reduced baseline uterine contraction frequency, and restricted activity has been generally accepted as a reasonable approach to the prolongation of pregnancy. Other studies have suggested that the birth weights of both twins or triplets may be increased if reduced activity and home bed rest is introduced in the mid-trimester. Further research is needed to define the impact of restricted activity and rest on both the duration of pregnancy, fetal growth, and the risk of pregnancy-induced hypertension.

Home Uterine Activity Monitoring Few issues are as controversial as home uterine activity monitoring (HUAM). HUAM has been advocated for multiples due to their increased risk of premature labor combined with observations that multiples may be less accurate in the self-detection of their own prelabor uterine activity compared to women with singleton gestations. Prospective randomized trials evaluating the efficacy of HUAM in multiples have provided conflicting results. Dyson and colleagues performed a prospective randomized trial of high-risk pregnancies allocated to one of three interventions. The first group received standard care including instruction in the signs and symptoms of preterm labor. The second group was in the education/palpation group who performed daily HUAM but transmitted the data so that it could not be analyzed. The education/palpation group was contacted at least 5 days per week by a study nurse to elicit their signs and symptoms of preterm labor and record the number of contractions detected by palpation. The third group received the same education/palpation instruction and also underwent daily HUAM, which was interpreted by a study nurse. Of the entire study group, 189 were twin gestations that were analyzed separately. The incidence of preterm birth less than 36 weeks was significantly decreased in the education/palpation group (29.8%; $P < .05$) and markedly decreased in the HUAM group (23.1%; $P < .01$) compared to the standard care group (46.3%). The infants in the HUAM group had the best neonatal outcomes with significant improvements in all measures compared to standard care. The HUAM infants were also significantly less likely to be of very low birth weight, to be admitted to the NICU, and had shorter hospital stays compared to the infants in the education/palpation group. Following their initial publication, Dyson and colleagues embarked on a second prospective, randomized, multicentered trial of HUAM involving 2,422 pregnant women including 844 twins who all received preterm birth prevention education. This educational program was then combined by a random assignment to three subsequent levels of surveillance:

1. Weekly contact by a perinatal nurse.
2. Daily contact by a perinatal nurse.
3. Daily contact with a perinatal nurse and daily HUAM.

Among the twins, there were no differences in the frequency of preterm birth less than 35 weeks gestation between those women receiving weekly contact (22%), daily contact (24%), or HUAM (24%). At the time that preterm labor was diagnosed, 75% of the weekly contact patients, 76% of the daily contact patients, and 80% of the HUAM patients were =2 cm with no differences in the mean cervical dilation. There was also no difference in the frequency of low–birth-weight or very low–birth-weight (VLBW) deliveries, mean number of days gained with tocolysis, or number of unscheduled visits. HUAM in twins has been associated with improved outcomes in two prospective, randomized trials that included a standard care control group. No benefit could be ascribed to HUAM when the comparison group received intensive education and was provided with frequent perinatal nursing contact. At present, the benefits of HUAM in twins remain controversial and its use should be highly individualized. There are no prospective data addressing the use of HUAM in triplets.

Endovaginal Ultrasound Cervical Length Measurements Endovaginal sonography to measure cervical length has been studied to determine its predictive value for spontaneous preterm delivery in twin gestations. In a large, multicentered study sponsored by the NICHD (National Institute of Child Health and Human Development), predictors of preterm delivery were evaluated in both singleton and twin gestations. A cervical length of =25 mm was significantly more common in twin gestations compared to singletons at both 24 and 28 weeks. Of all the potential predictors of preterm delivery, a cervical length =25 mm at 24 weeks gestation was the best predictor of preterm labor before 32, 35, or 37 weeks gestation in twin pregnancies. Shortened cervical length measurements by endovaginal sonography correlate with preterm delivery risk in twin gestations. Alternatively, normal mid-trimester cervical length measurements are associated with low rates of early preterm delivery. Again, there is no evidence that endovaginal sonography improves outcome, nor have there been any successful intervention trials based on endovaginal cervical length measurements. Currently there is insufficient evidence to recommend cerclage placement for an abnormally short cervix, although this is clearly an area for future investigation.

Cervical/Vaginal Fetal Fibronectin Fetal fibronectin is a high–molecular-weight, extracellular matrix glycoprotein that is normally found in amniotic fluid, fetal membranes, and placental tissues. Observational trials involving singleton gestations have demonstrated that cervical/vaginal fetal fibronectin at concentrations over 50 ng per mL between 21 to 37 weeks gestation is predictive of impending preterm delivery. Several observational trials have specifically investigated the predictive capability of cervical/vaginal fetal fibronectin in multiple gestations. In the NICHD Preterm Prediction Study, 147 twins underwent serial assessment for cervical/vaginal fetal fibronectin in addition to endovaginal ultrasound cervical length measurements. Positive fetal fibronectin results at 28 and 30 weeks gestation were associated with an increased risk of delivery prior to 32 weeks. However, the association of fetal fibronectin with preterm delivery was no longer significant after controlling for cervical length with logistic regression analysis. In one study of asymptomatic women with twins, fetal fibronectin in at least one sample was associated with a relative risk of 2.0 for birth prior to 35 weeks, and a relative risk of 18.0 for birth prior to 35 weeks if all samples were positive. A positive fetal fibronectin test at 24 weeks gestation had a sensitivity of 37%, a specificity of 91%, a positive predictive value of 54%, and a negative predictive value of 84% for delivery less than 35 weeks. Fetal fibronectin in cervical/vaginal secretions in the late second and early third trimester is associated with an increased risk of preterm birth in multiples. Data are conflicting as to whether fetal fibronectin has predictive value in addition to endovaginal cervical length measurements. Alterations in clinical management based on fetal fibronectin results have not yet been evaluated, and improved pregnancy outcomes have not yet been demonstrated.

Tocolytic Therapy Tocolytic therapy has generally been found to be of limited benefit in terms of prolonging pregnancy. In most investigations, singleton or multiple, tocolytic therapy can only be relied on to provide a short-term prolongation of pregnancy. Even a short-term prolongation, however, may be beneficial in terms of allowing tertiary care transport, administration of corticosteroids for enhancement of fetal lung maturity, and in some cases, a modest extension of gestation. Tocolytic use in multiples must be accompanied by very careful monitoring of both maternal and fetal condition. Women pregnant with multiples are at higher risk for a number of tocolytic-related complications, most notably pulmonary edema. Contributing to this risk is a proportionately increased maternal blood volume, lower colloid oncotic pressure, and anemia in many cases. Tocolytic factors that increase the risk of pulmonary edema include the use of ß-adrenergic agents and prolonging tocolytic therapy for more than 24 hours. Both myocardial ischemia and cardiac arrhythmias have also been reported as a rare consequence of tocolytic therapy. Beta-adrenergic agents are also known to increase maternal glucose levels, aggravating either overt or gestational diabetes of pregnancy.

Nonbeneficial Interventions

Prophylactic Cerclage Two prospective randomized trials have assessed the value of prophylactic cervical cerclage in twin pregnancies and neither revealed any

improvement in preterm birth rate or perinatal mortality. Unfortunately both studies lack substantial power due to small sample sizes. The two studies also suggest that cerclage imparts some risk, specifically an increased risk of maternal infection and PPROM. These findings are also supported by several retrospective studies, none of which reveal any improvement in mean gestational age at delivery or the proportion of preterm deliveries. In triplet pregnancies, the literature consists of small retrospective studies. One study reported a benefit, whereas two others found none. Sufficient evidence is lacking to support the elective placement of cervical cerclage in either twin or triplet pregnancies. Cerclage should be reserved for patients with a significant clinical suspicion of cervical incompetence. While a shortened endovaginal cervical length measurement correlates with preterm delivery risk in twins, there is insufficient evidence at present to conclude that cerclage placement for an abnormally short cervix will improve outcome, although this is clearly an area for future investigation.

Prophylactic Tocolysis Prescribing prophylactic oral ß-mimetics in twins to reduce the risk of preterm birth has been evaluated in seven prospective randomized trials. Evaluation of these trials is difficult due to their heterogenicity. While all studies used oral ß-mimetic agents, a variety of different drugs were used as well as various dosages and gestational ages at which the medications were started. Despite this heterogeneity, a meta-analysis of these trials failed to show any consistent effect on the risk of preterm birth, birth weight, or neonatal mortality. Other tocolytic agents, such as prostaglandin synthetase inhibitors, calcium channel blockers, and oral magnesium sulfate have not been studied in multiples. The potential risks of prolonged fetal exposure to ß-mimetic agents or other tocolytics are not completely known. Little evidence of efficacy of prophylactic tocolysis in triplets exists, although these data are obtained solely from retrospective review. The lack of efficacy in these retrospective studies may be biased if prophylactic tocolysis was used more often in triplets perceived to be at greater risk. The prophylactic use of oral tocolytic agents has not been associated with improved outcome or meaningful prolongation of pregnancy in either twin or triplet gestations.

Routine Hospitalization Four prospective randomized trials of hospitalized bed rest for women with an uncomplicated twin pregnancy have been conducted. The *Cochrane Database of Systematic Reviews* of these trials showed that neither stillbirth, neonatal death, or preterm birth were reduced by elective hospitalized bed rest (Fig. 14.4). In fact, significantly more women delivered VLBW infants and infants prior to 34 weeks gestation in the hospitalized cohort. This was also associated with an increased risk of early neonatal demise among the women routinely hospitalized with uncomplicated twins. Those patients at hospitalized bed rest did experience a lower frequency of maternal hypertension. One further study evaluated elective hospitalization using a prospective sequential study design. A policy of elective hospitalization until 34 weeks was used between 1983 and 1985 encompassing 134 twin deliveries, followed by a policy of outpatient management between 1985 and 1987 encompassing 177 twin deliveries. There were no differences in prematurity or perinatal morbidity between the two groups. There was a higher mortality rate and significantly higher costs associated with elective hospitalization. A final study by Crowther in 1989 prospectively randomized 139 women with twins whose pregnancies were complicated by preterm cervical dilation (cervical score -2 at or before 34 weeks gestation). Despite the higher risk nature of this cohort, there were no differences seen in the risk of preterm birth, perinatal mortality, fetal growth, or other neonatal outcomes.

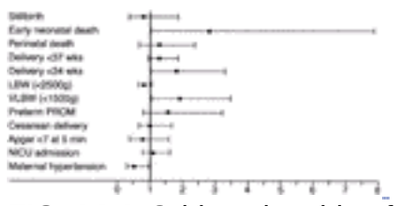

FIG. 14.4. Odds ratio table of the effect of routine hospitalization for bed rest on obstetric outcomes among women with uncomplicated twin pregnancies. (Adapted from Crowther CA. Hospitalization for bedrest in multiple pregnancy. In Neilson JP, Crowther CA, Hodnett ED, et al (eds). Pregnancy and childbirth module. *Cochrane Database of Systematic Reviews* [updated 03 June 1997] 1997:3.)

In triplets, there is a single small prospective trial involving 19 women randomized at 29 weeks gestation. The hospitalized group had a longer duration of pregnancy, fewer VLBW infants, and decreased neonatal morbidity. However due to the small sample size, the observed differences were compatible with chance variation. A retrospective sequential cohort study of 34 triplets managed by elective hospitalization at 24 weeks between 1985 and 1993 were compared to 32 triplets managed by bed rest at home between 1993 and 1996. Routine hospitalization increased gestational age at delivery by one week although this difference was not statistically significant. There is no obvious benefit of routine hospitalization in twin gestations. In triplet gestations, there is a single prospective randomized trial, which suggested improved outcome with routine hospitalization but included too few patients to draw definitive conclusions. Definitive benefits will be necessary to outweigh the social and financial costs associated with routine hospitalization.

INTRAPARTUM MANAGEMENT

Safe and successful intrapartum management of multiples requires attention to several important principles necessary to their care (Table 14.4). Most important is the presence of experienced and skilled obstetric, pediatric, anesthesia, and nursing personnel. Intrapartum management plans for twin gestations will depend to a great degree on their relative presentations. During labor, both fetuses should be continuously monitored as multiple gestations are at increased risk for several intrapartum complications which may manifest as abnormal fetal heart rate tracings. Ultrasonography should be available to ascertain presentation, estimate relative fetal weights, and to assist with fetal assessment during the interval between deliveries. When vaginal delivery is attempted, the delivery room should be doubly set up for a possible emergency cesarean section including immediate availability of anesthetic and neonatal services. Due to the relatively frequent need for emergency operative or manipulative obstetric procedures, continuous epidural anesthesia is preferred. Familiarity on the part of the obstetric attendants with the use of both obstetric forceps (Piper forceps if breech delivery is planned) and vacuum extractor is recommended. A variety of medications should also be available in the delivery suite including a premixed oxytocin infusion for stimulation of labor since uterine inertia is frequently encountered following delivery of the first twin. Tocolytic agents such as subcutaneous terbutaline and intravenous nitroglycerine should be available for uterine relaxation. Women with multiple gestations also experience an increased mean blood loss with delivery, an increased cesarean section rate, and are at increased risk of postpartum uterine atony. As a consequence, uterotonic agents such as methylergonovine maleate or 15-methyl prostaglandin F_2 should be immediately accessible and the availability of blood products should be insured.

Presence of skilled obstetric attendants for labor and delivery
Sufficient nursing and neonatal care personnel
Dual monitoring cardiotocograph
Intrapartum ultrasonic scanning capability
Intravenous access (16–18 gauge)
Premixed oxytocin infusion
Nitroglycerin or terbutaline for uterine relaxation
Methergine or 15-methyl $PGF_{2\alpha}$ to induce uterine contractions
Obstetric forceps and vacuum extractor available
Immediate availability of blood and blood products
Anesthesiologist available at delivery and capability for emergency cesarean

$PGF_{2\alpha}$, prostaglandin F2-alpha.

TABLE 14.4. *Principles of intrapartum care for the multiple gestation*

Timing of Delivery

The ideal time for delivery of uncomplicated multiple gestations is uncertain but an important issue in terms of optimizing perinatal outcome. A retrospective population-based analysis of all live births and fetal deaths in the United States from 1983 to 1988 revealed that the lowest fetal death rate per 1,000 conceptions for singletons was 0.9 at 3,700 to 4,000 g between 40 to 41 weeks. The lowest fetal death rate for twins was 3.3 per 1,000 conceptions at 2,500 to 2,800 g at 36 to 37 weeks gestation. The lowest fetal mortality rate for triplets was 5.2 per 1,000 conceptions at 1,900 to 2,200 g at 34 to 35 weeks gestation. A large retrospective, population-based study of almost 89,000 multifetal pregnancies and over 6 million singleton pregnancies delivered between 1989 and 1993 in Japan revealed similar findings. The incidence of stillbirth and early neonatal death gradually declined until 37 to 38 weeks gestation for multiples and increased thereafter. In singletons, the same parameters declined until 39 weeks before increasing. The lowest incidence of perinatal death (stillbirth plus early neonatal death) for multiples occurred at 38 weeks gestation. Most of the excess fetal mortality in twins was confined to infants with birth weights less than the 10th percentile. By 38 weeks gestation, overt asymmetric growth restriction encompasses nearly half of twin pregnancies and an even larger percentage of triplets. Obviously, these population-based analyses should be supplemented by clinical studies determining the neonatal and post-neonatal risks of prematurity-related morbidity among multiples born during these presumed optimal birth-weight and gestational age windows (i.e., 2,500 to 2,800 g at 36 to 38 weeks for twins and 1,900 to 2,200 g at 34 to 36 weeks for triplets).

Available data do not support the prolongation of a twin or triplet pregnancy beyond 38 or 36 weeks, respectively, in hopes of improving outcome. Beyond these points, multiples begin to experience increased combined fetal and neonatal morbidity and mortality primarily related to growth restriction. To safely prolong pregnancy requires reliable ultrasonographic evidence of adequate fetal growth, normal amniotic fluid volumes, and reassuring fetal testing, as well as a stable maternal condition. The identification of intrauterine growth restriction, significant discordance, oligohydramnios, maternal preeclampsia, or any other significant maternal–fetal complication at these gestational age limits should be a specific indication for delivery, which, in turn, will improve perinatal outcome. Unfortunately, this presumption has not been subjected to prospective randomized analysis. In the absence of any of these maternal or fetal complications and with reassuring fetal testing, there is no contraindication to continued observation beyond 38 weeks for twins or beyond 36 weeks for triplets while awaiting spontaneous labor or a more favorable cervix. Most agree that there are little data to suggest any value to prolonging a multiple gestation beyond 40 weeks.

Route of Delivery

The preferred route of delivery for multiples is controversial, particularly for the vertex/nonvertex presenting twins. The preferred route of delivery is usually determined based on presentation, which for twins is generally categorized into three large groups:

1. Twin A vertex, twin B vertex
2. Twin A vertex, twin B nonvertex
3. Twin A nonvertex.

Twin A Vertex/Twin B Vertex Approximately 40% of twin gestations will present with both in a vertex presentation. Vaginal delivery should be anticipated for this group of twins with high likelihood of success anticipated. More than 80% of vertex/vertex presenting twin gestations are successfully delivered vaginally. The presentation of the second twin should be reconfirmed following delivery of the first as a change in the presentation may occur in as many as 20% of cases.
Twin A Vertex/Twin B Nonvertex Opinions diverge regarding the optimal mode of delivery for vertex/nonvertex presenting twins, which represent another 40% of twins in labor. Reports of depressed Apgar scores and increased perinatal mortality during the 1970s and 1980s led to cesarean delivery being advocated by some whenever the second twin was in a nonvertex presentation. Since the early 1980s, however, there has been a significant accumulation of primarily observational, nonrandomized clinical experiences which have not found an increased risk of adverse neonatal outcome when the nonvertex second twin is delivered vaginally. Only one prospective randomized trial (by Rabinovici and colleagues) has been conducted. Sixty women in labor with twins at 35 to 41 weeks in which the first twin was vertex and the second a nonvertex were enrolled. Of the 33 women assigned to vaginal delivery, two underwent cesarean deliveries, four aftercoming twins spontaneously converted to vertex, 14 had assisted breech extraction, and 13 had total breech extractions. There were no differences between the groups in Apgar scores or neonatal morbidity and there was no birth trauma, stillbirth, or early neonatal death in either group. Women assigned to cesarean delivery had a significantly higher incidence of febrile morbidity and a trend toward greater receipt of general anesthesia (Fig. 14.5).

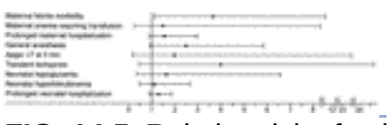

FIG. 14.5. Relative risk of selected obstetrical outcomes and the effect of cesarean delivery for the second twin. (Adapted from Rabinovici J, et al. Randomized management of the second nonvertex twin: vaginal delivery or cesarean section. *Am J Obstet Gynecol* 1987;156:52–56.)

Supporting the Rabinovici trial, there have been at least ten observational studies that have looked at the outcomes for the nonvertex second twin. Although each study is limited by its lack of prospective randomization, and in some cases by size, none have found that the nonvertex second twin was disadvantaged by vaginal delivery, especially if the birth weight was greater than 1,500 g. Maternal morbidity is routinely higher and length of stay longer for the groups undergoing cesarean delivery. Although not specifically studied, most clinicians would not recommend attempted breech extraction if the second twin was anticipated to be significantly larger (>500 g) than the presenting twin. Vaginal delivery of the nonvertex second twin by breech extraction or assisted breech delivery appears to be the best approach for infants over 1,500 g. There is no evidence that the increased maternal morbidity associated with routine cesarean delivery is offset by improved neonatal outcome. A policy of routine cesarean whenever the second twin is not presenting as a vertex can be expected to increase maternal morbidity and increase the need for general anesthesia without beneficial effects in terms of maternal or infant outcome. Recommendations for route of delivery for a nonvertex twin B whose birth weight is estimated to be less than 1,500 g is not so clear. A population-based study in Sweden encompassing 10 years of recorded deliveries allowed an assessment of 862 infants weighing less than 1,500 g delivered from 539 twin pairs. There was no significant difference in intrapartum or neonatal mortality related to the mode of delivery nor was there a difference of the subset of nonvertex second twins. Zhang and colleagues used a similar methodology in the United States but found somewhat different results. After controlling for maternal characteristics with multiple logistic regression, cesarean delivery was associated with a reduction in neonatal and infant death rates among all infants with a birth weight less than 1,000 g. The benefit of cesarean delivery was found primarily among second twins, whether vertex or nonvertex. Decisions on cesarean birth versus vaginal delivery for nonvertex second twins less than 1,500 g should be based on the specific clinical situation and the experience of the staff involved. In the absence of an experienced operator, cesarean delivery should be primarily performed. External cephalic version for the nonvertex second twin after delivery of the first has been described. This approach has been popular among physicians less comfortable with breech extraction. Although no prospective trials have been performed comparing the efficacy and safety of second twin version versus breech extraction, several retrospective studies have addressed this issue. Chauhan and co-workers reviewed this literature assembling 118 cases of external cephalic version of the nonvertex second twin. They found that despite a high rate of successful version, the rate of successful vaginal delivery of the second twin was highly variable between reports (46% to 80%) with an overall success rate of 58%. There was a combined complication rate of 10% including six cord prolapses, four episodes of fetal distress, one abruption, and one compound presentation. By way of comparison, the authors reviewed 683 second twin breech extractions in 11 published reports and reported a successful vaginal delivery rate of 98% with an overall complication rate of only 1%, which translated into three fractured humeri, two episodes of fetal distress, and two cord prolapses.
Twin A Nonvertex In approximately 20% of cases twin A presents as a nonvertex. Vaginal delivery of twins with a nonvertex presentation of twin A is problematic as little data exist evaluating its safety. Older retrospective reviews suggest an increased risk of perinatal loss when twin A delivers as a breech although other relatively small retrospective reviews have found no significance difference in perinatal outcome between breech/vertex twins delivered vaginally and similar groups delivered abdominally. For twins presenting breech/vertex, the possibility of interlocking exists. While this complication is extremely rare, it is typically catastrophic. While not so dramatic, fetal collision may also lead to cesarean delivery due to failure of the presenting breech to descend. When the first twin is presenting breech, the most commonly employed mode of delivery is cesarean. Vaginal delivery may be an option based on the experience of the staff and the capability for emergency cesarean delivery.
Triplets and Higher Order Multiples Cesarean is the most commonly recommended mode of delivery for triplets. A nationwide review of triplet births between 1985 and 1988 revealed that 94% of the deliveries were by cesarean, 4.5% were vaginal, and 1.5% were a combined vaginal/abdominal approach. Triplets and higher order multiples are at significant risk for prematurity, growth retardation, and malpresentation, and as a result, most clinicians prefer to deliver these pregnancies by cesarean section rather than attempt a vaginal delivery, which may require complex manipulation of preterm infants. Successful vaginal delivery of triplets has been reported in several small series without any apparent compromise of neonatal outcome. If a vaginal delivery is planned, it is imperative that an experienced obstetric team be available, malpresentation anticipated, and preparations made for emergency cesarean delivery if necessary. It would seem that optimal cases would be those with triplets estimated to weigh more than 1,500 g each and with at least the first two triplets in a vertex presentation.

Interval Between Deliveries

Previous data have suggested that time intervals between twin deliveries of more than 30 minutes would be associated with compromised outcomes. With the development of continuous electronic fetal monitoring and the intrapartum use of real-time ultrasonography, this no longer appears to be the case. Much of the data suggesting higher perinatal morbidity and mortality associated with long delays between deliveries are from an era when the presence of the second twin was frequently not apparent until after delivery of the first. Delays of more than one hour have not been associated with adverse outcomes for the second twin as long as continuous fetal heart rate monitoring is employed.

In some cases, there will be deterioration of the fetal condition following delivery of twin A. Both premature placental separation and prolapse of the umbilical cord are complications known to occur with increased frequency following the delivery of the first twin. Distress of the second twin should usually be managed by immediate cesarean or operative vaginal delivery. Internal podalic version and breech extraction should only be considered when emergency delivery is mandated and cesarean delivery is not immediately available. There are no current series documenting the safety of internal podalic version in cases of fetal distress. Due to the ever-present possibility of intrapartum fetal distress, the capability of immediate cesarean delivery should be considered the standard of care for multiples.

In the absence of any of the aforementioned complications, labor management for the second twin can be fairly aggressive. There is often a period of hypocontractility following delivery of the first twin. If labor has not resumed within a short period of time following delivery of twin A, a previously prepared oxytocin infusion can be started and the dosage escalated in relatively rapid fashion until adequate uterine contractions are achieved. Once effective uterine contractions are reestablished, the woman is encouraged to bear down in order to achieve further descent. Once the vertex is in the pelvic inlet, amniotomy can be performed during a contraction with moderate fundal pressure to help fix the vertex within the pelvis. The amniotic sac can be ruptured grossly if the fetal head is well applied to the cervix or leaked with a spinal needle if the vertex is not well applied.

Delayed Interval Delivery Due to an increased risk of both extremely preterm if not previable delivery, multiple gestations occasionally present the opportunity for delayed interval delivery. The optimal situation occurs in a diamniotic/dichorionic twin gestation where the loss of the presenting fetus is the consequence of extrusion following either PPROM or true cervical incompetence. Other reported cases in which delayed interval delivery has been successfully employed have been with separate implantations associated with müllerian anomalies, such as didelphic uterus. Less favorable circumstances would include those deliveries complicated by advanced preterm labor or vaginal bleeding suggestive of placental abruption. Contraindications to delayed interval delivery include significant hemorrhage, hemodynamic instability, intraamniotic infection, and monochorionic placentation. Although life-saving prolongation of pregnancy has been reported in case reports and small series, the patient should be informed of a relatively high failure rate associated with the procedure and risks including intrauterine infection, maternal sepsis, hemorrhage, and prolonged hospitalization. Successful delayed interval delivery has been achieved without the use of a rescue cerclage. However, based on available case reports, adjunctive rescue cerclage appears to offer a better chance of greatly prolonging the interval between deliveries. Most protocols make use of aggressive perioperative tocolysis and broad-spectrum antibiotic coverage, although there are no data to establish either the necessity or efficacy of either of these interventions in

this circumstance. Specific pathogens such as gonorrhea, chlamydia, and group B streptococci should be identified and treated. Following delivery of the first fetus, the umbilical cord is tied, cut short, and allowed to retract back into the uterus. At that point, most clinicians place a 5-mm Merseline band using the McDonald technique as a rescue cerclage procedure. Tocolytic therapy, antibiotic coverage, and hospitalized observation are continued for variable periods of time along with intensive maternal and fetal surveillance. At its most successful, delayed interval delivery has allowed prolongation of pregnancy from a previable stage of maturation to well within the third trimester, if not term.

POSTPARTUM MANAGEMENT

Because of the potential risk of uterine atony and postpartum hemorrhage, the other should be closely monitored during the initial hours after delivery. Adequate oxytocin should be administered and the uterine fundus should be regularly assessed to ensure that appropriate uterine tone is maintained. Lactation consultation may be useful to assist the mother in initiating breast-feeding of her twins or triplets. The maternal task of caring for multiple infants is often overwhelming. Follow-up and support for the mother in the early weeks after delivery are important, especially if the neonates require intensive care unit admission. Postpartum depression is likely more common in women delivering multiples and surveillance for this important complication should be ongoing.

SUMMARY POINTS

- Although multiples account for only a small percentage of all live births, they are responsible for a disproportionate share of all perinatal morbidity and mortality suffered in the United States.
- The dramatic increase in the frequency of dizygotic twinning in the United States is due, in part, to a national trend toward delayed childbearing but the majority is a consequence of ovulation induction therapy and recently developed assisted reproductive technologies.
- Women pregnant with multiples are more likely to be hospitalized antenatally for both an increased frequency and severity of pregnancy-related complications including preterm labor, PPROM, maternal anemia, placental abruption, preeclampsia, and urinary tract infections.
- The factors strongly correlated with both length of gestation and birth weight in multiples are maternal height, pregravid body mass index, maternal fat deposition, and weight gain, especially early weight gain in underweight women.
- Data do not support prolongation of a twin or triplet pregnancy beyond 38 or 36 weeks, respectively, due to the increased combined fetal and neonatal morbidity and mortality associated primarily with high rates of intrauterine growth restriction.
- There is no evidence that the increased maternal morbidity associated with routine cesarean delivery is offset by improved neonatal outcomes for the nonvertex second twin over 1,500 g; therefore, vaginal delivery by breech extraction or assisted breech delivery is the preferred method of delivery in these cases.

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Chapter 15

E. Albert Reece and Carol J. Homko

Diabetes Mellitus and Pregnancy

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INTRODUCTION

The discovery of insulin in 1921 brought about a significant improvement in the overall outlook for women with diabetes and their reproductive potential. The incidence of both maternal and perinatal mortality has decreased markedly over the past 80-plus years as a result of this discovery as well as a multitude of other scientific advances, including fetal heart rate and blood glucose monitoring and neonatal intensive care. However, despite these advances, women with diabetes and their offspring remain at increased risk for a number of complications. The increased morbidity is directly related to the severity of maternal hyperglycemia. Therefore, the management goal of these pregnancies is strict glycemic control prior to conception and throughout gestation. This is best accomplished through the provision of multidisciplinary team care and targeted self-management education.

FUEL METABOLISM

Pregnancy is recognized as having a profound effect on maternal fuel metabolism. These pregnancy-related alterations in maternal metabolism are necessary to meet the demands of the developing fetus. Studies in lean healthy pregnant women have demonstrated a greater than normal sensitivity to the blood glucose–lowering effect of exogenously administered insulin during early pregnancy as compared with late gestation. In addition, insulin responses to an oral glucose load have been demonstrated to be increased in early pregnancy as compared with the nonpregnant state in the same glucose-tolerant women.

These increases in serum insulin levels and insulin sensitivity produce a milieu during early gestation that favors maternal fat accumulation in preparation for the rise in energy requirements associated with the rapid growth of the fetal–placental unit during late pregnancy. Moreover, the increases in plasma concentrations of estrogen, progestins, and cortisol observed during early pregnancy are also likely to stimulate fat accumulation.

Late gestation is characterized by accelerated growth of the fetoplacental unit, rising plasma concentrations of several diabetogenic hormones including human placental lactogen and estrogens, and increasing insulin resistance. Several investigators have demonstrated increased first- and second-phase insulin release during late gestation, as well as increased plasma insulin-to-glucose ratios. Studies using the euglycemic-hyperinsulinemic clamp and minimal model techniques have reported that peripheral insulin sensitivity is reduced by 33% to 50% during late gestation. During the third trimester of pregnancy, insulin-stimulated carbohydrate oxidation is reduced out of proportion to the decrease observed in insulin-stimulated glucose uptake. Endogenous glucose production is also significantly less inhibited during the third trimester when compared with either the second trimester or the nonpregnant state. Thus, there appears to be general agreement that the second half of pregnancy is associated with increasing insulin resistance, both in the periphery (muscle) and at the hepatic level.

The cause or causes of the increased insulin resistance during late pregnancy are not entirely clear. The parallel development of insulin resistance and increases in blood levels of human placental lactogen, a hormone with strong lipolytic and anti-insulin action, suggests that human placental lactogen and perhaps other diabetogenic hormones, including cortisol, progesterone, and estrogens, may be responsible for much of the observed insulin resistance. In addition, there is also evidence to support a role for plasma free fatty acids in the development of insulin resistance during late pregnancy.

The development of peripheral and hepatic insulin resistance after midpregnancy can be seen as an effort of the mother to adapt to the fuel needs of the rapidly growing fetus. During the third trimester of pregnancy, glucose uptake by the fetus has been estimated to be approximately 33 µmol/kg per minute. To satisfy this additional need, peripheral insulin resistance increases in pregnant women, thus reducing maternal glucose utilization. In addition, hepatic insulin resistance increases, which increases hepatic glucose production. Moreover, by decreasing carbohydrate oxidation, much of the glucose entering muscle is shunted into alanine or lactate, which can be recycled into glucose.

CLASSIFYING DIABETES

Diabetes mellitus generally is classified into the following categories: type 1 or insulin-dependent diabetes mellitus, type 2 or non–insulin-dependent diabetes mellitus, and gestational diabetes mellitus (GDM). Approximately 10% of all individuals with diabetes mellitus have type 1 diabetes. Beta-cell destruction, with resulting insulin deficiency, is the hallmark of this disorder. Onset is generally before the age of 30 and, as a result, this type of diabetes frequently is encountered in women of childbearing age. It is estimated that type 1 diabetes complicates approximately 0.2% of all pregnancies in the United States annually.

Type 2 diabetes is the most common form of the disease, affecting nearly 90% of all individuals with diabetes. Type 2 diabetes is characterized by defects in both insulin action and secretion. It typically is seen in individuals over the age of 40 and, therefore, in the past was felt to be uncommon in women of childbearing age. However, the incidence of type 2 diabetes has been increasing steadily among younger individuals, and data from the National Maternal and Infant Health Survey indicate that type 2 complicates 0.3% of all pregnancies in the United States. GDM is defined as carbohydrate intolerance of variable severity, with onset or first recognition during the index pregnancy.

If the abnormality in glucose tolerance persists after pregnancy, the patient's diagnosis is revised to type 1, type 2, or impaired glucose tolerance.

GESTATIONAL DIABETES MELLITUS

Gestational diabetes is a common problem, complicating approximately 2% to 5% of all pregnancies in the United States. The likelihood of developing gestational diabetes is increased significantly among certain subgroups, and these include individuals with a positive family history of type 2 diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Excess risks for both gestational diabetes and impaired glucose tolerance have been demonstrated in African American, Hispanic, and Native American women, as well as in women from the Indian subcontinent and the Middle East.

Screening and Diagnosis for Gestational Diabetes

Screening of pregnant women for gestational diabetes remains a topic of great debate both in this country and throughout the world. In 1998, the Fourth International Workshop-Conference on GDM acknowledged that there were certain populations of low-risk women in whom it may not be cost effective to screen routinely for GDM. This low-risk group includes women who were not members of ethnic minorities, were less than 25 years of age, had no first-degree relatives with diabetes, and are of normal body weight. Although selective screening may be appropriate in certain populations with a low prevalence of type 2 diabetes, universal screening is still advocated in most centers. The American College of Obstetricians and Gynecologists recommends that all pregnant patients be screened for GDM whether by patient's history, clinical risk factors, or a laboratory screening test. However, the American, Canadian, and British diabetes associations recommend biochemical screening.

Screening should be performed between weeks 24 and 28 of gestation, although women with significant risk factors may benefit from being screened earlier in pregnancy. A 50-gram glucose challenge test is performed without regard to the time of day or interval since the last meal. A venous plasma glucose level is measured 1 hour later, with a value of =140 mg/dL indicating the need for a 3-hour, 100-gram oral glucose tolerance test (OGTT). However, lowering the cut-off value to 130 to 135 mg/dL increases the yield of cases of gestational diabetes by 10%. The use of either threshold is acceptable.

The OGTT is performed after an overnight fast and 3 days of an unrestricted carbohydrate diet. A fasting blood glucose level is drawn, and a 100-gram glucose load is then administered. Plasma glucose levels are drawn 1, 2, and 3 hours following ingestion of the glucose solution. Diagnosis requires that at least two of the four glucose levels of the OGTT meet or exceed the upper limits of normal. Two sets of diagnostic criteria are in use in the United States: those of the National Diabetes Data Group and those of Carpenter and Coustan. The Fourth International Workshop-Conference participants believed there was sufficient evidence to suggest that the Carpenter-Coustan criteria, with its lower cut-off values, more accurately predict neonatal risks and have recommended the use of these criteria. American College of Obstetricians and Gynecologists guidelines support the use of either set of criteria.

In addition, the Fourth International Workshop-Conference acknowledged an alterative to the two-step screening-diagnostic procedure described above. The evaluation of glucose intolerance during pregnancy may be made using a one-step approach or 2-hour 75-gram OGTT. This approach is considered most applicable in high-risk populations. Studies are underway to establish the relationships among the various diagnostic criteria and perinatal outcomes in these pregnancies.

Women with gestational diabetes should be evaluated at the first postpartum visit by a 2-hour OGTT using a 75-gram load. More than 90% of women will convert to normal glucose tolerance following delivery. However, studies indicate that the risk for overt diabetes may be as high as 20% to 50% in this population. Long-term annual follow-up is therefore indicated. GDM is greatly influenced by body weight, with the highest rate occurring in obese patients. Women with a history of GDM should be counseled regarding the use of lifestyle changes such as weight loss and regular exercise to reduce this risk.

PREGNANCY COMPLICATIONS

Despite improvements in pregnancy outcomes, women with both gestational and pregestational diabetes are at greater risk for a number of pregnancy-related complications (Table 15.1). These include preterm labor, infectious morbidities, hydramnios, and hypertensive disorders. In addition, multiple investigators have reported a significant association between poor glycemic control and hypertensive disorders, preterm labor, and infections. Furthermore, women with pregestational diabetes are at risk for the acute complications of diabetes because of the metabolic alterations associated with pregnancy, as well as the effects of strict glycemic control. The vascular alterations associated with long-term diabetes also contribute to the higher morbidity rates observed in women with diabetes. Both diabetic nephropathy and retinopathy may progress during pregnancy and should be monitored closely.

Maternal
Preterm labor
Infectious morbidities
Hydramnios
Hypertensive disorders
Worsening of diabetic retinopathy
Fetal and Neonatal
Stillbirth
Congenital malformations
Altered fetal growth
Metabolic abnormalities
Hypoglycemia
Hypocalcemia
Polycythemia
Hyperbilirubinemia
Cardiomyopathy
Respiratory distress syndrome
Long Term
Childhood obesity
Neuropsychological defects
Diabetes

TABLE 15.1. *Pregnancy complications in diabetes*

Current data would seem to indicate that pregnancy is an independent risk factor for diabetic retinopathy. Hypertension, poor control early in pregnancy, and rapid normalization all appear to be associated with the potential to accelerate retinal deterioration. Furthermore, women with more advanced forms of retinopathy and a longer duration of diabetes are at highest risk for progression. All women who have had type 1 diabetes for 5 years or more or type 2 diabetes at diagnosis require a thorough dilated ophthalmologic evaluation. This may necessitate preconception fluorescein angiography, because dye studies generally are contraindicated during pregnancy. These evaluations ideally should be completed prior to attempting conception. Laser therapy, if indicated, also needs to be completed prior to conception.

In contrast, most studies of the effects of pregnancy on diabetic nephropathy have suggested that pregnancy is not associated with either the development or progression of preexisting nephropathy in women with mild to moderate disease. However, diabetic nephropathy is the complication of diabetes most likely to affect pregnancy outcomes. There are increased risks for pregnancy-induced hypertension or a progression of already existing hypertension, intrauterine growth retardation resulting in small-for-gestational-age infants, preterm deliveries secondary to fetal distress, and a ten-fold increase in the incidence of stillbirth over women with diabetes but without nephropathy. Preeclampsia is the most frequent, serious complication of maternal nephropathy, with implications for both mother and fetus. Close monitoring of blood pressure, with addition or adjustment of antihypertensive agents as needed, is recommended. The drugs of choice are methyldopa, calcium channel blockers, and ß blockers. Select calcium channel inhibitors, such as diltiazem, induce mild reductions in blood pressure but have a potent effect on decreasing excess protein excretion.

NEONATAL COMPLICATIONS

The offspring of women with diabetes remain at increased risk for a number of complications, which include congenital anomalies, fetal macrosomia, respiratory distress syndrome (RDS), metabolic abnormalities, as well as long-term sequelae (see Table 15.1).

Perinatal Mortality

The two major causes of perinatal mortality are unexplained fetal death and congenital malformations. The causes of unexpected death are not well understood. In animal models sustained hyperglycemia has been associated with increased insulin secretion, elevated fetal oxygen consumption, acidosis, and death. It has been postulated that fetal polycythemia and increased platelet aggregation could explain the increased incidence of intravascular thrombosis in infants of diabetic mothers and that thrombotic episodes could be the underlying cause for late unexplained intrauterine deaths.

Approximately 40% of perinatal deaths that occur among infants of women with diabetes can be attributed to malformations. Diabetes mellitus is one of the most common maternal conditions that results in anomalous offspring. The frequency of major congenital anomalies is increased two-fold to three-fold over that of the general population. Great diversity is seen in the types of malformations associated with insulin-dependent diabetes mellitus. The most frequent types of malformations involve the central nervous system, cardiovascular, gastrointestinal, genitourinary, and skeletal systems, with cardiac malformations being the most common.

The defects most often associated with diabetes occur during organogenesis before 7 weeks gestation. Clinical series in humans have shown an association between malformations and glucose control early in pregnancy. In addition, other investigators have demonstrated that tight glucose control either prior to conception or very early during pregnancy can effectively reduce the rate of major malformations. As a result of these and other studies, the management goal for diabetic pregnancies has become the establishment and maintenance of near euglycemia beginning with the preconceptual period and continuing throughout gestation.

Altered Fetal Growth

Macrosomia is a classic hallmark of the pregnancy complicated by diabetes and is reported to occur in 20% to 25% of pregnancies complicated by diabetes. Macrosomia is defined as excessive birth weight (>90%) for gestational age or as a birth weight over 4,000 grams. Increased adiposity is the primary cause of the increased birth weight seen in the offspring of diabetic women. Numerous studies have established a relationship between the level of maternal glucose control and macrosomia. Mothers of macrosomic infants usually have significantly elevated plasma glucose levels at term, indicating increased glucose availability to the fetus, with hyperinsulinemia a likely intermediate step, during the third trimester. Other factors associated with an increased risk for fetal macrosomia include increased maternal weight, increased parity, previous delivery of a macrosomic infant, and insulin requirements greater than 80 units/day.

Macrosomic fetuses have higher perinatal and neonatal mortality and morbidity rates. Approximately 10% of infants weighing over 4,500 grams at birth will require admission to a neonatal intensive care nursery. In addition, the reported perinatal mortality is 2 to 5 times higher in this group of children than in average-sized children. Delivery of a macrosomic infant is dangerous because of the risk for birth trauma to the head and neck. Fetal asphyxia and meconium aspiration may occur as a result of prolonged labor secondary to unrecognized cephalopelvic disproportion and shoulder dystocia.

At the other extreme, women with type 1 diabetes are also at increased risk for delivering a small-for-gestational-age infant. In general, the risk of growth retardation increases with the severity of the mother's clinical diabetes. Vascular complications, such as retinopathy and nephropathy, are believed to be associated with uteroplacental insufficiency in pregnant women with diabetes. Poor maternal renal function, hypertension, and placental lesions all have been associated with intrauterine growth retardation in the offspring of diabetic mothers. However, more recent evidence suggests that the growth retardation may be related to disturbances in maternal fuels during organogenesis.

Metabolic Abnormalities

Hypoglycemia occurs when plasma glucose levels fall below 35 mg/dL in the term infant and 25 mg/dL in the preterm infant. Infants of diabetic mothers can develop hypoglycemia during the first few hours of life, particularly in cases of poor glycemic control. Macrosomic infants and infants with elevated cord blood C-peptide or immunoreactive insulin levels are also at increased risk. The incidence of hypoglycemia is reported to range from 25% to 40% in infants of mothers with diabetes. Both poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of its occurrence.

The incidence of hypocalcemia also is increased significantly in the infants of women with diabetes. Hypocalcemia generally occurs in association with hyperphosphatemia and occasionally with hypomagnesemia. Neonatal hypocalcemia is defined as a calcium level at or below 7 mg/dL. Serum calcium levels are usually lowest on the second or third day of life. Polycythemia is defined as a venous hematocrit that exceeds 65% and is reported to occur in one third of neonates born to diabetic women. The polycythemia is believed to occur as a result of chronic intrauterine hypoxia, which leads to an increase in erythropoietin and results in an increase in red blood cell production. Neonates born to women with diabetes also have a higher incidence of hyperbilirubinemia as compared with nondiabetic controls. Neonatal hyperbilirubinemia develops in approximately 20% to 25% of cases. Animal studies have demonstrated an association between fetal insulin levels and elevated levels of erythropoietin, which is the major regulator of erythropoiesis in the neonate.

Other Infant Morbidities

Offspring born to women with diabetes mellitus are also at increased risk of developing various hypertrophic types of cardiomyopathy and congestive heart failure. The exact incidence is not known, but one study reported that 10% of infants born to women with diabetes may have evidence of myocardial and septal hypertrophy. Thickening of the interventricular septum and of the left or right ventricular wall can occur, and it is felt to be a result of the fetal hyperinsulinemic state. In the majority of cases the infants are asymptomatic, and the myocardial changes are detectable only by electrocardiogram or echocardiogram. In severe cases, left ventricular outflow obstruction can result and may lead to reduced cardiac output and congestive heart failure during the first few days of life. The abnormalities do not appear to damage the myocardium permanently and in most cases regress by 6 months of age.

RDS is another common complication associated with diabetes. In the past, offspring born to women with diabetes had a four-fold to six-fold greater incidence of RDS at every week of gestation. This incidence was decreased dramatically with the initiation of strict metabolic control. More recent studies seem to indicate that stringent metabolic control may reduce the incidence of RDS in neonates of women with diabetes to near background level in the population.

Lastly, there are long-term consequences of diabetic pregnancies. These include childhood obesity, neuropsychological deficits, and an increased tendency to develop overt diabetes.

PRECONCEPTION CARE

Care of women with type 1 or type 2 diabetes ideally begins before conception. Although numerous clinical trials have demonstrated that strict glycemic control prior to and during early gestation can reduce the rate of structural defects, the vast majority of women with diabetes still seek medical care only after they learn they are pregnant. Consequently, the rate of congenital malformations in infants of mothers with diabetes has continued to remain significantly higher than that of the general population.

A prepregnancy assessment should be undertaken to document a woman's overall fitness for pregnancy. This includes a careful history and thorough physical examination to assess the patient's vascular status. Baseline creatinine clearance and protein excretion levels should be evaluated and an electrocardiogram performed. These women also should be referred for an ophthalmologic consultation. Optimization of blood glucose control should be achieved before the woman is advised to become pregnant. Women should receive appropriate contraceptive therapy while they are preparing for pregnancy. For patients who are not already following an intensive regimen, an extensive period of education and the institution of self–blood glucose monitoring is also necessary.

Prepregnancy counseling for women with gestational diabetes should begin immediately after delivery. These women need to be advised that they are at significant risk for developing GDM in subsequent pregnancies and that they are at increased risk for developing type 2 diabetes as they age.

DIABETES MANAGEMENT

The main goal of management for pregnancies complicated by either gestational or pregestational diabetes is to achieve and maintain euglycemia throughout gestation. The treatment approach requires a combination of diet, exercise, intensive insulin regimens, and daily multiple blood glucose determinations.

Diet

Diet therapy is the cornerstone of diabetes management in pregnancy, just as it is in the nonpregnant state. The goal of diet therapy is to meet the additional nutrition requirements of pregnancy while at the same time maintaining good glycemic control.

All pregnant women with diabetes should be seen by a nutritionist for individualized diet counseling. There are no universal recommendations for determining the number of calories required during pregnancy. Most experts advocate an additional intake of 300 to 400 kcal/day to meet the needs of pregnancy. Recommendations regarding total caloric intake often are based on the mother's pregravid weight: 30 kcal/kg of body weight per day for normal-weight women with diabetes, 40 kcal/kg per day for underweight women, and 24 kcal/kg per day for overweight women (Table 15.2). Although it is generally agreed that pregnancy is not the time for weight reduction, obese women with type 2 or GDM should be encouraged to achieve weight gain of no more than 15 pounds. Modest caloric restrictions have not been associated with either ketonuria or elevated plasma ketone concentrations.

Determination of Calories	
Normal weight	30 kcal/kg/day
Underweight	40 kcal/kg/day
Overweight	24 kcal/kg/day
Components of Diet	
Carbohydrate	40%–45% of calories
Fat	Up to 40% of calories, with saturated fat limited to one third of calories
Protein	About 60 g, accounting for 12%–20% of calories

TABLE 15.2. *Preparation of a diet for a pregnant diabetic woman*

The most current guidelines suggest that the composition of the diabetic diet be based on an individualized nutrition assessment. Because the postprandial blood glucose level has been shown to be a major factor in the development of neonatal macrosomia, a goal of nutrition therapy is to blunt postprandial hyperglycemia. The postprandial blood glucose level is most influenced by the carbohydrate content of the meal (see Table 15.2). Carbohydrate levels of 40% to 45% of total calories are considered appropriate during pregnancy. To achieve euglycemia, dietary fat can be liberalized up to 40% of calories. Saturated fats should be limited to one third of fat calories or less. The remaining calories should come from either monounsaturated or polyunsaturated fats. The recommended dietary allowance for protein in pregnancy is 60 grams per day, and this typically ranges from 12% to 20% of total calories.

A number of different approaches to meal planning can be used and range from general guidelines for good nutrition to structured meal planning strategies. The most appropriate approach will depend on the patient's type of diabetes, educational level, lifestyle, habits, motivation, and economic restraints. Although the nutrition needs and distribution of calories for women with gestational diabetes and pregestational diabetes are similar, the number and timing of snacks will vary. Two or more snacks generally are recommended for women with type 1 diabetes, while women with type 2 diabetes or gestational diabetes require only a bedtime snack. The bedtime snack should include a complex carbohydrate and protein to prevent late-night hypoglycemia and early morning starvation ketosis. Artificial sweeteners are considered safe to use during pregnancy, although no specific recommendations concerning intake levels exist.

Exercise

Although exercise has been demonstrated to be beneficial in nonpregnant individuals, evidence regarding the risk and benefits of either periodic or regular exercise in pregnant women with diabetes is limited. Little has been published regarding exercise during pregnancy complicated by preexisting diabetes, either type 1 or type 2. However, walking is possible for most women and has been reported to improve lipid profiles and blood glucose control.

Pregnancy is not a time to initiate a new exercise program, although women who have been exercising regularly prior to pregnancy can be counseled to continue. Appropriate exercises are those that use upper body muscles and place little mechanical stress on the trunk region. Women should be taught to palpate their uterus during exercise and stop the exercise if they detect contractions. Until additional studies are completed, however, medical supervision is recommended for all pregnancies complicated by diabetes. Women with type 1 diabetes are vulnerable to exercise-related hypoglycemia and, therefore, should monitor their blood glucose levels closely and always have a readily available source of glucose. Women should be cautioned against becoming dehydrated, overheated, tachycardic, or dyspneic. Exercise should not be prescribed for patients with hypertension or an autonomic dysfunction with a diminished counter-regulatory response.

In regard to gestational diabetes, exercise has been recommended as an adjunct to nutrition therapy. Regular aerobic exercise has been shown to lower fasting and postprandial glucose concentrations. Several randomized controlled trials have demonstrated that upper extremity exercise for 20 minutes 3 times a week can lower blood glucose levels significantly in women with gestational diabetes. In addition, these trials found no significant increase in either maternal or neonatal complications related to exercise.

Insulin Therapy

Other than diet, insulin is the only therapy recommended to treat diabetes during pregnancy. The safety of all available oral agents has not been established in pregnancy and could lead to prolonged neonatal hypoglycemia. Therefore, they not recommended. However, a study in women with GDM has found glyburide to be a safe and clinically effective alternative to insulin.

The goal of insulin therapy is to achieve blood glucose levels that are nearly identical to those observed in healthy pregnant women. Therefore, multiple injections of insulin usually are required. Human insulin is the least immunogenic of all insulins and is recommended exclusively in pregnancy. Insulin requirements may change dramatically throughout the various stages of gestation. In the first trimester, the maternal insulin requirement is approximately 0.7 U/kg of body weight per day. This is increased in the third trimester to 1.0 U/kg per day.

Several different approaches to insulin administration can be used during pregnancy. The superiority of one regimen over another never has been fully demonstrated. The new rapid-acting insulin analogs, with peak hypoglycemic action 1 to 2 hours after injection, offer the potential for improved postprandial glucose control. However, their safety during pregnancy and their ability to improve perinatal outcomes has yet to be established. Studies in women with gestational diabetes have demonstrated that these agents do not cross the placenta.

The continuous subcutaneous insulin infusion pump is another treatment option which has been used successfully during pregnancy. Insulin therapy delivered by this mode more closely resembles that of physiologic insulin release. The pump delivers a continuous basal rate of insulin infusion, with pulse-dose increments before meals. In published studies, researchers have demonstrated that comparable glucose control and pregnancy outcomes can be achieved by both conventional insulin therapy and pump therapy. However, it has been reported that hemoglobin A_{1C} (HbA_{1C}) levels were significantly lower 1 year after delivery in women who elected to remain on pump therapy after delivery compared with women who had continued to use conventional insulin treatment. Other advantages of insulin pump therapy during pregnancy include more rapid and predictable insulin absorption, enhanced lifestyle flexibility, and simplified morning sickness management.

Insulin therapy should be initiated in all women with GDM who fail to maintain euglycemia with diet. Women typically are started on a dosage of 20 U of NPH and 10 U of regular insulin daily. Insulin dosage is adjusted according to blood glucose levels, and an evening injection is added if fasting hyperglycemia persists. Some investigators have advocated the use of prophylactic insulin in GDM to reduce the risk of macrosomia. However, the advantages of this therapy must be weighted against the disadvantages.

MONITORING METABOLIC STATUS

Self-monitoring of Blood Glucose

Self-blood glucose monitoring has become the mainstay of management for pregnancies complicated by diabetes mellitus. A variety of small, battery-powered blood glucose reflectance meters are available for home use. Accurate readings depend on performing the test correctly; however, most of the newest models are less technique dependent. Some models are extremely sophisticated, having memories that permit the storage of results with the date and time they were collected, whereas others can even be downloaded onto a personal computer. Each woman should be seen by a qualified nurse educator to ensure that her technique is accurate. Ongoing education also is important to help the woman make necessary changes in her treatment plan to maintain euglycemia throughout gestation.

Although it has been shown that, in general, self-monitored blood glucose values correlate very well with those measured in automated laboratories, reports have shown that sometimes patients report blood glucose levels falsely both during and outside of pregnancy. These findings are worrisome, because accurate information is essential for optimal management of the pregnancy complicated by diabetes. Therefore, verified blood glucose determinations (i.e., the use of blood glucose meters with memory) are recommended to enhance the reliability and accuracy of self-monitored blood glucose results.

Blood glucose measurements should be obtained at least 4 times a day (fasting and 1–2 hours after meals) in women with gestational diabetes and 5 to 7 times a day in women with preexisting diabetes (Table 15.3). In addition to this regular monitoring, patients also should test whenever they feel symptoms of either hyperglycemia or hypoglycemia. Detailed record keeping helps to identify glucose patterns. Daily urine ketone testing should be performed to ensure early identification of starvation ketosis or ketoacidosis. Ketone testing also should be performed anytime the blood glucose level exceeds 200 mg/dL, during illness, or when the patient is unable to eat.

Maternal Surveillance
Self-blood glucose monitoring 4–7 times daily
Hemoglobin A_{1C}
Urinary ketones
Blood pressure
Retinal and renal status (for women with preexisting diabetes)
Fetal Surveillance
Level II ultrasonography and fetal echocardiogram (for women with preexisting diabetes)
Serial assessment (4–6 wks) of fetal growth
Daily fetal movement counts
Weekly NST or BPP

BPP, biophysical profile; NST, nonstress test.

TABLE 15.3. *Monitoring the diabetic during pregnancy*

Blood glucose levels are measured in both the fasting and postprandial states. A randomized controlled trial compared the efficacy of preprandial and postprandial glucose determinations in reducing the incidence of neonatal macrosomia and other complications in women with gestational diabetes. Women requiring insulin treatment were randomly assigned to have their diabetes managed according to the results of preprandial self–blood glucose monitoring or postprandial monitoring performed 1 hour after meals. Both groups had similar success in achieving blood glucose level targets and demonstrated similar degrees of adherence with the monitoring schedule. Nevertheless, the women in the postprandial monitoring group received significantly more insulin and achieved a greater decrease in glycosylated hemoglobin values during treatment than those in the preprandial monitoring group. In addition, there was significantly less macrosomia and neonatal hypoglycemia among the offspring of the mothers in the postprandial monitoring group. These data suggest that adjustment of insulin therapy according to the results of postprandial blood glucose values improves glycemic control and pregnancy outcomes.

Previous studies in pregnant women with pregestational diabetes also have found that postprandial blood glucose levels are better predictors of fetal macrosomia than are fasting blood glucose levels. The Diabetes in Early Pregnancy Study demonstrated that third-trimester nonfasting glucose levels to be the strongest predictors of percentile birth weight in infants of diabetic mothers. Similar results have been reported by Combs and colleagues, who found that the incidence of macrosomia rose progressively with increasing postprandial glucose levels. Postprandial glucose levels of less than 130 mg/dL reduced the incidence of macrosomia, but levels of less than 120 mg/dL totally eliminated this complication. They recommended 130 mg/dL as a reasonable target for 1-hour postprandial glucose levels.

Although it is widely accepted that the level of metabolic control achieved in the pregnancy complicated by diabetes significantly affects perinatal outcome, what constitutes optimal control has not been established. Emerging evidence suggests that a continuum of risk exists between carbohydrate intolerance and both perinatal and neonatal morbidity. In theory, then, the target ranges for blood glucose values during pregnancy should be based on maternal plasma glucose levels in normal pregnancy. The logical approach is to achieve as near-to-normal glucose levels as possible without undue severe hypoglycemia. Current recommendations are that whole blood glucose levels should not exceed 95 mg/dL in the fasting state and 120 mg/dL after meals.

Although the current data demonstrate a relationship between metabolic control and neonatal complications, maternal glycemia may not be the sole parameter of optimal control. Buchanan and colleagues have suggested the use of fetal ultrasonography in women with gestational diabetes to identify pregnancies at risk for fetal macrosomia and related morbidity. They have found that during the late second trimester or early third trimester, a fetal abdominal circumference under or over the 75th percentile for gestational age can distinguish pregnancies at low risk from those at high risk, respectively, for producing large-for-gestational-age infants. Their data suggest that maternal glucose concentrations alone may not accurately predict which fetuses are at high risk for excessive fetal growth and support the use of fetal criteria to direct metabolic therapies in GDM.

Glycosylated Hemoglobin

The glycosylated hemoglobin assay is an accurate, objective measure of long-term glycemic control in diabetes. It can be measured either as total glycohemoglobin or as the particular configuration known as HbA_{1C}. Proteins undergo a nonenzymatic, postsynthetic modification that results in the attachment of glucose to various amino acids. This process, which is known as glycosylation, occurs slowly and is irreversible. The amount of hemoglobin that becomes glycosylated depends on the concentration of glucose over the time of the exposure and, therefore, is not influenced significantly by recent or transient blood glucose excursions. Because erythrocytes in the peripheral circulation have a half-life of 100 days, the glycosylated hemoglobin level reflects glycemic control over the preceding 2 to 3 months. Most studies have found positive correlation between HbA_{1C} values and other parameters of glucose control during gestation, similar to findings in the nonpregnant state.

Several investigators have reported an association between malformations and glucose control early in pregnancy. The higher the woman's glycosylated hemoglobin level, the greater is her risk of having a severely affected infant. The risk of miscarriage also has been shown to be increased with marked elevations in first-trimester glycosylated hemoglobin. Ideally, glycosylated hemoglobin levels should be measured before conception, and pregnancy should be delayed until normal levels are reached. Unfortunately, the majority of pregnancies in women with and without diabetes are not planned. Therefore, the HbA_{1C} level can be obtained at the first prenatal visit and reassessed every 4 to 6 weeks to document the degree of glycemic control maintained throughout the pregnancy. Although elevations in first-trimester glycosylated hemoglobin levels indicate an increased risk for congenital malformations, an elevation during the second half of pregnancy appears to identify infants at risk for perinatal morbidity and mortality. Several investigators have demonstrated an association between HbA_{1C} and neonatal hypoglycemia, neonatal hyperbilirubinemia, perinatal death, and macrosomia. In women with gestational diabetes, however, HbA_{1C} levels have not been found useful as either a screening or diagnostic tool.

FETAL ASSESSMENT

All pregnancies complicated by diabetes require additional fetal evaluation and assessment (see Table 15.3). Ultrasonography provides the clinician with essential information about the fetus and its development. A first-trimester scan should be performed to date the pregnancy and establish viability. All women with pregestational diabetes should also be evaluated for possible fetal anomalies. Although the risk for delivering an anomalous infant cannot be fully determined by a glycosylated hemoglobin level, an elevated HbA_{1C} should alert the practitioner to an increased risk for structural defects. Evaluation includes targeted ultrasonography to survey general fetal anatomy and fetal echocardiography at approximately 20 to 22 weeks gestation. In addition, the maternal serum a-fetoprotein screening test should be performed at 16 to 18 weeks gestation because of the increased risk of neural tube defects.

Because women with diabetes are at risk for fetal growth aberrations, frequent ultrasonographic scans are recommended to identify states of altered growth. Ultrasonographic examinations should be performed at 4- to 6-week intervals during the second and third trimesters of pregnancy to assess not only fetal growth, but amniotic fluid volume as well.

Fetal death is more common in pregnancies complicated by diabetes than in the general population. The goal of antepartum surveillance is avoidance of intrauterine death by early detection of fetal compromise. The nonstress test (NST) has become the preferred antepartum fetal heart rate test for screening the fetal condition in pregnancies complicated by diabetes. The NST evaluates the presence of accelerations from the baseline fetal heart rate. An alternative fetal test is the fetal biophysical profile (BPP), which also is used to evaluate the significance of a nonreactive NST. Because the BPP employs ultrasonography, it permits evaluation of amniotic fluid volume and may detect major fetal malformations in patients who have not been studied earlier in pregnancy. Maternal evaluation of fetal movement counts should be integrated into the surveillance program. Women with diabetes are instructed to count fetal movements beginning as early as 28 weeks of gestation. Although the false-positive rate is high, the technique is inexpensive and simple and augments the total antepartum surveillance program.

Most perinatal centers institute a program of weekly fetal monitoring beginning at 32 to 34 weeks gestation. Because fetal death is more common in women with poor glycemia control, hydramnios, fetal macrosomia, hypertension, or vasculopathy, these women receive twice weekly NST testing. Patients with diet-controlled gestational diabetes who maintain normal fasting and postprandial glucose levels are probably at low risk for an intrauterine fetal death and are not tested as early or as frequently. However, women with gestational diabetes and chronic hypertension, a previous stillbirth, preeclampsia, and who require insulin therapy receive more intense surveillance.

Timing and Mode of Delivery

It is generally accepted that if a pregnant diabetic patient is in good metabolic control and is receiving fetal surveillance on a regular basis, delivery may be delayed safely until term or the onset of spontaneous labor. Women with poor metabolic control, worsening hypertensive disorders, fetal macrosomia, growth retardation, or polyhydramnios may be delivered electively after fetal lung maturity has been confirmed. If an elective delivery is planned before 38 weeks gestation, amniocentesis should be performed for confirmation of fetal lung maturity. Fetal lung maturation is better predicted by the amniotic fluid phosphatidylglycerol content than by the lecithin/sphingomyelin ratio.

Cesarean delivery should be performed on most patients with an estimated fetal weight of greater than 4,500 grams to prevent shoulder dystocia and birth trauma. Management should be individualized for patients with an estimated fetal weight between 4,000 and 4,500 grams. The decision is based on the size of the pelvis and progress of labor, as well as the patient's obstetric history. A history of shoulder dystocia is often an indication for repeat caesarean section.

During labor and delivery, good blood glucose control should be maintained to prevent neonatal hypoglycemia. Blood glucose levels should be maintained below 100 mg/dL with the use of an insulin infusion. After delivery, insulin requirements tend to fall dramatically as a result of the significant decrease in levels of placental hormones. Once the patient is able to eat regular meals, she should receive subcutaneous insulin at approximately one half of her prepregnancy dose.

CONTRACEPTION AND FAMILY PLANNING

The use of contraception in all women with diabetes or a history of GDM cannot be emphasized strongly enough. This is the only way to ensure that preconception care can be provided. A variety of contraceptive methods are available. Barrier methods of contraception create mechanical or chemical barriers, or both, to fertilization

and include diaphragms, male condoms, spermicidal foam or jelly, cervical caps, and female condoms.

Although these methods pose no health risks to women with diabetes, they are user dependent, require correct application or insertion before intercourse, and have a high failure rate of 12% to 28% during the first year because of improper use. With experience and motivation, these failure rates may be reduced to levels of 2% to 6%.

Oral contraceptives remain the most popular form of birth control despite controversy over potential side effects. The main reasons for their popularity are their failure rate of generally less than 1% and ease of use. Low-dose formulations are preferred and are recommended only for patients without vascular complications or additional risk factors, such as smoking or a strong family history of myocardial disease. Progestin-only (“mini-pill”) oral contraceptives are an option for women with contraindications to the estrogen component, such as hypertension or thrombosis.

An intrauterine device is the most effective nonhormonal device. It should be offered only to women with diabetes who have a low risk of sexually transmitted diseases, because any infection might place the patient with diabetes at risk for sepsis and ketoacidosis. Patient education should include the early signs of sexually transmitted diseases, such as increased and abnormal vaginal discharge, dyspareunia, heavy or painful menses, lower abdominal pain, and fever.

Depo-Provera is a long-acting progestin that provides highly effective pregnancy prevention. Depo-Provera is administered intramuscularly every 3 months and works by inhibiting ovulation. The high efficacy and long period of action of Depo-Provera makes it an attractive option for women with diabetes, especially women with a history of poor medication compliance. Unfortunately, this long-acting progestin has not been studied in women with diabetes.

Permanent sterilization, including tubal ligation and vasectomy, may be considered by the patient or her partner when they desire no more children.

CONCLUSION

The diagnosis of diabetes mellitus during pregnancy has certain implications for the well-being of both the mother and the fetus. Advances in medical and obstetric care have dramatically improved the outlook for women with diabetes and their offspring. However, both mother and child remain at increased risk for a number of complications. Research indicates that the majority of these complications are associated with hyperglycemia. The achievement and maintenance of euglycemia has, therefore, become the major focus of management.

SUMMARY POINTS

- The development of insulin resistance during late pregnancy is a normal physiologic adaptation that shifts maternal energy metabolism from carbohydrate to lipid oxidation and thus spares glucose for the growing fetus.
- All pregnant women should be screened for GDM between 24 and 28 weeks gestation.
- Women with diabetes and their offspring are at greater risk for a number of pregnancy-related complications.
- Strict blood glucose control prior to conception and throughout gestation can reduce and or eliminate the excess risk for both mother and baby.
- All diabetic women of childbearing age should be counseled regarding the importance of preconception care and planning their pregnancies.

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Chapter 16

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Hypertensive Disorders of Pregnancy

DEFINITIONS AND CLASSIFICATIONS
Gestational Hypertension
Preeclampsia and Eclampsia
Chronic Hypertension
PREECLAMPSIA
Etiology
Pathophysiology
Prediction
Prevention
MILD PREECLAMPSIA
Diagnosis of Mild Preeclampsia
Management of Mild Preeclampsia
SEVERE PREECLAMPSIA
Management of Severe Preeclampsia
HELLP SYNDROME
Diagnosis of HELLP Syndrome
Differential Diagnosis of HELLP Syndrome
Management of HELLP Syndrome
ECLAMPSIA
Management of Eclampsia
MAGNESIUM SULFATE
Counseling
CHRONIC HYPERTENSION
MANAGEMENT
ANTIHYPERTENSIVE AGENTS
Centrally Acting Drugs
Beta Blockers
Calcium Channel Blockers
Vasodilators
Diuretics
Angiotensin-converting Enzyme Inhibitors
Contraception
SUMMARY POINTS

RECOMMENDED READINGS

Hypertensive disorders are the most common medical complications of pregnancy, affecting 5% to 10% of all pregnancies. These disorders are responsible for approximately 15% of maternal mortality. This includes hypertension preceding pregnancy, known as *chronic hypertension*, and the group of hypertensive disorders unique to pregnancy, called *gestational hypertension and preeclampsia.* Preeclampsia, eclampsia, and transient hypertension fall under the broad category of gestational hypertension. Approximately 30% of hypertensive disorders in pregnancy are due to chronic hypertension and 70% are due to gestational hypertension. The spectrum of disease ranges from mildly elevated blood pressures with minimal clinical significance to severe hypertension and multiorgan dysfunction. The incidence of disease is dependent upon many different demographic parameters including maternal age, race, and associated underlying medical conditions. Understanding the disease process and the impact of hypertensive disorders on pregnancy is of the utmost importance, because these disorders remain a major cause of maternal and perinatal morbidity and mortality worldwide.

DEFINITIONS AND CLASSIFICATIONS

Making an appropriate diagnosis can at times be difficult in the gravid patient, however adhering to the following definitions and classification schemes will help to eliminate confusion. Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mm Hg or greater. These measurements must be present on at least two occasions at least 6 hours apart, but no more than a week apart. No longer in use are the criteria of increase in blood pressure above baseline measurements of =30 mm Hg systolic, =15 mm Hg diastolic, or =20 mm Hg mean arterial pressure. It is important to note that choosing the appropriate size cuff will help to eliminate falsely lowered or elevated blood pressure measurements and render more accurate readings.

Abnormal proteinuria in pregnancy is defined as the excretion of 300 mg or more of protein in 24 hours. The most accurate measurement of proteinuria is obtained with a 24-hour urine collection. However, in certain instances, semiquantitative dipstick measurement may be the only mode available to assess urinary protein. A value of 1+ or greater correlates with 30 mg/dL. Proteinuria by dipstick is defined as 1+ or more on at least two occasions at least 6 hours apart but no more than 1 week apart. The accuracy of semiquantitative dipstick measurements on spot urine samples as compared with 24-hour urine collections is highly variable. Therefore, should time allow, a 24-hour urine collection should be performed as part of the diagnostic criteria to define proteinuria. Care should be taken when obtaining urine protein measurements to use a clean sample, because blood, vaginal secretions, and bacteria can increase the amount of protein in urine.

Edema is a common finding in the gravid patient, occurring in approximately 50% of women. Lower extremity edema is the most typical form. Pathologic edema is seen in nondependent regions such as the face, hands, or lungs. Excessive, rapid weight gain of 5 pounds or more per week is another sign of fluid retention.

The classification system of hypertension in pregnancy was proposed originally by the American College of Obstetricians and Gynecologists Committee on Terminology in 1972. Further modifications by the National High Blood Pressure Education Program Working Group in 2000 arrived at the classification scheme used today, which offers simple, concise, and clinically relevant features for each of the four categories. This system recognizes four major categories of hypertension in pregnancy—gestational hypertension, preeclampsia or eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension. Table 16.1 lists these categories and the features of each.

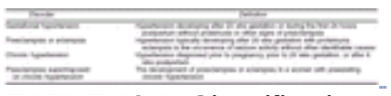

TABLE 16.1. *Classification of hypertension in pregnancy with definitions*

Gestational Hypertension

Gestational hypertension is the elevation of blood pressure during the second half of pregnancy or in the first 24 hours postpartum without proteinuria and without symptoms. Normalization of blood pressure will occur during the postpartum period, usually within 10 days. Treatment generally is not warranted, because most patients have mild hypertension. Gestational hypertension in and of itself has little effect on maternal or perinatal morbidity or mortality. However, approximately 46% of patients diagnosed with preterm gestational hypertension will develop proteinuria and progress to preeclampsia. Women with gestational hypertension are likely to have elevated blood pressure with subsequent pregnancies and to develop essential hypertension later in life.

Preeclampsia and Eclampsia

The syndrome of preeclampsia is defined by the classic triad of hypertension, proteinuria, and symptoms. Hypertension is defined as a blood pressure of 140 mm Hg systolic or 90 mm Hg diastolic on two separate occasions 6 hours apart. Significant proteinuria is defined as 300 mg or more in 24 hours. The symptoms of

preeclampsia are headaches, visual changes, and epigastric or right upper quadrant pain.

Preeclampsia may be subdivided further into mild and severe forms. The distinction between the two is made on the basis of the degree of hypertension and proteinuria, and the involvement of other organ systems. The criteria for mild preeclampsia and severe preeclampsia are presented in Table 16.2 and Table 16.3, respectively. Close surveillance of patients with either mild or severe preeclampsia is warranted, because either type may progress to fulminant disease. A particularly severe form of preeclampsia is the HELLP syndrome, which is an acronym for hemolysis, elevated liver enzymes, and low platelet count. This syndrome is manifest by laboratory findings consistent with hemolysis, elevated levels of liver function, and thrombocytopenia. The diagnosis may be deceptive, because blood pressure measurements may be elevated only marginally. A patient diagnosed with HELLP syndrome is automatically classified as having severe preeclampsia. Another severe form of preeclampsia is eclampsia, which is the occurrence of seizures not attributable to other causes.

Blood pressure ≥140 mm Hg systolic and ≥90 mm Hg diastolic on two occasions at least 6 hours apart, typically occurring after 20 wks gestation (no more than 1 wk apart)
Proteinuria of 300 mg in a 24-hour urine collection or ≥1+ on two random sample urine dipsticks at least 6 hours apart (no more than 1 wk apart)

TABLE 16.2. *Criteria for the diagnosis of mild preeclampsia*

Blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic on two occasions at least 6 hours apart
Proteinuria of ≥5 g/24 hours
Oliguria ≤500 cc/24 hours
Thrombocytopenia—platelet count ≤100,000/mm^3
Elevated liver function test results with persistent epigastric or right upper quadrant pain
Pulmonary edema
Persistent severe cerebral or visual disturbances

TABLE 16.3. *Criteria for the diagnosis of severe preeclampsia*

Chronic Hypertension

Hypertension complicating pregnancy is considered chronic if a patient was diagnosed with hypertension before pregnancy, if hypertension was present prior to 20 weeks gestation, or if it persists longer than 6 weeks after delivery. Women with chronic hypertension are at risk of developing superimposed preeclampsia. Superimposed preeclampsia is defined as an exacerbation of hypertension with new onset of proteinuria.

PREECLAMPSIA

Preeclampsia is a hypertensive disorder unique to human pregnancy. The incidence of preeclampsia is reported to be between 2% to 7%, depending on the population. Preeclampsia occurs more frequently in primigravidas and usually occurs after 20 weeks gestation. The reported rate of preeclampsia ranges from 6% to 7% in primigravidas and from 3% to 4% in multiparous patients. Several risk factors for preeclampsia have been identified and are listed in Table 16.4. Neonatal outcome in patients with preeclampsia relates largely to the gestational age at delivery. Risk to the mother can be significant and includes the possible development of disseminated intravascular coagulation, intracranial hemorrhage, renal failure, retinal detachment, pulmonary edema, liver rupture, abruptio placentae, and death. Therefore, astute and experienced clinicians should be caring for women with preeclampsia.

Nulliparity
Pregestational diabetes
Thrombophilia
Nephropathy
Connective tissue disease
Molar pregnancy
Fetal hydrops
Multifetal gestation
Chronic hypertension
Obesity
Prior pregnancy complicated by preeclampsia
Antiphospholipid antibody syndrome
Family history of preeclampsia or eclampsia
Fetal aneuploidy

TABLE 16.4. *Risk factors for preeclampsia*

Etiology

The etiologic agent responsible for the development of preeclampsia remains unknown. The syndrome is characterized by vasospasm, hemoconcentration, and ischemic changes in the placenta, kidney, liver, and brain. These abnormalities usually are seen in women with severe preeclampsia. Theories as to the causative mechanisms include placental origin, immunologic origin, and genetic predisposition, among others. A list of etiologic theories is shown in Table 16.5. A great deal of research is dedicated to solving the etiologic enigma of preeclampsia. Without a definitive etiology, predicting patients at risk for the development of preeclampsia and effecting a treatment for this morbid disease remain difficult.

Abnormal or increased immune response
Genetic predisposition
Abnormal coagulation or thrombophilias
Alterations in prostaglandin activity
Endothelial cell injury
Alterations in nitric oxide levels
Increased oxygen free radicals
Abnormal cytotrophoblast invasion
Abnormal calcium metabolism
Dietary deficiencies

TABLE 16.5. *Etiologic theories in preeclampsia*

Pathophysiology

Cardiovascular The hypertensive changes seen in preeclampsia are attributed to intense vasospasm thought to be due to increased vascular reactivity. The underlying mechanism responsible for the increased vascular reactivity is presumed to be alterations in the normal interactions of vasodilatory (prostacyclin, nitric oxide) and vasoconstrictive (thromboxane A_2, endothelin) substances. Another vascular hallmark of preeclampsia is hemoconcentration. Patients with preeclampsia have lower intravascular volumes and have less tolerance for the blood loss associated with delivery.

Hematologic The most common hematologic abnormality in preeclampsia is thrombocytopenia (platelet count <100,000/mm ^{3}). The exact mechanism for thrombocytopenia is unknown. Another possible hematologic abnormality is microangiopathic hemolysis, as seen in HELLP syndrome, and can be diagnosed by schistocytes seen on peripheral smear and increased lactate dehydrogenase (LDH) levels. Interpretation of the baseline hematocrit in a preeclamptic patient may be difficult. A low hematocrit may signify hemolysis, and a falsely high hematocrit may be due to hemoconcentration.

Renal Vasospasm in preeclampsia leads to decreased renal perfusion and subsequent decreased glomerular filtration rate (GFR). In normal pregnancy the GFR is increased up to 50% above prepregancy levels. Because of this, serum creatinine levels in preeclamptic patients rarely rise above normal pregnancy levels (0.8 mg/dL). Close monitoring of urine output is necessary in patients with preeclampsia, because oliguria (defined as <500 cc/24 hours) may occur due to renal insufficiency. Rarely, profound renal insufficiency may lead to acute tubular necrosis. The pathognomonic renal lesion in preeclampsia is called glomerular capillary endotheliosis, which is swelling of the glomerular capillary endothelial and mesangial cells.

Hepatic Hepatic damage associated with preeclampsia can range from mildly elevated liver enzyme levels to subcapsular liver hematomas and hepatic rupture. The latter usually are associated with HELLP syndrome. The pathologic liver lesions seen on autopsy are periportal hemorrhages, ischemic lesions, and fibrin deposition.

Central Nervous System Eclamptic convulsions are perhaps the most disturbing central nervous system (CNS) manifestation of preeclampsia and remain a major cause of maternal mortality in the third world. The exact etiology of eclampsia is unknown, but is thought to be attributed to coagulopathy, fibrin deposition, and

vasospasm. Radiologic studies may show evidence of cerebral edema and hemorrhagic lesions, particularly in the posterior hemispheres, which may explain the visual disturbances seen in preeclampsia. Other CNS abnormalities include headaches and visual disturbances including scotomata, blurred vision and, rarely, temporary blindness.

Fetus and Placenta The hallmark placental lesion in preeclampsia is acute atherosis of decidual arteries. This is due in part to the abnormal adaptation of the spiral artery–cytotrophoblast interface and results in poor perfusion. This may lead to poor placental perfusion, resulting in oligohydramnios, intrauterine growth restriction, placental abruption, fetal distress, and ultimately fetal demise.

Prediction

No good screening test for the prediction of preeclampsia exists. Several methods have been proposed but have not been found to be cost effective or reliable (Table 16.6). Given that nulliparity has a 5% to 7% risk of preeclampsia and multiparity carries only a 3% risk, an accurate and thorough maternal history with identification of risk factors is the most cost-effective screening method available.

Maternal serum uric acid levels
Uterine artery Doppler determinations
Roll-over test
Angiotensin II infusion test
Elevated second-trimester MSAFP, β-hCG levels
Plasma fibronectin values
Midpregnancy blood pressure measurements
Urinary calcium excretion
Urinary kallikrein concentration
Platelet activation
Excessive weight gain
Calcium-to-creatinine ratio

β-hCG, β-human chorionic gonadotropin; MSAFP, maternal serum α-fetoprotein.

TABLE 16.6. *Proposed methods of prediction of preeclampsia*

Prevention

Preventive interventions for preeclampsia could impact maternal and perinatal morbidity and mortality worldwide. As a result, during the past decade there have been many studies done to find a method for the prevention of preeclampsia. Consideration has been given to low-salt diets, diuretics, bed rest, and strict control of weight gain, but none of these is beneficial. Disappointingly, studies using low-dose aspirin (Table 16.7), calcium supplementation (Table 16.8), magnesium supplementation, and fish oil supplementation have shown no reduction in the rates of preeclampsia. Antioxidant use with vitamin C and E supplementation has shown promise in one study but will require further confirmation by larger studies.

TABLE 16.7. *Prevention of preeclampsia with aspirin—summary of randomized trials*

TABLE 16.8. *Prevention of preeclampsia with calcium—summary of randomized trials*

MILD PREECLAMPSIA

Diagnosis of Mild Preeclampsia

The diagnosis of mild preeclampsia requires the presence of hypertension and proteinuria in pregnancy. The diagnosis may be suspected also in the presence of hypertension and maternal symptoms. The diagnosis is considered to be mild preeclampsia if systolic blood pressure remains less than 160 mm Hg and diastolic blood pressure remains less than 110 mm Hg and urinary protein remains below 5 g/24 hours. The criteria for severe preeclampsia are listed in Table 16.3.

Because the spectrum of disease in preeclampsia is variable, it is important to monitor patients for the development of severe preeclampsia. Patients with mild preeclampsia are at risk of developing eclampsia, potentially suddenly, without warning, and with minimal blood pressure elevations. Another risk is abruptio placentae. However, both of these risks are less than 1%.

Management of Mild Preeclampsia

Any patient suspected of having preeclampsia should be hospitalized while confirming the diagnosis. Management of the patient with mild preeclampsia should include baseline laboratory evaluation including 24-hour urine collection for protein, hematocrit, platelet count, serum creatinine value, and aspartate aminotransferase (AST) level. At the time of diagnosis, ultrasonography should be performed to evaluate amniotic fluid volume and estimated fetal weight.

The only definitive cure for preeclampsia is delivery. In patients diagnosed with mild preeclampsia at term (>37 weeks), the general consensus is delivery. For the patient who is preterm (<37 weeks), controversy arises regarding management with respect to level of activity, diet, antihypertensive medications, and delivery. Usually these patients do not require immediate delivery and expectant management is warranted. Hence, the clinical decision making in patients with mild preeclampsia is two-fold. If expectant management is chosen, the second question then becomes where to manage the patient, in the hospital or at home?

In the past, once diagnosed with mild preeclampsia, a woman was either delivered immediately or managed in the hospital for the remainder of the pregnancy. Several studies have shown that a management plan including immediate delivery may not be justified. Sibai and colleagues studied 200 women with preeclampsia who were managed as inpatients with unrestricted activity, but they were randomized to receive labetalol or no medications. The mean pregnancy prolongation was 21 days. The rate of placental abruption was 1.1% and the perinatal mortality rate was 5.4 per 1,000. Another study by Matthews and colleagues evaluated the effect on preeclampsia of bed rest versus unlimited activity. They, also, found no significant difference in maternal or fetal outcomes.

At-home management of these patients or use of a day care setting is appropriate in most cases, provided the patient is compliant, has readily available transportation, and is reliable with follow-up. Using this approach, it is important to educate patients regarding the signs and symptoms to report (Table 16.9). They should be advised to return immediately to the hospital should any of these arise. Should the disease progress from mild to severe, or if there is any indication of fetal compromise, including non-reassuring fetal heart rate test results, oligohydramnios, or growth restriction, the patient should be hospitalized and evaluated for delivery. Serial laboratory evaluation of platelet counts and liver enzyme values should be performed every 3 to 7 days to monitor for worsening disease. Significant abnormalities in any of these laboratory criteria warrants hospitalization. Antenatal surveillance should include at least twice-weekly nonstress tests. Patients should also be instructed to monitor fetal movement. Given the slightly increased risk of intrauterine growth restriction, it is also appropriate to perform an ultrasonographic examination for fetal growth every 3 to 4 weeks.

Nausea and vomiting
Persistent severe headache
Right upper quadrant or epigastric pain
Scotomata
Blurred vision
Decreased fetal movement
Rupture of membranes
Vaginal bleeding
Regular contractions

TABLE 16.9. *Signs and symptoms of preeclampsia that warrant prompt evaluation*

Optimal timing of delivery is dependent on maternal and fetal status. In the preterm pregnancy, the sole benefit of expectant management is for the fetus. Once a pregnancy reaches term, the plan should be for delivery. Induction of labor is indicated in those patients with a favorable cervix. At 37 weeks or beyond, if the cervix is unfavorable, there are two options: either cervical ripening and delivery or continued expectant management with maternal and fetal evaluation. The preferred mode of delivery remains vaginal. A cesarean section should be performed for obstetric indications only.

While in labor, patients may receive intravenous magnesium sulfate ($MgSO_4$) for seizure prophylaxis. A regimen for $MgSO_4$ administration is presented later in this chapter. The exact point in labor at which to start the $MgSO_4$ remains unknown. There is no support in the literature for the need or the optimal timing to begin the $MgSO_4$ infusion, and this should be left to the discretion of the individual physician. Pain management in labor should be individualized, also. Intravenous narcotics and regional anesthesia are both appropriate options. Close monitoring of blood pressure intrapartum is necessary. Antihypertensive medications may be needed in order to keep blood pressure values below 160 mm Hg systolic and below 110 mm Hg diastolic. The most commonly used intravenous medications for this purpose are labetalol and hydralazine. The recommended dosages of medications for the immediate treatment of hypertension are listed in Table 16.10. Care should be taken not to drop the blood pressure too rapidly, because a marked decrease in mean arterial pressure may lead to reduced renal perfusion and reduced placental perfusion. Preeclamptic women receiving $MgSO_4$ are also at risk for postpartum hemorrhage due to uterine atony.

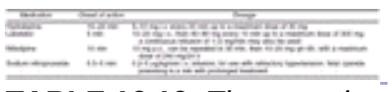

TABLE 16.10. *Therapeutic options in the acute treatment of hypertension*

Patients should be monitored closely for at least 12 to 24 hours postpartum. Postpartum eclampsia occurs in 25% of patients. It is not clear if $MgSO_4$ should be continued in the postpartum period. There is no need for continued seizure prophylaxis beyond 24 hours postpartum.

SEVERE PREECLAMPSIA

Management of Severe Preeclampsia

Any patient with severe preeclampsia should be admitted and observed initially in a labor and delivery unit. Workup should include assessment for fetal well-being, monitoring of maternal blood pressures and symptomatology, and laboratory evaluation. Laboratory evaluation should include 24-hour urine collection for total protein, hematocrit, platelet count, and serum creatinine and AST levels. An initial ultrasonographic examination for fetal growth and amniotic fluid index should be obtained, also.

It is well accepted that delivery is considered in all women with severe preeclampsia at >34 weeks, because prolonging the pregnancy may be hazardous to the mother with little benefit to the fetus. In patients at a gestational age of 33 to 34 weeks, steroids should be administered and delivery planned within 48 hours.

In patients with severe prematurity (=32 weeks), expectant management significantly improves neonatal outcome. The goal in these patients is to gain at least 48 hours so that antenatal glucocorticoids can be administered for fetal benefit. Patients should be selected carefully to undergo expectant management. They should be counseled regarding the risks and benefits of expectant management. Guidelines for expectant management are outlined in Table 16.11. Fetal well-being should be assessed on a daily basis by nonstress testing and weekly amniotic fluid index determinations. The patient should also be instructed on fetal movement assessment. Ultrasonography for fetal growth should be performed every 2 to 3 weeks. Maternal laboratory evaluation should be done daily or every other day. If a stable maternal and fetal course is maintained, expectant management may be continued until 34 weeks. The development of any worsening change in maternal or fetal status warrants delivery regardless of gestational age, as in Table 16.12. A woman with a nonviable fetus should be presented with the option of pregnancy termination. In the United States, it typically is accepted that the fetus is potentially viable at 23 weeks, and at this gestation expectant management may be considered. Consultation with the neonatology team may aid in making this decision.

Controlled hypertension (blood pressures below severe range)
Urinary protein of any amount
Oliguria that resolves with fluid challenge or oral intake
Elevated liver enzyme levels without symptoms
Reassuring fetal status—including biophysical profile ≥4, normal amniotic fluid volume, and appropriate fetal weight (>5th percentile for gestational age)

TABLE 16.11. *Criteria for expectant management of severe preeclampsia*

Uncontrolled severe hypertension
Eclampsia
Persistent oliguria (<500 cc/24 h)
Abruptio placentae
Platelet count <100,000/mm^3
Elevated liver enzyme levels with epigastric pain or right upper quadrant tenderness
Pulmonary edema
Persistent severe headache or visual changes
Fetal death
Spontaneous labor
Rupture of membranes
Gestational age ≥34 wks
Evidence of fetal distress including repetitive late decelerations, biophysical profile <4 on two occasions 4 hours apart, severe oligohydramnios, intrauterine growth retardation (<5th percentile for gestational age)

TABLE 16.12. *Criteria for delivery in severe preeclampsia*

Maternal blood pressure control is essential during either expectant management or during delivery. Medications can be given either orally or by the intravenous route, as necessary, to maintain a desired blood pressure range between 140 and 160 mm Hg systolic and 90 and 110 mm Hg diastolic. Drugs typically used in the management of acute hypertension are hydralazine and labetalol. The dosage of each is presented in Table 16.10. Once again, care must be taken to avoid a sudden drop in maternal blood pressure precipitating cerebral ischemia, decreased renal perfusion, and decreased placental perfusion. These patients typically do not require invasive hemodynamic monitoring. However, in patients with pulmonary edema and those with underlying cardiac disease, consideration should be given to the use of invasive hemodynamic monitoring.

Intrapartum management should include close blood pressure control, continuous fetal monitoring, and intravenous $MgSO_4$ administration. An indwelling urinary catheter should be placed in order to closely monitor fluid balance. Urine output should be =100 cc/ 4 hours. A trial of labor is indicated in patients with severe preeclampsia. However, an appropriate time frame should be established during which to achieve active labor. Pain management should be dealt with on an individual basis. Epidural anesthesia is a reasonable option provided the patient is without a coagulopathy. Patients with preeclampsia tolerate blood loss poorly due to volume contraction, and type-specific blood should be readily available for transfusion if needed. Appropriate steps should be taken to minimize postpartum hemorrhage in patients who develop uterine atony while receiving continuous $MgSO_4$ infusion. Methylergonovine (Methergine) is contraindicated in these patients.

$MgSO_4$ infusion should continue for 24 hours postpartum. The patient should be kept under close observation for 24 hours after delivery to monitor blood pressure, reflexes, and fluid status. Most patients will show improvement in the disease process within the first 24 hours postpartum. On the other hand, approximately 30% of

HELLP cases develop postpartum, and all patients with severe preeclampsia should be monitored for the development of HELLP syndrome after delivery. If hypertension persists after delivery, the patient may need to continue taking antihypertensive medication after being discharged to home. Patients should be seen every week or two as a outpatients until they become normotensive. If the hypertension persists beyond 6 weeks postpartum, the diagnosis of chronic hypertension should be entertained.

HELLP SYNDROME

Diagnosis of HELLP Syndrome

The term *HELLP syndrome* is used to describe preeclampsia in association with hemolysis, elevated liver enzyme levels, and low platelet count. It is found in about 10% of pregnancies complicated by severe preeclampsia. The diagnosis is not always clear and the syndrome may be confused with other medical conditions. Any patient diagnosed with HELLP syndrome should be considered to have severe preeclampsia.

In the past, the diagnostic criteria for HELLP syndrome were variable and led to inconsistent diagnoses. The newer criteria used for the diagnosis of HELLP syndrome are those reported by Sibai and include specific laboratory abnormalities demonstrating hemolysis, elevated liver enzyme levels, and low platelet count as shown in Table 16.13.

Hemolysis
Abnormal peripheral smear
Lactate dehydrogenase >600 U/L
Bilirubin ≥1.2 mg/dL
Elevated Liver Enzyme Levels
Serum aspartate aminotransferase >70 U/L
Lactate dehydrogenase >600 U/L
Low Platelets
Platelet count <100,000/mm³

Source: Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol* 1990;162:311–316, with permission.

TABLE 16.13. *Criteria for the diagnosis of HELLP syndrome*

The clinical picture of patients with HELLP syndrome is highly variable. However, in general, patients with HELLP are multiparous white females who will be diagnosed at less than 35 weeks gestation. The typical symptomatology of these patients consists of vague complaints, further skewing the diagnosis. A large percentage of patients will have a history of general malaise for the few days prior. Other complaints include epigastric or right upper quadrant pain (67%), nausea or vomiting (30%), and nonspecific viral syndrome–like complaints. Thus, any pregnant woman with suspected preeclampsia who makes these complaints should undergo a minimum workup of a complete blood count with platelet count and liver enzyme levels.

Sibai has noted that hypertension may be absent (20%), mild (30%), or severe (50%) in women diagnosed with HELLP syndrome. Therefore, the diagnosis of HELLP syndrome cannot necessarily be ruled out in the normotensive patient who has other signs and symptoms consistent with preeclampsia.

Differential Diagnosis of HELLP Syndrome

HELLP syndrome may be easily confused with many other medical conditions, particularly when the patient is normotensive. It is important to be aware of the differential diagnosis of HELLP and be able to discern this condition from others. A list of the differential diagnosis is found in Table 16.14.

Acute fatty liver of pregnancy
Appendicitis
Cerebral hemorrhage
Diabetes insipidus
Gallbladder disease
Gastroenteritis
Glomerulonephritis
Hemolytic uremic syndrome
Hyperemesis gravidarum
Idiopathic thrombocytopenia
Pancreatitis
Pyelonephritis
Systemic lupus erythematosus
Thrombophilias
Thrombotic thrombocytopenic purpura
Viral hepatitis including herpes

Source: Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol* 1990;162:311–316, with permission.

TABLE 16.14. *Differential diagnosis of HELLP syndrome*

HELLP syndrome can easily be confused with two other specific medical conditions, acute fatty liver of pregnancy and thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP/HUS). The differentiation among the three entities is made largely based on specific laboratory findings. Table 16.15 presents detailed laboratory comparisons among the three disorders.

	HELLP	TTP/HUS	AFLP
Edema	Normal	Normal	Elevated
Anemia	Present	Severe	Normal
Antithrombin III	May be reduced	Normal	Decreased in all cases
Aspartate transaminase	Elevated	Usually normal	Elevated
Bilirubin	Elevated, mostly indirect	Elevated	Elevated, mostly direct
Creatinine	May or may not be elevated	Significantly elevated	Significantly elevated
Fibrinogen	Normal	Normal	Decreased in all cases
Glucose	Normal	Normal	Decreased
Hypertension	Present	May or may not be present	May or may not be present
Liver enzymes	Elevated	Significantly elevated	Elevated
Proteinuria	Present	May or may not be present	May or may not be present
Thrombocytopenia	Present	Present	May or may not be present

AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

TABLE 16.15. *Clinical and laboratory findings in HELLP syndrome, TTP/HUS, and AFLP*

Management of HELLP Syndrome

The initial evaluation of women diagnosed with HELLP syndrome should be like that for severe preeclampsia. The patient should be cared for at a tertiary care center. Management initially should include maternal and fetal assessment, control of severe hypertension, if present, initiation of $MgSO_4$ infusion, correction of coagulopathy, if present, and maternal stabilization. A potentially life-threatening complication of HELLP syndrome is a subcapsular liver hematoma. If the suspicion for a subcapsular liver hematoma is high, then it is appropriate to proceed with obtaining a computed tomography scan.

Immediate delivery should be performed in patients =34 weeks gestation. In patients less than 34 weeks and without proven fetal lung maturity, glucocorticoids should be given for fetal benefits and delivery planned in 48 hours provided no worsening of maternal or fetal status occurs. Multiple studies have been done using steroids, volume expanders, plasmapheresis, and antithrombotic agents in patients with HELLP to attempt to prolong gestation. These studies show only marginal results. Some evidence exists as to the benefit of steroid therapy for improvement in maternal condition. In a study by O'Brien and colleagues, the antepartum use of glucocorticoids showed a dose-dependent prolongation in latency, reduction in liver enzyme abnormalities, and improvement in platelet count in patients with HELLP syndrome. Conservative management of HELLP syndrome has significant risk, including abruptio placentae, pulmonary edema, adult respiratory distress syndrome (ARDS), ruptured liver hematoma, acute renal failure, disseminated intravascular coagulation (DIC), eclampsia, intracerebral hemorrhage, and maternal death. It is the author's opinion that expectant management longer than 48 hours after glucocorticoid administration is not warranted for the potential minimal fetal benefits when weighed against the profound maternal risk.

Patients with a favorable cervix and a diagnosis of HELLP syndrome should undergo a trial of labor, particularly if they arrive in labor. HELLP syndrome does not automatically mandate cesarean delivery. An operative delivery in some situations may even be harmful. Any patient with a favorable cervix, regardless of length of gestation, should undergo induction of labor with either oxytocin or prostaglandins. Elective cesarean section should be considered in patients in very early gestation

who have an unfavorable cervix. A management paradigm is presented in Table 16.16 for patients with HELLP undergoing cesarean section.

1. Control severe hypertension
2. Initiate intravenous magnesium sulfate infusion
3. Glucocorticoids for 24–48 hours for fetal benefit if <34 wks
4. General anesthesia for platelet count <75,000/mm^3
5. Platelets 5–10 units before surgery if platelet count <50,000/mm^3
6. Leave vesicouterine peritoneum (bladder flap) open
7. Subfascial drain
8. Secondary closure of skin incision or subcutaneous drain
9. Postoperative transfusions as needed
10. Intensive monitoring for at least 48 hours postpartum

TABLE 16.16. *Perioperative management of a patient with HELLP syndrome requiring cesarean section*

Pain management of the patient with HELLP during labor should be discussed between the obstetrician and the anesthetist. The anesthetist should be made aware of the patient's condition due to the potential of laryngeal edema and difficulties with intubation or extubation. Typically the decision of whether to use epidural anesthesia is at the discretion of the anesthetist. Regional anesthesia should be used with caution in patients with particularly low platelet counts. A study by O'Brien and co-workers supported the use of glucocorticoids to improve platelet counts and to allow a more liberal use of regional anesthesia in patients with HELLP syndrome. The anesthetist should be updated as to the trend in platelet count of patients with HELLP. Intravenous narcotics can be given to achieve analgesia. Local infiltration can be used without concern during vaginal deliveries and for perineal repairs. Pudendal blocks should be avoided due to the potential for unrecognized bleeding into this area.

Should a patient with HELLP syndrome require cesarean delivery, precautions should be taken to minimize adverse outcomes. Platelet transfusion of approximately 5 to 10 units should be done en route to the operating room for patients with severe thrombocytopenia. Platelet consumption is rapid with a platelet transfusion, and the effects are temporary. Intraoperative considerations should include drain placement, either subfascial, subcutaneous, or both, due to anticipated generalized oozing. The choice of skin incision should be made entirely on the surgeon's best clinical judgment. In a study by Briggs and colleagues, patients with HELLP syndrome undergoing cesarean section were evaluated for wound complications. No statistical difference was found between midline incision versus Pfannenstiel, whether primary or delayed closure.

Another potential life-threatening complication of HELLP syndrome is a subcapsular liver hematoma. Clinical findings consistent with subcapsular hematoma include physical examination with peritoneal irritation and hepatomegaly and referred pain from the phrenic nerve. Pain to the pericardium, peritoneum, pleura, shoulder, gallbladder, and esophagus are consistent with referred pain from the phrenic nerve. Confirmation of the diagnosis can be made by computed tomography, ultrasonography, or magnetic resonance imaging. Conservative management in a hemodynamically stable patient with an unruptured subcapsular hematoma is an appropriate plan, provided that close hemodynamic monitoring, serial evaluations of coagulation profiles, and serial evaluation of hematoma status by radiologic studies are performed. Should the patient decompensate hemodynamically, the diagnosis of ruptured subcapsular hematoma should be entertained.

If rupture of a subcapsular liver hematoma is suspected, immediate intervention is necessary. Liver hematoma rupture with hemodynamic shock is a life-threatening surgical emergency. Treatment at this point is from a multidisciplinary approach and should involve general surgeons and vascular surgeons to perform a laparotomy. Furthermore, correction of coagulopathy and massive blood product transfusion is essential. The rupture typically involves the right lobe of the liver. Maternal and fetal mortality is over 50% with immediate intervention. The recommendation in the literature for rupture of a subcapsular liver hematoma in pregnancy is packing and drainage. According to a study by Smith and co-workers, overall survival reached 82% with this method.

Postpartum management of the patient with HELLP should include close hemodynamic monitoring for at least 48 hours. Serial laboratory evaluations should be done to monitor for worsening abnormalities. Most patients will show reversal of laboratory parameters within 48 hours postpartum. Small studies have shown a more rapid reversal in laboratory abnormalities with postpartum administration of plasma exchange and steroids.

ECLAMPSIA

The rate of eclampsia in the United States is 0.05% to 0.1%. The rate is much higher in developing countries. Eclampsia continues to be a major cause of maternal and perinatal morbidity and mortality worldwide. The maternal mortality rate is approximately 4.2%. The perinatal mortality rate is higher, ranging from 13% to 30%. Eclampsia can occur antepartum (50%), intrapartum (25%), or postpartum (25%). Patients with eclampsia can exhibit a wide spectrum of signs and symptoms, from mild isolated hypertension to multiorgan failure. Prevention of eclampsia is one of the goals in treating preeclamptic patients with $MgSO_4$.

Management of Eclampsia

During the eclamptic seizure, the main therapy is supportive care. This includes avoiding injury, maintaining oxygenation, and minimizing the risk of aspiration. An outline to the specific steps to care for an eclamptic patient are in Table 16.17. Most seizures are self-limited, lasting 1 to 2 minutes. However, some patients may have repeated convulsions, which can result in hypoxia or acidosis both in mother and fetus. $MgSO_4$ is the drug of choice for the prevention of eclamptic seizures and should be used for the prevention of recurrent seizures. Approximately 10% of eclamptic women receiving $MgSO_4$ will have further seizures.

1. Avoid injury
a. Padded bedside rails
b. Physical restraints
c. Padded tongue blade
2. Maintain oxygenation to mother and fetus
a. Oxygen at 8–10 L/min by face mask
b. Monitor oxygenation and metabolic status with transcutaneous pulse oximetry or arterial blood gas measurements
3. Minimize aspiration
a. Lateral decubitus position
b. Suctioning of vomitus and oral secretions
c. Obtain chest x-ray after cessation of convulsion to rule out aspiration
4. Initiate $MgSO_4$ to prevent recurrent seizures
5. Control severe hypertension
6. Initiate the delivery process

$MgSO_4$, magnesium sulfate.

TABLE 16.17. *Management of the eclamptic patient*

Immediately following an eclamptic seizure, it is common to see abnormalities in the fetal heart rate pattern. These include fetal bradycardia, decreased variability, late decelerations, and reflex tachycardia. These abnormalities typically resolve within 5 to 10 minutes after the convulsion. It is important not to proceed directly to cesarean delivery after a seizure. Stabilization of the mother is the number one priority. Generally the fetus will respond favorably once the mother is treated. If prolonged signs of fetal compromise occur indicating possible abruptio placentae, consideration should be given to proceed with operative delivery.

Vaginal delivery is the preferred route after an eclamptic seizure. Cesarean delivery should be performed for obstetric indications only. Induction of labor should be performed with oxytocin or prostaglandins. The patient should be maintained on $MgSO_4$ throughout her labor. Careful attention must be made to the overall fluid status of the patient. Patients with eclampsia have profound hemoconcentration. Because of this, close hemodynamic monitoring is required with the use of epidural anesthesia and in case of severe blood loss. Patients who are hypovolemic will not respond well to acute blood loss, in contrast to healthy parturients. It is also important to limit fluids, because these patients have capillary leakage and are predisposed to developing pulmonary edema.

$MgSO_4$ should be continued for 24 hours postpartum. Intracranial imaging typically is not warranted unless coma or focal neurologic signs persist or the diagnosis is uncertain. Most patients are normotensive at discharge and do not require medication. Eclamptic patients should be evaluated in the outpatient setting within 1 week of discharge.

Postpartum eclampsia offers a diagnostic dilemma. Any woman seizing in the postpartum period should be considered to have a diagnosis of eclampsia, although other disorders must be ruled out. Late postpartum eclampsia, defined by Sibai as occurring more than 48 hours after delivery, happens in 56% of postpartum eclampsia. Patients who develop postpartum eclampsia usually will have symptoms prior to seizure activity, including severe persistent headache, blurred vision, photophobia, epigastric pain, nausea and vomiting, and transient mental status changes. Therefore, it is important to educate patients about reporting these symptoms to health care providers. All such women should receive preeclamptic evaluation. These patients should receive $MgSO_4$ for 24 hours after seizure activity. If the

patient has normal laboratory values and hypertension is controlled, she can be discharged after $MgSO_4$ treatment to return in 1 week for outpatient evaluation.

MAGNESIUM SULFATE

$MgSO_4$ is used in the management of preeclamptic patients for the prevention of eclamptic seizures. The exact mode of action of $MgSO_4$ for preventing seizures is unknown, although it has been in use since the early 1900s. Multiple studies have been done which show $MgSO_4$ to be superior to both phenytoin and diazepam for the prevention of seizures. Most notable of these is the Collaborative Eclampsia Trial, in which women with eclampsia were randomized to receive $MgSO_4$, phenytoin, or diazepam. The trial found that $MgSO_4$ was superior to both phenytoin and diazepam in the prevention of recurrent seizures and of maternal and perinatal death.

The administration of $MgSO_4$ is usually intravenous. The therapeutic range is considered a serum plasma level from 4 to 8 mg/dL. Multiple regimens have been prescribed to achieve these levels. The recommended regimen is presented in Table 16.18. The intravenous route is the preferred method, because intramuscular injections of $MgSO_4$ are very painful and occasionally can cause gluteal abscess formation. Lidocaine at the injection site may decrease discomfort. The intramuscular route should be reserved for rare situations when intravenous infusions may not be possible, such as lack of intravenous access, unavailability of infusion pumps, or during patient transport.

Loading dose: 6 g i.v. over 20–30 min (6 g of 50% solution diluted in 150 cc D5W)
Maintenance dose: 2–3 g i.v. per hr (40 g in 1 L D5LR at 50 cc/hr)
Additional 2 g over 5–10 min (1–2 times) can be given with persistent convulsions
If convulsions persist (2% of cases), give 250 mg sodium amobarbital i.v. over 5 min
In status eclampticus: intubation and muscular paralysis
Intramuscular dose: 10 g i.m. (20 mL of 50% $MgSO_4$, one half of the dose in each buttock)

$MgSO_4$, magnesium sulfate.

TABLE 16.18. *Recommended regimens of magnesium sulfate in the treatment of eclamptic convulsions*

$MgSO_4$ is not an entirely benign medication. Any member of the health care team caring for a patient receiving $MgSO_4$ should be familiar with potential side effects and complications of its administration. Patients receiving $MgSO_4$ are at increased risk for postpartum hemorrhage due to uterine atony. This should be anticipated and steps taken to prepare cross-matched blood if the need arises. Monitoring patients for signs of magnesium toxicity should be done throughout the course of administration. This includes eliciting deep tendon reflexes, assessing mental status, and checking respiratory rate. Table 16.19 lists the clinical findings associated with various serum magnesium levels. If a patient develops signs of magnesium toxicity, the infusion should be stopped immediately. The patient should then be evaluated for respiratory compromise by examination and pulse oximetry, oxygen administered, and a serum magnesium level obtained. If magnesium toxicity is diagnosed, the patient should be treated with 10 cc of 10% calcium gluconate (1 g) slow push intravenously. Calcium competitively inhibits magnesium at the neuromuscular junction and decreases the effect of the magnesium. The effect of the calcium is transient, and the patient should be monitored closely for continued magnesium toxicity. Should respiratory or cardiac arrest occur, immediate resuscitation including intubation and mechanical ventilation should be performed. A summary of the treatment of magnesium toxicity is seen in Table 16.20.

Clinical finding	Serum level
Loss of patellar reflex	8–12 mg/dL
Feeling of warmth, flushing	9–12 mg/dL
Double vision	
Somnolence	10–12 mg/dL
Slurred speech	10–12 mg/dL
Muscular paralysis	15–17 mg/dL
Respiratory difficulty	15–17 mg/dL
Cardiac arrest	30–35 mg/dL

TABLE 16.19. *Serum magnesium levels and associated clinical findings*

Discontinue magnesium sulfate infusion
Begin supplemental oxygen administration
Obtain serum magnesium level
Administer 1 g calcium gluconate (10 cc of 10% calcium gluconate) by slow intravenous push
Repeat calcium gluconate administration if necessary
If respiratory arrest occurs, begin cardiopulmonary resuscitation

TABLE 16.20. *Management of magnesium toxicity*

Counseling

Any patient diagnosed with preeclampsia is at significantly greater risk of having an underlying medical condition than is a normotensive gravidae. A study by Dekker and Sibai found 39% of patients with a history of early-onset severe preeclampsia developed chronic hypertension. Another study by Nisell and co-workers found that 37% of patients with a history of pregnancy-induced hypertension and 20% of patients with a history of preeclampsia were noted to have hypertension at 7-year follow-up. It is thus essential that women diagnosed with preeclampsia receive close follow-up.

With regard to future pregnancies, patients with preeclampsia are at increased risk of developing preeclampsia during subsequent gestations. The risk is dependent on severity of preeclampsia, as well as gestational age at onset in the index pregnancy. The recurrence rate is 65% if preeclampsia develops in the midtrimester and 20% if it develops at term. Sibai and associates reviewed recurrence rates of preeclampsia and HELLP in patients who had pregnancies complicated by HELLP syndrome. Their findings noted that the recurrence risk for preeclampsia in the otherwise normotensive group was 19% and the risk for recurrence of HELLP was 3%. This is in contrast to a group of patients with underlying chronic hypertension who had recurrence rates of preeclampsia and HELLP of 75% and 5%, respectively. The rate of recurrence of eclampsia is about 1% to 2%.

CHRONIC HYPERTENSION

Chronic hypertension is defined by elevated blood pressure occurring prior to pregnancy or elevated blood pressure measurements prior to 20 weeks gestation. The rate of chronic hypertension is 1% to 5% in pregnancy. This number is effected by many factors, including maternal age and race. The incidence of chronic hypertension among African Americans is 2.5% in comparison with 1% among other racial groups. The Third National Health and Nutrition Examination Survey, 1988 to 1991, studied the incidence and stratification of patients with chronic hypertension. The results of this study showed that the rate of chronic hypertension among women ages 18 to 29 was 2.0% for African Americans, 0.6% for Caucasians, and 1.0% for Mexican Americans. In the 30 to 39 age category, the rates were 22.3%, 4.6%, and 6.2%, respectively. And from 40 to 49 years of age, the prevalence was 30.5%, 12.7%, and 10.6% for each group. Given the trend in delayed childbearing as women pursue career and educational goals, increasing numbers of pregnancies will be complicated by chronic hypertension.

Determination of associated underlying medical conditions and the classification of hypertension is important in the management and counseling of patients with chronic hypertension in pregnancy. Chronic hypertension can be classified as either mild or severe, depending on blood pressure criteria. Systolic blood pressure =160 mm Hg or diastolic blood pressure =110 mm Hg, or both, constitute severe chronic hypertension. The etiology of chronic hypertension can be either primary or secondary. Primary hypertension, also referred to as idiopathic hypertension or essential hypertension, occurs in 90% of pregnancies. Secondary hypertension occurs in the remaining 10% of pregnancies and is associated with the following underlying medical conditions: renal disease, endocrine disease, collagen vascular disease, and coarctation of the aorta.

Women with chronic hypertension in pregnancy are at increased risk for the development of superimposed preeclampsia, abruptio placentae, intrauterine growth restriction, and preterm delivery. The rate of superimposed preeclampsia in women with chronic hypertension is 25%. If the patient has chronic hypertension of over 4 years' duration, renal insufficiency, or had hypertension in a prior pregnancy, the rate of superimposed preeclampsia increases. Overall, abruptio placentae occurs in 1.5% of pregnancies complicated by chronic hypertension. This rate varies from 1% in women with uncomplicated chronic hypertension to 3% in women with superimposed preeclampsia. Proteinuria is an independent risk factor for adverse perinatal outcome, regardless of the development of superimposed preeclampsia. A

maternal serum creatinine greater than 1.4 mg/dL at conception is another risk factor for increased fetal loss and progressive worsening of maternal renal disease. Fetal loss is increased 10-fold in women with uncontrolled chronic hypertension and impaired renal function at conception as compared with normotensive women and women with well-controlled hypertension. Therefore, management of women with chronic hypertension should begin prior to conception.

Women with chronic hypertension should be counseled regarding the increased risk of adverse maternal and fetal outcomes as above. These patients should also be evaluated for end-organ damage such as retinopathy, renal disease, and left ventricular hypertrophy. The possibility of worsening maternal condition during pregnancy must be discussed with the patient. Blood pressure control prior to pregnancy should be optimized and lifestyle changes initiated, if possible. Patients should be discouraged from tobacco or alcohol use, because both of these may exacerbate hypertension, not to mention other known obstetric risks. Daily salt intake should be limited to 2 g. Appropriate antihypertensive medications should be prescribed. This would include the discontinuation of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, if the patient was previously taking these medications. In addition, atenolol should be discontinued early in pregnancy.

The diagnosis of superimposed preeclampsia may be difficult to make in the patient with chronic hypertension, particularly with baseline nephropathy. To make the diagnosis, the patient should have increasing or difficult-to-control blood pressure, HELLP syndrome, new-onset proteinuria, or significant increase in preexisting proteinuria. Any patient with chronic hypertension who develops headache, right upper quadrant pain, or visual disturbances requires further evaluation for superimposed preeclampsia. If superimposed preeclampsia is suspected in a patient with chronic hypertension, she should be hospitalized for close maternal and fetal evaluation.

MANAGEMENT

The management of pregnancies complicated by chronic hypertension differs for the low-risk group versus the high-risk group. Patients considered in the low-risk group have, by definition, mild hypertension without evidence of organ damage. The high-risk group has either severe hypertension (systolic blood pressure =160 mm Hg or diastolic blood pressure =110 mm Hg) or mild hypertension with evidence of organ involvement.

Patients with low-risk chronic hypertension who do not develop superimposed preeclampsia have pregnancy outcomes similar to those of the general population. Studies have shown that antihypertensive treatment in this group does not effect perinatal outcome and is not necessary, provided they remain in the mild hypertension range by blood pressure criteria. Antihypertensive use may be discontinued at the first prenatal visit in any patient with mild hypertension. These patients should be observed closely throughout gestation, because they may become high risk at any time. Pharmacologic agents should be reinstituted if systolic blood pressures reach 160 mm Hg or diastolic pressures reach 105 mm Hg or target organ damage develops. Prenatal care should include 24-hour urine collection for total protein determination in the first trimester and at least monthly visits in the first and second trimester. Visits should be every 1 to 2 weeks after 32 weeks, looking carefully for the development of superimposed preeclampsia. Fetal surveillance should include interval ultrasonography for fetal growth and amniotic fluid assessment every 4 weeks beginning at 32 weeks, unless there is suspicion of poor fetal growth, and then testing should be started earlier. Weekly fetal heart rate testing with nonstress tests should begin at 34 weeks. Fetal well-being assessment should be increased to twice weekly with evidence of growth restriction or oligohydramnios. The patient should also be instructed on fetal movement counts. Timing of delivery should be determined on an individual basis. Patients in the low-risk group may continue their pregnancies up to 41 weeks, provided that blood pressure remains controlled and no evidence of superimposed preeclampsia or fetal growth restriction develops.

Central to the management of the high-risk chronic hypertensive pregnancy is the use of antihypertensive pharmacotherapy. The choice of agent is dependent on their pharmacologic actions and will be covered in the next section. Prenatal care of the high-risk patient includes a first-trimester 24-hour urine collection for total protein level. The frequency of visits in the first and second trimesters should be every 2 to 3 weeks, and weekly in the third trimester if clinically indicated. Fetal surveillance should include ultrasonography for estimated fetal weight and amniotic fluid volume every 4 weeks starting at 26 weeks. Weekly nonstress testing or biophysical profile assessments should begin at 28 weeks. The frequency of prenatal care visits and fetal testing may need to be increased dependent upon clinical findings such as increasing hypertension, superimposed preeclampsia, decreased amniotic fluid volume, or fetal growth restriction. If superimposed preeclampsia is suspected or uncontrolled hypertension develops, the patient should be hospitalized, preferably at a tertiary care center. The timing of delivery is dependent upon the development of confounding complications and gestational age. In general, pregnancies in patients with high-risk chronic hypertension should not be continued past 40 weeks.

ANTIHYPERTENSIVE AGENTS

Many agents are available for the control of hypertension. It is important to be familiar with the maternal and fetal side effects, as well as mode of action, in order to choose the most effective agent for your patient. Antihypertensive agents exert their activity through the following five methods: they decrease cardiac output, decrease peripheral vascular resistance, decrease blood pressure centrally, diurese, and inhibit angiotensin production. Commonly used drugs in pregnancy are listed in Table 16.21 and we will discuss them in this section. For the postpartum patient who is breast-feeding, little information is known for most drugs regarding excretion in breast milk and neonatal effects. In general, ACE inhibitors are discouraged secondary to potential renal effects on the neonate.

Medication	*Dosage*	*Maximum*	*Half-life*
Methyldopa	250–500 mg p.o. q6–12h	4 g/24 h	2 h
Labetalol	100 mg p.o. b.i.d.	2,400 mg/24 h	5–8 h
Thiazide Diuretic	12.5 mg p.o. b.i.d.	50 mg/24 h	3 h
Nifedipine	10–20 mg p.o. q4–6h	240 mg/24 h	2 h

TABLE 16.21. *Antihypertensive drugs commonly used in pregnancy*

Centrally Acting Drugs

Methyldopa Methyldopa is the most commonly used antihypertensive in pregnancy. Its mode of action is by central inhibition of the sympathetic drive. The safety and efficacy of methyldopa is well established. Studies have documented no known congenital malformations or adverse long-term follow-up of children exposed in utero. Maternal side effects include tiredness, dry mouth, and somnolence. In addition, about 5% to 10% may have elevated liver enzyme values. Methyldopa is the agent of choice for long-term, nonemergent oral therapy.
Clonidine Clonidine is not commonly used and there is limited data regarding safety and efficacy of its use. Limited studies regarding congenital defects associated with the use of clonidine reveal no increased risk.

Beta Blockers

The main mode of action of ß-adrenergic blockade is through the reduction in cardiac output. The drugs in this group are a heterogeneous mixture exerting their effects dependent upon receptor selectivity, lipid solubility, and intrinsic sympathomimetic activity. Fetal effects of ß blockers may include growth restriction and neonatal hypoglycemia. Atenolol in the first trimester in particular has been linked to intrauterine growth restriction. Labetalol is a nonselective ß blocker and a postsynaptic ß-1 blocker. It has lower ß blocking effect than other ß blockers, which does not reduce cardiac output. It is probably, thus, less responsible for fetal growth restriction. The side effects are tremors, headache, and scalp tingling. The use of labetalol should be avoided in patients with asthma and congestive heart failure.

Calcium Channel Blockers

Calcium channel blockers act by inhibiting extracellular calcium influx into cells through slow calcium channels. This, then, reduces peripheral vascular resistance. Studies have found no increase in congenital malformations associated with the long-term use of calcium channel blockers. However, adverse maternal and fetal outcomes have been associated with sublingual use of nifedipine, including maternal myocardial infarction and profound hypotension. Maternal side effects are flushing, headache, and palpitations.

Vasodilators

Hydralazine Hydralazine works through direct and potent vasodilatation. It may be used orally but is most effective as an intravenous agent to control hypertensive crisis. No congenital defects have been associated with hydralazine. It may cause hypotension in hypovolemic patients, so giving intravenous fluids may be warranted. Side effects include fluid retention, tachycardia, palpitations, headache, lupuslike syndrome, and neonatal thrombocytopenia.

Diuretics

Diuretics, in general, are not contraindicated in pregnancy. There is no increased risk of congenital defects with their use, but their efficacy is uncertain. It is recommended that women receiving diuretics prior to pregnancy be continued on them throughout pregnancy. However, diuretics should be discontinued in patients with preeclampsia or oligohydramnios or if there is evidence of reduction in uteroplacental flow.

Thiazide The thiazide diuretics have minimal effect on lowering blood pressure in pregnancy and are rarely used. Limited studies show no increased congenital anomalies with the use of thiazide. The side effect profile includes maternal and fetal hyponatremia and acute pancreatitis, rise in blood uric acid levels, and neonatal thrombocytopenia. It can also precipitate hyperglycemia and glycosuria in the diabetic patient.
Furosemide Furosemide is rarely used as a sole pharmacologic agent but is useful in conjunction with other antihypertensives. Studies showed no increase in congenital anomalies with use in the second and third trimesters, but first trimester use may be associated with hypospadias. Furosemide use in pregnancy should be limited to postpartum management of fluid overload and pulmonary edema in the preeclamptic patient.

Angiotensin-converting Enzyme Inhibitors

ACE inhibitors act by inhibiting the production of angiotensin II and by reducing peripheral vascular resistance. The use of ACE inhibitors has been associated with an increased risk of intrauterine demise, renal dysgenesis, oligohydramnios, pulmonary hypoplasia, fetal growth restriction, and neonatal renal dysfunction. The mechanism of action is thought to be due to continuous inhibition of the renin-angiotensin system, leading to the development of tubular dysfunction. Therefore, ACE inhibitors are contraindicated in pregnancy, mainly during the second and third trimesters. However, ACE inhibitors may be an excellent choice for hypertensive control in the postpartum period.

Contraception

Women with hypertensive diseases in pregnancy, whether preeclampsia or chronic hypertension, will seek advice regarding contraceptive methods postpartum. It is important to be familiar with options available to patients and be able to discuss potential risk factors.

No contraindications exist with the use of barrier methods with regard to hypertension. The user failure rate, however, may be significant if failure results in a pregnancy with increased morbidity due to hypertensive disease. There are no contraindications for hypertensive patients desiring to use an intrauterine device. It is important to be aware of any associated underlying medical problems or therapies that the patient may have that would prohibit the use of an intrauterine device. Natural family planning continues to be an acceptable form of contraception when used appropriately.

The greatest concern in finding appropriate contraception for the hypertensive patient is with regard to hormonal contraception. Oral contraceptive pills are the most widely used reversible form of birth control in the United States. Combination oral contraceptives are known to elevate blood pressure minimally, increase clotting factors, and increase total cholesterol levels. Once again, it is extremely important to be familiar with any coexisting disease in a hypertensive patient. Hypertension may have associated underlying antiphospholipid syndrome, for example, which would be a contraindication to combination oral contraceptives given the increased risk for thromboembolic phenomena. Progestin-only contraceptive methods may be a suitable alternative for women with underlying hypercoagulability, because they do not interfere with coagulation. Overall, the contraceptive choices afforded hypertensive patients are basically the same as in normotensive patients. The risks and benefits of contraception must be weighed and patients counseled accordingly. Avoiding the morbidity associated with pregnancy in some patients may be a benefit that outweighs the risk of contraceptive use.

SUMMARY POINTS

- Making an appropriate diagnosis is essential in caring for women with hypertensive disease in pregnancy.
- There is no known etiology, prevention, or screening method for preeclampsia.
- The use of $MgSO_4$ is warranted in patients with preeclampsia and eclampsia to prevent seizures.
- Fetal outcome in patients with preeclampsia is based largely upon gestational age at delivery; as such, prolonging pregnancies in patients with preeclampsia should be done with close maternal and fetal observation.
- Blood pressure =170 mm Hg systolic and =110 mmHg diastolic requires intervention.
- Any patient with symptoms of HELLP syndrome should have laboratory evaluation performed, regardless of blood pressure measurements.
- Evaluation of a patient with chronic hypertension should include monitoring for target organ damage. Management of these patients is dependent upon the degree of hypertension.
- Any patient with chronic hypertension is at increased risk of developing superimposed preeclampsia.

RECOMMENDED READINGS

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Chapter 17

Maureen P. Malee

Medical and Surgical Complications of Pregnancy

Hematologic Disease
Anemias
Platelet Disorders
Coagulation Defects
GASTROINTESTINAL DISEASE
Nausea and Vomiting
Gastrointestinal Reflux Disease
Peptic Ulcer Disease
Upper Gastrointestinal Bleeding
Cholelithiasis and Biliary Disease
Pancreatitis
Inflammatory Bowel Disease
Hepatitis
Pregnancy Following Liver Transplantation
Acute Fatty Liver
CARDIOVASCULAR DISEASE
Physiologic Changes in Pregnancy
Other Cardiac Abnormalities
Thromboembolic Disease
PULMONARY DISEASE
Asthma
Tuberculosis
Viral Pneumonia
Cystic Fibrosis
Sarcoidosis
RENAL DISEASE
Renal Infections
Urinary Calculi
Chronic Renal Disease
Acute Renal Failure
Dialysis
Renal Transplantation
NEUROLOGIC DISORDERS
Headache
Migraine Headache
Epilepsy
Subarachnoid Hemorrhage
Ischemic or Thrombotic Stroke
Cerebral Venous Sinus Thrombosis
Pseudotumor Cerebri
Multiple Sclerosis
Myasthenia Gravis
Myotonic Dystrophy
Spinal Cord Injury
ENDOCRINOLOGY
Pituitary Tumors
Diabetes Insipidus
Thyroid Disease
Adrenal Disease
DERMATOLOGIC DISEASE
Physiologic Changes During Pregnancy
Pregnancy-specific Dermatologic Disease
Non–pregnancy-specific Dermatologic Disease
ACUTE ABDOMEN AND SURGICAL DISEASE IN PREGNANCY
Appendicitis
Intestinal Obstruction
Cholecystitis
Pancreatitis
Liver Disease
Peptic Ulcer Disease
MATERNAL TRAUMA
Physiologic Changes in Pregnancy
The ABCs
Abdominal Trauma
Penetrating Abdominal Trauma
Head Trauma
Burns
Electrical Injury
SUMMARY POINTS

RECOMMENDED READINGS
Hematologic Disease
Gastrointestinal Disease
Cardiovascular Disease
Renal Disease
Pulmonary Disease
Neurologic Disease
Endocrinologic Disease
Dermatologic Disease
Acute Abdomen and Surgical Disease
Maternal Trauma

Hematologic Disease

Anemias

Anemia is defined as a hemoglobin (Hb) concentration of less than 12 g/dL in nonpregnant women. Anemia can be acquired or inherited. During pregnancy, plasma volume expands proportionately more than Hb or red blood cell volume, resulting in Hb dilution, such that anemia is defined as a Hb concentration of less than 10 g/dL. In addition to blood loss, anemia can result from decreased production or increased destruction of red blood cells. The initial workup consists of a history and physical examination, as well as an examination of the red blood cell indices and a peripheral smear, with additional tests as indicated (Fig. 17.1).

FIG. 17.1. Workup of anemia in pregnancy.

Acquired Anemias

Iron Deficiency Anemia Iron deficiency is an acquired anemia and is the most common cause of anemia in gravid women, occurring in 15% to 25% of all pregnancies. Iron deficiency is suspected when the mean corpuscular volume (MCV) is less than ã80/µm ^{3} and is confirmed by demonstrating an elevated total iron-binding capacity (TIBC), a low serum iron level, a serum iron-to-TIBC ratio less than 20%, or a low ferritin level. Effects of iron deficiency on the fetus are usually minimal, although neonatal anemia is increased. Iron is transported actively across the placenta, and fetal iron and ferritin levels are 3 times higher than maternal levels. However, iron deficiency anemia has been weakly associated with preterm birth, and when maternal anemia is severe (Hb less than 6 g/dL), intrauterine growth restriction (IUGR) may occur. In pregnant women, iron deficiency can cause symptoms including fatigue, headache, lightheadedness, and reduced exercise tolerance. Blood loss at delivery may be tolerated poorly in anemic patients, and postpartum tissue healing may be compromised. For these reasons, treatment during pregnancy is recommended. The total iron requirement of pregnancy is 1,000 mg: 500 mg increases the maternal red blood cell mass, 300 mg is transported to the fetus and placenta, and 200 mg compensates for blood loss at delivery. The iron requirements of pregnancy increase steadily toward term but average 3.5 mg per day. Even though iron absorption efficiency increases during pregnancy, excess iron must be ingested to ensure sufficient dosage. Recommended supplementation for nonanemic gravidas is 300 mg of ferrous sulfate per day, which contains 60 mg of elemental iron. Anemic gravidas (Hb of 8 or 9 g/dL) should take 300 mg ferrous sulfate 2 or 3 times a day. Patients who cannot tolerate iron tablets may take an enteric-coated tablet or a liquid suspension (Table 17.1). Vitamin C facilitates iron absorption. Therapeutic results can be expected after 3 weeks of therapy.

TABLE 17.1. *Iron preparations and dosages*

The severely anemic patient (Hb less than 8 g/dL) may require parenteral therapy in the form of intramuscular or intravenous iron dextran. Because 0.2% to 0.3% of patients have an anaphylactic response to iron dextran, all patients should receive a small test dose 1 hour before the initiation of treatment, and therapy should be provided in an area with ready access to resuscitative medication and equipment. The total dose of iron required can be calculated using this formula: Total dose of iron dextran (mL) = (0.0476 × body weight in kg × [desired Hb concentration - observed Hb concentration]) + 1 mL/5 kg of body weight up to a maximum of 14 mL This dose can be given intramuscularly or intravenously (by slow push), 2 mg per day, until the total dose has been given, or the entire dose can be given diluted in 500 to 1,000 mL of 0.9% saline and administered intravenously over 1 to 6 hours. Adequate parenteral therapy should result in a marked increase in the reticulocyte count within 7 to 14 days.

Megaloblastic Anemia Megaloblastic anemia is characterized by red blood cells with increased MCV and white blood cells with altered morphology (hypersegmented neutrophils, anisocytosis, and poikilocytosis). It complicates up to 1% of pregnancies and usually is caused by folate deficiency, although it can occur after exposure to sulfa drugs or hydroxyurea or, rarely, because of vitamin B $_{12}$ deficiency. Folate deficiency can develop over a relatively short time, because liver stores of folate are sufficient to meet the body's needs for only 1 to 2 months. Malnutrition (e.g., alcoholism), malabsorption, anticonvulsant therapy, oral contraceptive use, or pregnancy can rapidly deplete the body's folate stores. Hypersegmented neutrophils (more than 5% of neutrophils having five or more lobes) appear after 7 weeks of deficiency, red blood cell folate is reduced after 18 weeks, and anemia occurs after 20 weeks. The daily folate requirement for a nonpregnant individual is 50 to 100 µg; a pregnant woman needs 300 to 400 µg. This dosage may be difficult to achieve through dietary manipulation, because folate is found primarily in fresh fruits and vegetables and is destroyed by cooking. As a separate issue, it now seems apparent that some women require excess folate to overcome a relative enzyme deficiency leading to high blood and amniotic fluid levels of homocysteine and an increased risk for fetal neural tube defects. For these reasons, women contemplating pregnancy should be advised to ingest a daily folic acid supplement (0.4 mg per day if there is no family history of neural tube defects; 4 mg per day if there is a family history) beginning before conception and continuing throughout the first trimester of pregnancy. In contrast, vitamin B $_{12}$ deficiency is rare, because very little of the body's stores is used each day. Ingested vitamin B $_{12}$ is bound to intrinsic factor produced by the parietal cells of the stomach and then absorbed through the mucosa of the distal ileum. Patients who have had a gastrectomy, ileitis, or ileal resection, or who have pernicious anemia, pancreatic insufficiency, or intestinal parasites eventually may become vitamin B $_{12}$ deficient. When megaloblastic anemia is suspected, the history should be reviewed for predisposing factors. The peripheral smear should be examined both to confirm altered cell morphology and to rule out a mixed (i.e., folate and iron) deficiency. Serum folate and vitamin B $_{12}$ levels should be measured. A fasting folate level less than 3 ng/mL or a vitamin B $_{12}$ level less than 80 pg/mL indicates deficiency. Folate deficiency responds to 0.5 to 1.0 mg folate orally per day, while a B $_{12}$ deficiency requires vitamin B $_{12}$, 1 mg intramuscularly, weekly for 6 weeks.

Hereditary Anemias The most commonly encountered hereditary anemias in pregnancy are the thalassemias and sickle cell variants. Hb is a tetramer composed of two copies each of two different polypeptide chains; the identity of the chains determines the type of Hb produced. During embryonic and fetal life, genes directing production of different types of polypeptide chains and, thus, different types of Hb, are switched on and then off sequentially. At birth, a normal individual produces a and ß chains, along with very small quantities of d and t chains (Fig. 17.2). Normal adults produce primarily hemoglobin A (HbA), composed of two a and two ß polypeptide chains.

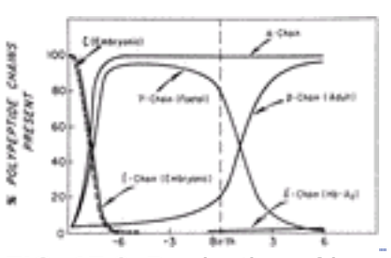

FIG. 17.2. Production of hemoglobin polypeptide chains in relationship to gestational age. (From Rucknagel DL, Laros RK. Hemoglobinopathies: genetics and implications for studies of human reproduction. *Clin Obstet Gynecol* 1969;12:4, with permission.)

Thalassemias Thalassemias are characterized by impaired production of one or more of the peptide chains. Thalassemia has a high incidence in certain ethnic groups, especially those originating in the Mediterranean basin, the Middle East, Africa, Asia, and India. Four clinical syndromes are associated with a-thalassemia, and two syndromes are associated with ß-thalassemia. Two genes direct ß-chain production, one on each copy of chromosome 11. Over 100 different gene mutations have been identified that prevent or reduce ß-chain transcription; if one gene carries such a mutation, ß-chain production will be reduced by one half, and abnormally low quantities of Hb will be produced. This results in ß-thalassemia minor. The excess a chains combine, instead, with d chains, producing a molecule called HbA $_2$, or with ? chains, producing fetal hemoglobin (HbF). If ß-thalassemia minor is suspected because the patient has microcytic anemia without iron deficiency, Hb electrophoresis should be performed. Levels of HbA $_2$ greater than 3.5% and HbF greater than or equal to 2% confirm the diagnosis (Table 17.2). The gravid patient with ß-thalassemia minor generally tolerates pregnancy well. She should receive folic acid supplementation, but not iron supplementation unless iron deficiency is diagnosed, also.

TABLE 17.2. *Hemoglobin electrophoresis findings in various hemoglobinopathies*

Patients with mutations preventing transcription of both ß-chain genes have ß-thalassemia major (ß-thalassemia), or Cooley anemia. Erythropoiesis is ineffective because there is no ß-chain production, and the a chains precipitate, causing red blood cell destruction. Occasionally, the mutations allow some ß-chain production, resulting in a less severe reduction of Hb synthesis (ß-thalassemia). Aggressive intervention in infancy using transfusion therapy ultimately leads to iron overload and hemosiderosis, with multiple organ system dysfunction and infertility. Increasing numbers of pregnancies in this population are being reported by virtue of aggressive transfusion and iron chelation therapy. Such pregnancies can be complicated by an increased risk of cardiac arrhythmias and congestive heart failure secondary to severe anemia, chronic hypoxemia, and myocardial hemosiderosis. Folate supplementation is routine. The safety of iron-chelating agents such as deferoxamine has not been established in pregnancy. Prenatal diagnosis is available, and such pregnancies show improved outcome with stable maternal disease. An entity designated *thalassemia intermedia* has been described also, in which the clinical course is milder than with homozygous ß-thalassemia. Some individuals with this condition produce large quantities of t chains that combine with a chains to produce fetal HbF; the presence of 17% to 35% HbF defines hereditary persistence of HbF. Alternatively, these individuals may have some degree of a-thalassemia in addition to ß-thalassemia, resulting in less ß-chain precipitation and hemolysis. Patients with

thalassemia intermedia have severe hemolytic anemia but generally are not transfusion dependent. Before genetic counseling is provided to the patient with ß-thalassemia minor, MCV screening, followed by Hb electrophoresis if the MCV is low, should be offered to the father of the fetus. If the father has normal Hb, the fetus has a 50% chance to have ß-thalassemia minor and a 50% chance to have normal Hb. If the father has ß-thalassemia minor, the fetus has a 25% chance to have ß-thalassemia major, which is associated with increased morbidity and mortality, a 50% chance of thalassemia minor, and a 25% chance of having normal hemoglobin. Prenatal testing of the fetus should be offered to high-risk women; at least 20% of ß-chain mutations can be detected by chorionic villus sampling (CVS) or amniocentesis. Alpha-chain production is directed by four genes, two on each copy of chromosome 16. Mutation of only one gene results in no clinical or laboratory abnormalities and is thus referred to as the silent carrier state. Mutations in two of the four genes results in ß-thalassemia minor, a condition characterized by mild microcytic hypochromic anemia. Patients with ß-thalassemia minor have a low MCV but normal levels of HbA_2. The patient with these laboratory results should be referred for genetic evaluation and family studies to confirm the diagnosis, but typically they tolerate pregnancy fairly well. Mutation of three of the four a genes results in hemoglobin H (HbH) disease. Affected patients have some HbA and a large percentage of HbH (four ß chains). The clinical course is characterized by chronic hemolytic anemia that may worsen during pregnancy. Loss of all four ß-chain genes causes ß-thalassemia major, resulting in fetal hydrops and perinatal death. As with ß-thalassemia, testing of the father is crucial for accurate genetic counseling. Consideration of the patient's ethnic background is also important. Asians with ß-thalassemia minor usually have the two mutant genes on the same chromosome (*cis* position) and thus have a 50% risk of passing on both affected genes with each conception. In contrast, patients of other ethnic origins usually carry the mutant genes on opposite chromosomes (*trans* position), so that only one affected gene can be transmitted with each conception. All forms of ß-thalassemia can be detected by CVS or amniocentesis.

Hemoglobinopathies Hemoglobinopathies involve Hb gene mutations. Over 400 have been identified that alter polypeptide function instead of preventing production. These Hb variants generally have either reduced oxygen transport capabilities or cause hemolytic anemia. Hemoglobin S (HbS) and hemoglobin C (HbC) are the most frequent variants and can occur in association with thalassemia, as well (Table 17.3).

Hemoglobinopathy	*Frequency*
Sickle cell trait (HbSA)	1:10
Sickle cell disease (HbSS)	1:400
Hemoglobin SC disease (HbSC)	1:800
Hemoglobin S/ß-thalassemia	1:1,250
Hemoglobin C trait (HbAC)	1:35
Hemoglobin C disease (HbCC)	1:4,800

TABLE 17.3. *Frequency of sickle hemoglobinopathies in African Americans*

Sickle Disease A mutation causing a single amino acid substitution of valine for glutamic acid at position 6 on the ß chain changes normal Hb to sickle Hb. An individual who is homozygous for this mutation has sickle cell anemia, producing only HbS and a small quantity of HbF, but no HbA. Sickle Hb functions well in the oxygenated state but aggregates, forming rod-shaped polymers, in the deoxygenated state. Polymerized Hb precipitates in the red blood cell, changing the cell from a biconcave disc to an elongated crescent or sickle shape. Sickled red blood cells are not deformable and cannot squeeze through the microcirculation. Microvascular obstruction results in local hypoxia that leads to a vicious cycle of further sickling and obstruction. Localized schemia and infarction cause tissue damage. Patients with sickle cell anemia usually produce increased quantities of HbF. HbF is not distributed uniformly among all red blood cells but is present at levels of zero to 20% per cell. In cells containing HbF, restoration of normal oxygen tension may reverse the sickling and halt the destructive process. Cells containing little or no HbF become irreversibly sickled and are rapidly cleared from the system in a process leading to hemolytic anemia. Patients with homozygous HbS typically have hematocrits of 20% to 30% and reticulocyte counts of 10% to 25%. Hydroxyurea therapy has been shown to increase both the number of red blood cells containing HbF and the quantity of HbF per cell. Unfortunately, there are few data regarding the safety of hydroxyurea use in pregnancy. It is a category D drug. Any pathologic state causing acidosis, dehydration, or hypoxemia can precipitate sickling, hemolysis, vasoocclusion, and infarction. Pregnancy often is characterized by an increase in sickle crises and associated problems (e.g., pneumonia, pyelonephritis, pulmonary emboli, congestive heart failure) and by pregnancy complications such as IUGR, preterm birth, and preeclampsia. The goal of pregnancy management should be to maintain adequate hydration and oxygen delivery to the tissues, and to avoid or rapidly control infections or other stressors that could precipitate a crisis. Patients with sickle cell anemia should ingest 1 mg of folate per day to support increased erythropoiesis in the face of chronic hemolysis and should receive the polyvalent pneumococcal vaccine, because chronic splenic infarction leads to functional asplenia by adulthood. Iron supplementation should not be given prophylactically but should be prescribed if there is laboratory evidence of iron deficiency anemia. All sickle cell patients should undergo a funduscopic examination, with laser therapy as needed, because they are at increased risk for proliferative retinopathy. Asymptomatic bacteriuria (ASB) and other infections should be treated aggressively. One controversy concerns the possible benefit of antepartum prophylactic exchange transfusions. Available data indicate that although some women with sickle cell anemia may escape prophylactic transfusion because they have no associated organ damage, very few crises, and a high percentage of HbF, many will require antepartum transfusion. Even those patients who avoid transfusion during pregnancy should be transfused prior to delivery, because the stresses of labor, anesthesia, operative delivery, and any associated complications (e.g., preeclampsia, chorioamnionitis) can precipitate a serious crisis. Transfusions should be planned to achieve a hematocrit above 30% and HbA above 50%. Unless complications dictate otherwise, delivery can be at term, with cesarean section for obstetric indications only. Substitution of lysine for glutamic acid at the sixth position of the a chain results in the production of HbC. HbC is less soluble than HbA and can cause a mild hemolytic anemia, but it is more stable than HbS under hypoxic conditions. Nonpregnant women who are compound homozygotes for HbS and HbC generally have less severe anemia and fewer pain crises than women with HbSS, but under the stress of pregnancy, they experience the same maternal morbidity and pregnancy complications. Additionally, severe bone pain frequently occurs in individuals with HbSC, and acute respiratory compromise as the result of embolization of necrotic bone marrow has been reported. The antenatal management of women with HbSC should be the same as that of women with HbSS. If one ß-chain gene carries the sickle cell mutation and the other gene is functionally deleted, the patient has sickle cell ß-thalassemia. Pregnancy-related morbidity in these patients is the same as for sickle cell anemia, and they should be managed similarly. Patients with HbCC or C-ß-thalassemia have a very mild anemia and usually do not experience hemoglobinopathy-related pregnancy complications. Heterozygotes for the sickle Hb mutation have sickle cell trait. Individuals with sickle trait have red blood cells that sickle under conditions of markedly reduced oxygen tension (i.e., the sickle Dex test), but Hb electrophoresis confirms the presence of 55% to 60% HbA, in addition to 35% to 40% HbS. Sickling does not occur in vivo, except under conditions of severe stress and hypoxia. Because the renal medulla is especially sensitive to reduced oxygen tension, patients with sickle trait may have episodes of painless, self-limited hematuria. During pregnancy they exhibit an increased susceptibility to urinary tract infections. There are also reports of increased preeclampsia in these patients. Patients with sickle trait should be offered genetic counseling. The father of the fetus should be tested so that the precise risk to the fetus can be provided. Prenatal diagnosis is possible by CVS or amniocentesis. No special therapy is required generally during labor and delivery.

Congenital Hemolytic Anemias

Hereditary Spherocytosis, Elliptocytosis, and Pyropoikilocytosis Hemolytic anemia can occur for a variety of reasons. It may result from a hemoglobinopathy, may be autoimmune, drug induced, or pregnancy induced (very rarely), or may occur as the result of inherited red blood cell membrane abnormalities. Hereditary spherocytosis, elliptocytosis, and pyropoikilocytosis result from congenital defects of different red blood cell membrane proteins. All are autosomal dominant disorders occurring at an incidence of 1 in 4,000 to 5,000. All result in variant red blood cell shapes, such that affected red blood cells cannot pass readily through the spleen. While trapped in the spleen, the cell membranes are damaged, leading to red blood cell lysis, hemolytic anemia, jaundice, and splenomegaly. Splenectomy is the treatment of choice and effectively eliminates the anemia. Most women of reproductive age will already have undergone splenectomy. Although the abnormality of red blood cell shape persists, affected women tolerate pregnancy, labor, and delivery well, with few associated problems. The rare patient who has not undergone splenectomy may experience hemolytic anemia sufficient to require red blood cell transfusions. All patients should receive the polyvalent pneumococcal vaccine and should ingest a folic acid supplement throughout pregnancy. Infection should be treated aggressively, because it may cause hemolysis. The offspring of affected individuals have a 50% chance of inheriting the condition. Affected neonates may experience severe neonatal jaundice requiring exchange transfusion or splenectomy.

Glucose-6-phosphate Dehydrogenase Deficiency Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited defect of an enzyme essential to the hexose monophosphate shunt. Because of this defect, when under oxidant stress, Hb sulfhydryl groups become oxidized and Hb precipitates in the red blood cell, leading to hemolytic anemia. The gene is most prevalent among individuals of African, Asian, Mediterranean, or Middle Eastern origin. Known stressors include viruses, bacteria, toxins, fava beans, and certain drugs such as antimalarial agents, sulfa drugs, and nitrofurantoin. Over 400 different gene mutations leading to G6PD deficiency have been described; the A variant is most common and is present in 1 in 20 black men and 1 in 10 black women in the United States. Although G6PD deficiency is X linked and males are affected preferentially, women with this gene defect can be symptomatic. Some heterozygotes have markedly reduced G6PD levels because unfavorable lyonization can lead to a large proportion of cells expressing the defect, and homozygosity for G6PD deficiency can occur (in at least 1 in 400 black women). Precipitating drugs should be avoided in known carriers.

Platelet Disorders

Thrombocytopenia, defined as a platelet count less than 150,000/mm^3, occurs relatively frequently in pregnancy, complicating 7% to 8% of all pregnancies. The diagnosis of benign or essential gestational thrombocytopenia is one of exclusion, however, requiring that other pathologic forms of thrombocytopenia be ruled out. Thrombocytopenia in pregnancy can be caused by defective platelet production (bone marrow pathology such as leukemia, lymphoma, metastatic disease), sequestration (splenomegaly), or accelerated platelet destruction. Accelerated destruction occurs most commonly. Destructive processes may be nonimmunologic and unique to pregnancy (e.g., preeclampsia, placental abruption), may occur as part of sepsis or disseminated intravascular coagulation, or may result from immune dysfunction (e.g., systemic lupus erythematosus, immune thrombocytopenic purpura). These causes of thrombocytopenia are discussed elsewhere.

Thrombotic Thrombocytopenic Purpura Thrombotic thrombocytopenic purpura (TTP) is a disorder characterized by the pentad of thrombocytopenia, hemolytic anemia, fever, neurologic abnormalities, and renal failure. It is rare and of unknown etiology. TTP affects individuals of all ages, although most commonly young women. The untreated mortality rate exceeds 90%. Patients typically experience bleeding (uterine, gastrointestinal, or other) along with a mild Coombs-negative hemolytic anemia, thrombocytopenia, and mild jaundice. Hypertension and renal failure occur later in the course of the disease. All disease signs and symptoms result from microvascular damage caused by platelet thrombi, fibrin deposition, and microaneurysms in arterioles. Endothelial cell function, including prostaglandin production, is abnormal, although it is not known whether this causes TTP or results from it. Immune dysfunction may play a role. When TTP manifests in the third trimester, it may be difficult to distinguish from preeclampsia or the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). One distinguishing feature is that tests of coagulation (prothrombin time, partial thromboplastin time, fibrinogen, fibrin dimers) usually have normal results in TTP. The

advent of a fever of unknown origin or transient neurologic symptoms, as well as nonspecific complaints of arthralgias, nausea, or abdominal pain, may aid in the diagnosis of TTP. End-organ damage worsens as the disease persists. Delirium, seizures, hemiparesis, visual field defects, and coma indicate a very poor prognosis and an increased risk of mortality. Distinguishing TTP from preeclampsia in its various forms is vital, because management is dramatically different. TTP responds only to plasmapheresis or exchange transfusion, although delivery is eventually curative for preeclampsia. Steroids, heparin, splenectomy, and antiplatelet drugs have had only variable success in management of TTP. Plasmapheresis should be initiated as soon as the diagnosis is made, regardless of the clinical severity. If the patient is at or near term, magnesium sulfate therapy and delivery should also be initiated because of the possibility that the true diagnosis is preeclampsia. Cesarean delivery should be for obstetric indications only.

Hemolytic Uremic Syndrome Hemolytic uremic syndrome (HUS) is similar to TTP, with similar microangiopathy, except that the kidneys are primarily affected in HUS. The patient usually manifests hemolytic anemia, thrombocytopenia, and oliguric renal failure. Laboratory evaluation reveals a normal coagulation profile and hemoglobinuria. Most patients are hypertensive. The pathologic process usually is confined to the kidney, although some patients have mild neurologic symptoms. Postpartum renal failure is probably the same entity, except that the pregnancy has already ended. Treatment in both cases consists of dialysis and red blood cell transfusions to maintain the hematocrit above 20%. Maternal morbidity and mortality are significant, with death frequently resulting from uncontrollable hemorrhage.

Coagulation Defects

Von Willebrand Disease Von Willebrand disease is an inherited defect of von Willebrand factor (vWF), one of the proteins in the coagulation cascade. vWF is a large glycoprotein synthesized by endothelial cells and megakaryocytes and serves two functions: it is the plasma carrier for factor VIII, and it allows normal platelet aggregation at sites of endothelial injury. These two functions are directed by two different regions of the molecule, and several different mutations in both of these domains have been identified. There are three forms of von Willebrand disease. Type I (approximately 75% of cases) and type II von Willebrand disease (25%) are inherited as autosomal dominant traits. Affected individuals have one normal vWF gene in addition to the abnormal gene, and some normal vWF will, therefore, be produced. As a result, individuals with type I disease usually are mildly affected, exhibiting easy bruising or bleeding only after dental procedures. Individuals with type II disease usually experience more severe bleeding problems, such as menorrhagia or corpus luteum hemorrhage. Type III disease is autosomal recessive and extremely rare. It usually is associated with severe symptoms, because affected patients have no normal allele and thus produce no vWF. Clinical manifestations in Type III disease are similar to those associated with hemophilia. The many different known mutations and heterozygosity in the majority of cases account for the variability observed in symptoms and in laboratory test results. If the diagnosis is not made before pregnancy, it may be considered after excessive bleeding from a surgical or episiotomy site. Retrospectively, the patient may describe easy bruising or heavy menses. The pedigree is likely to include other similarly affected family members. The diagnosis is confirmed by all or some combination of the following laboratory tests: a prolonged bleeding time, decreased vWF concentration, reduced ristocetin cofactor activity, and reduced factor VIII activity. Women with von Willebrand disease usually tolerate pregnancy well, in large part because the production of all coagulation factors is increased and vWF factor levels can reach near-normal levels. Despite this, the bleeding time may still be prolonged, and treatment may be required. If the bleeding time is prolonged at term, levels of vWF must be increased so that postpartum or surgical hemorrhage can be avoided. One way to increase the vWF level is to administer desmopressin acetate (DDAVP) for 48 hours prior to planned delivery. Patients with type I disease have the best response to desmopressin; those with type III disease usually do not respond at all. Thus, a trial of the therapy should be conducted in the second trimester. Alternatively, vWF replacement can be provided. Fresh frozen plasma contains all coagulation factors in equal proportions, cryoprecipitate contains factor VIII, vWF, and fibrinogen, and lyophilized factor VIII contains only that protein. For patients with von Willebrand disease, the recommended therapy is 15 to 20 U of cryoprecipitate given twice daily just prior to delivery and for 2 to 3 days afterward. Factor VIII concentrate can be administered instead. Effective treatment should normalize the bleeding time. Women with type I or type II von Willebrand disease have a 50% risk of having an affected child; those with type III disease have minimal risk, unless they are related to their spouses. Prenatal diagnosis is possible but, unless termination is a consideration, is unlikely to affect labor and delivery management, because affected neonates experience minimal bleeding difficulties.

Hemophilias A and B Hemophilias A and B result from X-linked deficiencies of two different coagulation proteins. Female carriers of hemophilia A have a mutation in one factor VIII gene, while carriers of hemophilia B have a mutation in one gene for factor IX; levels of these factors are thus reduced by one half or more. These decreased factor levels are adequate for normal hemostasis, and carrier women usually are clinically unaffected. In rare circumstances, a woman may exhibit all the classic features of hemophilia (i.e., if she is homozygous for the mutation or if she is a carrier and has unfavorable lyonization leading to preferential expression of the X chromosome carrying the mutation); such patients benefit from factor replacement. Carrier mothers should be offered genetic counseling. One half of their daughters will be carriers, and one half of their sons will have hemophilia. Prenatal diagnosis is available. Knowledge of fetal hemophilia status allows consideration of pregnancy termination. In ongoing pregnancies, knowledge that a male fetus carries a hemophilia gene allows the obstetrician to plan to avoid placing a scalp electrode during labor and to avoid vacuum-assisted or forceps-assisted vaginal delivery. Cesarean delivery should be for obstetric indications only, because atraumatic spontaneous vaginal delivery does not entail additional risk for the affected fetus.

GASTROINTESTINAL DISEASE

Nausea and Vomiting

Mild and self-limited nausea and vomiting in the first trimester of pregnancy occur in 60% to 80% of women. Chronic nausea and vomiting, or hyperemesis gravidarum, complicates 1 in 200 to 300 pregnancies. This disorder is characterized by dehydration, electrolyte imbalance, and nutrition depletion and prompts medical intervention.

The etiology of hyperemesis is unclear. Theories have suggested the influence of human chorionic gonadotropin, the pituitary–adrenal axis, transient hyperthyroidism, and psychogenic factors. Regardless of the cause, intervention is appropriate, ranging from intravenous hydration and antiemetic medications (e.g., droperidol, metoclopramide, and prochlorperazine) to nasogastric enteral feeding and hyperalimentation. Pregnancies complicated by mild or severe hyperemesis are not at increased risk for growth abnormalities, congenital anomalies, or prematurity (Table 17.4).

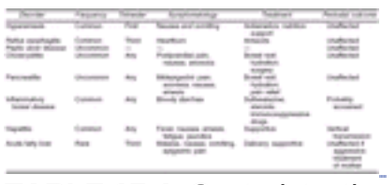

TABLE 17.4. *Gastrointestinal disease in pregnancy*

Gastrointestinal Reflux Disease

One half of all pregnant women complain of gastroesophageal reflux disease (GERD), commonly known as heartburn, sometime during pregnancy and particularly in the third trimester. Complaints include burning substernal discomfort with or without radiation, dysphagia exacerbated by meals, and increased intraabdominal pressure, all worsening in the recumbent position. The differential diagnosis includes angina, achalasia, and structural or functional causes of dysphagia.

Risk factors for gestational GERD include heartburn prior to or in previous pregnancies, multiparity, and advanced gestational age. There is no association between GERD and race, prepregnancy weight, or weight gain during pregnancy. Treatment options are similar to treatment of the nonpregnant population, depend on the severity of symptoms, and are initiated sequentially beginning with lifestyle modifications and antacids. In severe refractory cases, cimetidine and metoclopramide are appropriate therapeutic interventions.

Peptic Ulcer Disease

Gastric secretion and motility are reduced and mucus secretion is increased during gestation. As a result, peptic ulcer disease (PUD) is uncommon in pregnancy, and its complications, such as hemorrhage and perforation, quite rare. Patients with PUD often experience considerable improvement, if not remission, of disease in pregnancy. However, PUD recurs in most women within 2 years of delivery.

Upper Gastrointestinal Bleeding

Hyperemesis can be accompanied by gastrointestinal bleeding. Although gastrointestinal bleeding prompts a concern for PUD with hemorrhage, most pregnant women with hematemesis will prove to have Mallory-Weiss tears. These small, linear mucosal tears near the gastroesophageal junction respond to iced saline lavage, antacids, and intravenous cimetidine. Endoscopy can be performed during pregnancy and will detect esophageal rupture with bleeding (Boerhaave syndrome), a much more serious diagnosis for which surgery and gastroenterology consultations are appropriate.

Cholelithiasis and Biliary Disease

Studies using serial ultrasonographic examinations over the course of pregnancy confirm that the risk of gallstones is increased, to an incidence of 2% to 10%, because pregnancy is characterized by decreased gallbladder motility and increased biliary sludge. Many women with cholelithiasis are relatively asymptomatic during pregnancy and require no intervention. However, acute cholecystitis complicates about 1 in 1,000 to 1,600 gestations. It is heralded by postprandial pain in the right upper quadrant or epigastric area, with radiation to the back or shoulder. This type of pain, with anorexia, nausea, emesis, low-grade fever, and leukocytosis, suggests stone obstruction of a duct. Ultrasonographic examination is very helpful, detecting approximately 95% of stones.

Management is the same as in a nonpregnant individual. Three fourths of patients with acute cholecystitis will respond to medical therapy consisting of bowel rest, nasogastric suction, intravenous hydration, antibiotics, and analgesics. The remainder will require surgical intervention for persistent pain, empyema, gangrene, or perforation. Open laparoscopic cholecystectomy during pregnancy is becoming more widely accepted. Although the second trimester is considered optimal for any surgical procedure, delay in treatment should be avoided regardless of gestational age.

Pancreatitis

Pancreatitis occurs with an incidence of 1 in 1,500 to 4,000 during pregnancy, with the majority of cases due to cholelithiasis. Other far less common etiologies include ethanol abuse, certain medications, trauma, and hypertriglyceridemia. Symptoms include midepigastric pain with back radiation, anorexia, nausea, and emesis. In normal pregnancy, serum amylase and lipase levels tend to increase only slightly with advancing gestation. The upper limits of normal for amylase and lipase in the first two trimesters are 100 U/dL and 200 U/dL, respectively. Significant elevations of these enzymes are, therefore, consistent with pancreatitis, although the degree of elevation does not correlate with disease severity. As in the nonpregnant population, pancreatitis is managed by bowel rest, nasogastric suction, analgesia, and intravenous hydration.

In most patients, inflammation subsides within 2 to 7 days. In the minority, abscess or pseudocyst formation prompts abdominal exploration. In this population, perinatal morbidity ranges from 5% to 15%, and perinatal mortality can be as high as 38%, most likely resulting from accompanying hypovolemia, hypoxia, and acidosis.

Inflammatory Bowel Disease

The term *inflammatory bowel disease (IBD)* refers to two forms of intestinal inflammation, namely, Crohn disease and ulcerative colitis. These diseases share many features but usually can be differentiated. IBDs are genetic diseases with complex nonmendelian patterns of inheritance. The greatest risk factor for IBD is a family history of IBD. When both parents have IBD, the risk to the offspring is as high as 36% and is unaffected by disease activity in either parent at the time of conception. Figures for healthy offspring, congenital abnormalities, spontaneous abortions, and fetal demise are the same in pregnancies complicated by IBD as in the control population. Some report an increased risk of low birth weight in patients with Crohn disease, particularly if there is ileal disease, a history of bowel resection, or current tobacco abuse.

Ulcerative Colitis Ulcerative colitis is a mucosal disease, almost always involves the rectum, and extends proximally and continuously for a variable distance. Symptoms include diarrhea, often with bleeding, and some degree of abdominal pain. Affected individuals may also have arthritis, uveitis, or erythema nodosum. Colon cancer occurs in 1% per year. The clinical course is one of exacerbations and remissions. The most serious complication is toxic megacolon, which can necessitate an emergency colectomy. Medical management includes sulfasalazine, 5-aminosalicylic acid, and prednisone. If ulcerative colitis is quiescent at the time of conception, only one third to one half of patients will experience reactivation, often in the first trimester. Active disease at the time of conception has a worse prognosis. When the disease is active, aggressive medical management, including parenteral nutrition, is essential.
Crohn Disease Crohn disease is a transmural granulomatous inflammatory process, which involves the rectum about 50% of the time. It may involve any part of the gastrointestinal tract but most often involves the terminal ileum and colon. “Skip” areas are common. Diarrhea and hematochezia can occur, and abdominal pain is almost always a problem. Nutritional deficiencies are more common than with ulcerative colitis. Complications include toxic megacolon and fistula formation, which is problematic for vaginal delivery if the perineum is involved. Eighteen percent of patients develop de novo perineal involvement after vaginal delivery, most often if an episiotomy was performed. As in ulcerative colitis, the patient may also have arthritis, and the risk of cancer is increased. Cancer risk correlates with the extent of mucosal pathology (pancolitis confers the highest risk) and the duration of the disease. In patients with long-standing disease, the risk exceeds 1% per year. Quiescent disease at conception carries a good prognosis. Prednisone, sulfasalazine, and immunosuppressant drugs help control disease activity. Surgery is necessary in about 5% of such pregnant patients.

Hepatitis

Acute viral hepatitis in pregnancy is a systemic illness with fever, nausea, emesis, and fatigue. Jaundice is common initially, and liver function tests are elevated markedly. With the exception of hepatitis E viral (HEV) infection, viral hepatitides do not occur more frequently or with greater severity in pregnancy. HEV infection is more dangerous in a pregnant patient, with a mortality of 15% to 20%. It is transmitted by the fecal-oral route and occurs most frequently in countries with poor sanitation (e.g., the Middle East, Africa, and India). Infection in the third trimester often is associated with fulminant hepatitis, as well as preterm delivery, and neonatal and maternal death.

Hepatitis A Hepatitis A virus (HAV) is an RNA virus, with fecal-oral transmission and an incubation period of 15 to 50 days. This highly contagious disease is self-limited, with resolution over 2 to 3 weeks. Acute HAV infection is confirmed by a positive anti-HAV immunoglobulin M (IgM) antibody test. There are no chronic sequelae, and HAV does not cross the placenta. A single dose of hepatitis immune globulin is recommended as soon as possible after exposure. If the exposed pregnant patient becomes infected, close contacts, including the neonate, should be offered passive immunotherapy.
Hepatitis B Hepatitis B virus (HBV) is a double-stranded DNA virus with worldwide distribution, transmitted by parenteral and sexual contact. Risk factors include multiple sexual partners, intravenous drug abuse, and receipt of blood products. Its incubation period is 40 to 100 days, and it can be recovered from all body fluids, most importantly, blood, breast milk, and amniotic fluid. HBV surface antigen (HBsAg) and anti-HBc IgM antibody are seen in the early clinical phase of infection, before icteric changes or elevations in liver function tests. They indicate infectivity (Fig. 17.3). The presence of HBe antigen (HBeAg) denotes active viral replication. Although HBeAg usually indicates acute infection, its persistence correlates both with the chronic carrier state and with the ultimate development of hepatocellular carcinoma. The risk of maternal–fetal transmission increases dramatically to 90% when acute infection occurs in the third trimester or in the presence of both HBsAg and HBeAg positivity, and is a consequence of intrapartum exposure to blood and genital secretions. If the mother develops HBV infection remote from delivery and has developed anti-HB antibodies, the risk of fetal or neonatal infection is considerably less. The neonate's risk of active or chronic disease is reduced significantly by HB immune globulin and the HBV vaccine; these should be given at delivery. Breast-feeding does not increase the risk of infection in these infants. The absence of HBsAg excludes active or chronic infection, and there is no risk for neonatal transmission. In the at-risk patient who is HBsAg negative and antibody negative, vaccination should be offered, because it is not contraindicated in pregnancy.

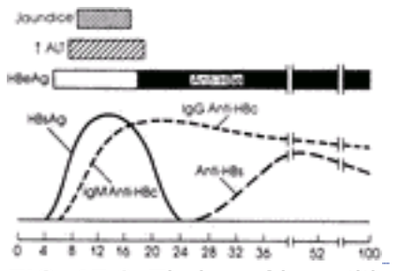

FIG. 17.3. Timing of hepatitis B antigen and antibody production in acute hepatitis B infection. (From Dienstag JL, Isselbacher KJ. Acute hepatitis. In: Isselbacher KJ, Braunwald E, Wilson JD, et al., eds. *Harrison's principles of internal medicine*, 13th ed. New York: McGraw-Hill, 1994:1458, with permission.)

Hepatitis C Hepatitis C virus (HCV) is the agent primarily responsible for non-A, non-B (posttransfusion) hepatitis. HCV is a single-stranded RNA virus. Principal risk factors for HCV transmission are blood product transfusion and intravenous drug use. Acute HCV infection follows an incubation period of 3 to 60 days, and only 25% of infected patients will be symptomatic. The presence of HCV antibody indicates chronic infection and does not confer immunity; approximately one half of those infected develop chronic liver disease. No specific therapy has been shown to be efficacious in decreasing the morbidity of the disease. Coinfection with HCV and human immunodeficiency virus (HIV) is thought to accelerate the progression of hepatic injury. Seroprevalence studies in pregnant patients in the United States indicate an incidence of HCV of 2% to 4%. Vertical transmission is proportional to the maternal HCV RNA titer, and approximately 8% of patients transmit the disease to their offspring. Coinfection with HIV is associated with an increased rate of perinatal transmission to 23% to 44%. Breast-feeding in the HCV-positive patient is not contraindicated by virtue of the 4% transmission rate in breast and bottle-fed infants.
Hepatitis D Hepatitis D virus (HDV) is an RNA virus that is dependent on coinfection with HBV for replication. HDV is acquired as a coinfection with HBV or as a superinfection in a chronic HBV carrier. Coinfection rarely leads to chronic disease, whereas superinfection is associated with an 80% likelihood of chronic hepatitis. Perinatal transmission of HDV can be prevented by the immunoprophylaxis used for HBV.

Pregnancy Following Liver Transplantation

Following liver transplantation, most authorities recommend that pregnancy be avoided for at least 12 months, so that graft viability can be assessed and immunosuppression can be achieved and maintained with the lowest possible medication dosages. Thirty-eight percent of liver transplant patients are hypertensive; pregnancy does not increase this incidence or hasten graft rejection. The incidence of spontaneous abortion is similar to that of the general pregnant population, and the incidence of preeclampsia is 13.5%. Anemia complicates 31% of pregnancies in liver transplant patients, and rejection develops or worsens in 9%. Fifty-eight percent deliver at term, and the majority deliver appropriately-grown babies vaginally.

Acute Fatty Liver

Acute fatty liver of pregnancy (AFLP) has an incidence of 1 in 13,000 deliveries. AFLP accounts for a large percentage of severe liver disease in pregnancy and is accompanied by a mortality of up to 25%. Primiparity, male fetal sex, and multiple gestation appear to confer a higher risk. The etiology is unknown, and liver biopsy reveals microvesicular fatty infiltrates.

Symptoms typically appear in the late third trimester and include malaise, persistent nausea, and vomiting. Right upper quadrant or epigastric pain is noted in 50% to 80%. Laboratory abnormalities include elevated liver function tests, increased ammonia and uric acid levels, hemolysis, hypoglycemia, and coagulopathy. Early recognition is essential; if untreated, AFLP progresses to multiorgan system failure and death. Once it is diagnosed, intensive supportive care is provided, and delivery is necessarily accomplished. Under these circumstances, maternal and fetal mortality are less than 20%. Survivors have no long-term sequelae, and recurrence in subsequent pregnancies is a rarity.

CARDIOVASCULAR DISEASE

Physiologic Changes in Pregnancy

Normal pregnancy entails many physiologic changes that can stress the cardiovascular system. Plasma volume increases are measurable by 6 to 8 weeks gestation and 45% greater by 30 to 34 weeks. Red blood cell volume increases about 25%, resulting in a physiologic anemia. Cardiac output increases by 30% to 50% during the first half of pregnancy (as the result of an increase in both stroke volume and heart rate), by a further 30% during active labor, and by 45% during pushing. Systemic vascular resistance decreases during pregnancy, with both systolic and diastolic blood pressures falling during the second trimester and then returning to prepregnancy values in the third trimester. During labor, each uterine contraction results in an autotransfusion of 300 to 500 mL of blood. Cardiac output during this time is influenced by maternal vascular volume, maternal position, pain, and the method of pain relief (epidural anesthesia, spinal anesthesia, or intravenous narcotics). Cardiac output rapidly increases at delivery as the result of autotransfusion and relief of caval compression by the involuting uterus.

Women with cardiovascular disease may tolerate these physiologic changes poorly. Knowledge of the pregnancy-associated risks and complications associated with each type of heart disease allows the physician to choose management that optimizes the chances for a good pregnancy outcome. For each patient, the prepregnancy cardiovascular status should be established and used as a reference in assessing any pregnancy-related cardiac changes. The New York Heart Association (NYHA) classification scheme is useful for quantifying symptomatology:

- Class I: patients are asymptomatic in all situations.
- Class II: patients are symptomatic with greater-than-normal exertion.
- Class III: patients are symptomatic with normal activities.
- Class IV: patients are symptomatic at rest.

Although useful for categorizing symptoms, this classification scheme does not necessarily predict pregnancy outcome. In one large retrospective study, for example, the majority of cases of pulmonary edema and maternal death occurred in women who were functional class I or class II. However, this scheme can be used to assess changes in cardiac function. Any change in cardiac classification during the pregnancy, even if only from class I to class II, can be ominous and should prompt a thorough evaluation and aggressive management. Bed rest or hospitalization often is required.

Rheumatic Heart Disease Approximately 4% of reproductive-age women have heart disease. Although this number has remained fairly constant, the relative incidence of the various forms of heart disease has changed dramatically during the last few decades. During most of the 20th century, the majority of heart disease resulted from rheumatic fever (group A ß-hemolytic *Streptococcus*); the ratio of rheumatic heart disease to congenital heart disease was 20 to 1. During the last few decades, however, the prevalence of rheumatic heart disease has decreased significantly, while the number of adult survivors with congenital heart disease has increased; the ratio is now 3 to 1 or less. Nevertheless, rheumatic valvular disorders still account for a substantial proportion of heart disease in reproductive-age women.

Mitral Stenosis Mitral stenosis is the most common form of rheumatic heart disease in women. Rheumatic fever typically occurs at ages 6 to 15 years. If myocarditis is present, mitral insufficiency will develop, followed in approximately 5 years by mitral stenosis. Symptoms usually do not begin for another 15 years after that, with severe complications such as right-sided heart failure occurring in another 5 to 10 years. The mean age for the initiation of symptoms is thus 31, with incapacity occurring at age 38 if the condition is not treated. Initial symptoms include fatigue and dyspnea on exertion, which progress to dyspnea at rest and hemoptysis. Atrial arrhythmias, infection, or pulmonary embolism can lead to heart failure. The stenotic mitral valve impairs left ventricular filling and thus limits any increase in cardiac output. Pregnancy-mediated cardiovascular changes, especially increased intravascular volume and increased heart rate, can exacerbate the impaired filling and lead to decompensation during pregnancy and especially during labor, delivery, and the puerperium. Left atrial volume and pressure increase, pulmonary venous pressure increases and, eventually, features of pulmonary hypertension and right ventricular hypertrophy and failure can develop. The goals of management are to optimize cardiac output by preventing rapid ventricular rates and avoiding decreases in systemic vascular resistance, and to reduce stress on the right ventricle by minimizing increases in blood volume and avoiding situations in which pulmonary artery pressure is increased (i.e., hypercarbia, hypoxia, or acidosis). Two serious complications associated with mitral stenosis are atrial fibrillation and pulmonary edema. Both have been associated with maternal death. During pregnancy, tachyarrhythmias should be treated, because a rapid heart rate prevents adequate ventricular filling and decreases cardiac output. Beta blockers should be considered for the patient with a heart rate above 90 beats per minute. Digoxin and heparin may be required for the patient with atrial fibrillation. Rarely, surgery becomes necessary during the pregnancy, including balloon valvuloplasty and surgical commissurotomy. During labor, bedside cardiac monitoring is routine; central hemodynamic monitoring is routine if the patient is in NYHA class III to IV or the valve diameter is less than 2.5 cm^2. Pain must be managed effectively. Epidural anesthesia can be used if care is taken not to overload the patient with fluid beforehand and not to decrease systemic vascular resistance during the infusion. Fluid management must be meticulous, with extra attention given to the patient during the immediate postpartum period, when autotransfusion rapidly increases the central blood volume. Pulmonary function must be followed closely for pulmonary edema. A pulmonary artery catheter may assist in the management of patients with severe disease. Because the pulmonary capillary wedge pressure (PCWP) may not accurately reflect left ventricular filling pressure in severe mitral stenosis, the PCWP should be maintained in the high-normal to elevated range. If general anesthesia becomes necessary, agents that produce tachycardia (e.g., atropine, meperidine, ketamine) should be avoided. The high-risk period for severe decompensation continues for 24 to 48 hours postpartum. Although the American Heart Association recommends antibiotic prophylaxis only for women who have a vaginal delivery in the presence of an infection or who undergo urethral catheterization, many clinicians provide prophylaxis to all cardiac patients. Subacute bacterial endocarditis (SBE) prophylaxis usually includes ampicillin 2 g and gentamicin 1.5 mg/kg intravenously, 30 minutes before delivery, and ampicillin 1 g intravenously or amoxicillin 1 g orally 6 hours after delivery. Penicillin-allergic patients should receive vancomycin 1 g before delivery and again 8 hours later, instead of ampicillin.

Mitral Insufficiency Mitral insufficiency results in regurgitation of blood from the left ventricle back into the left atrium, with resulting left atrial enlargement. Most patients tolerate mitral insufficiency well and remain asymptomatic for 30 to 40 years. However, because pulmonary edema or embolism, atrial tachycardia, and infective endocarditis can occur during pregnancy, patients with mitral insufficiency should be monitored closely. Anything that stresses or impairs the function of the left ventricle should be avoided. Increases in systemic vascular resistance, atrial fibrillation, bradycardia, or myocardial depressants can all result in left ventricular decompensation. During labor, pain should be treated effectively and fluid management calculated to maintain left ventricular volume without increasing it. Epidural anesthesia can be very effective, as long as preprocedure hydration is conducted cautiously. SBE prophylaxis should be given. Occasionally, surgical valve replacement is necessary during pregnancy.

Aortic Insufficiency Aortic insufficiency (AI) usually occurs 7 to 10 years after an episode of rheumatic fever myocarditis and the patient remains asymptomatic for another 7 to 10 years. The regurgitant valve causes a chronic increase in left ventricle volume, eventually leading to increased compliance, increased end-diastolic pressure, and pulmonary congestion and edema. Most pregnant women with AI are relatively asymptomatic. This is, in part, because the decreased systemic vascular resistance and increased heart rate typical of pregnancy tend to increase forward flow through the insufficient valve. However, cardiovascular changes occurring during labor and delivery can lead to decompensation, especially if intravascular volume is increased markedly or systemic vascular resistance is increased by pain or other stressors. Epidural anesthesia is ideal for such patients, because it eliminates pain and decreases systemic vascular resistance. However, care must be taken not to reduce diastolic blood pressure or provoke a bradycardic episode, because left ventricular output will decrease as a result. Myocardial depressants should be avoided, and fluids must be managed carefully to maintain adequate volume but not overload the left side of the heart. Frequent pulmonary examinations to rule out pulmonary congestion may be helpful. SBE prophylaxis should be given.

Aortic Stenosis Aortic stenosis (AS) resulting from rheumatic fever rarely complicates pregnancy, because the time lag between the rheumatic fever episode and the occurrence of stenosis is usually 35 to 40 years. However, AS can occur in reproductive-age women, and those who are symptomatic (e.g., angina, syncope,

shortness of breath) have a risk of sudden death out of proportion to the severity of their symptoms; left ventricular failure and infective endocarditis are other serious complications. The normal cross-sectional area of the aortic valve is 2.6 to 3.5 cm^2; an orifice less than 2.6 cm^2 usually is heralded by a loud systolic murmur, while an orifice less than 1 cm^2 produces symptoms of dyspnea, chest pain, and syncope. AS results in a relatively fixed stroke volume that is dependent on both adequate diastolic filling and heart rate. Although some increase in heart rate helps to maintain an adequate cardiac output, tachycardia greater than 140 beats per minute, bradycardia, and decreased systemic vascular resistance are poorly tolerated. For these reasons, epidural anesthesia may be a poor choice for pain relief during labor, and the patient could instead be managed with parenteral narcotics and pudendal block. Fluid management must be meticulous, taking care to maintain an adequate intravascular and thus end-diastolic volume. A pulmonary artery catheter may be very helpful in directing fluid management. Because hypovolemia is a far greater threat to this patient than is pulmonary edema, the pulmonary artery wedge pressure should be maintained in the range of 14 to 16 mm Hg to provide a margin of safety against unexpected peripartum blood loss.

Congenital Heart Disease Congenital heart disease accounts for the majority of all heart disease in reproductive-age women. Many women now reach adulthood without surgical correction of their lesions, while for others, early surgery has been lifesaving. Women who have undergone surgical correction, have normal hemodynamics, and are completely asymptomatic generally tolerate pregnancy, labor, and delivery well without special considerations. Women with uncorrected lesions, however, require special management. The most common uncorrected heart abnormalities seen in pregnancy are atrial septal defect (ASD), patent ductus arteriosus (PDA), ventricular septal defect (VSD), pulmonic stenosis, congenital AS, coarctation of the aorta, and tetralogy of Fallot. Both maternal and fetal outcomes depend on the nature of the cardiac lesion, the patient's functional capacity, the history of surgical repair (if any), and the presence or absence of pulmonary hypertension or cyanosis. In the presence of cyanosis, there is an increased risk of functional deterioration, congestive heart failure, maternal mortality, IUGR, preterm birth, miscarriage, and stillbirth. In one series, only 55% of pregnancies in cyanotic mothers resulted in a live birth. A woman with congenital heart disease should receive genetic counseling regarding the etiology of the lesion and risks to her fetus. Isolated congenital heart malformations are considered multifactorial in origin and, thus, have a general recurrence risk of 3% in first-degree relatives. However, a more precise recurrence risk can be provided if the heart defect is categorized according to the aspect of cardiac development that went awry: Cell migration abnormalities, defective cell death, extracellular matrix abnormalities, targeted growth defects, and blood flow-related lesions. However, only flow-related heart defects have a significant risk of recurrence of approximately 11% to 13.5%. Many structural cardiac defects can be identified by second-trimester ultrasonographic examination or fetal echocardiogram.

Mitral Valve Prolapse Mitral valve prolapse (MVP) is the most common congenital valvular lesion, with an incidence of 5% to 10% in the general population. The majority of patients with MVP are asymptomatic and tolerate pregnancy, labor, and delivery well. Occasionally, arrhythmias occur. Although the patient's cardiovascular status should be monitored closely, usually no special therapy is required other than SBE prophylaxis.

Left-to-right Intracardiac Shunts Left-to-right intracardiac shunts can result from ASDs, VSDs, or PDAs. Small shunts often are well tolerated for many years. If there is no pulmonary hypertension and the patient is asymptomatic, pregnancy does not impose significant increased risk and may actually improve cardiac hemodynamics, because the decreased systemic vascular resistance encourages forward flow. Increased systemic vascular resistance or increased maternal heart rate may increase the shunt and should be avoided; epidural anesthesia for labor and delivery can be very helpful. Patients with ASDs are at increased risk of developing supraventricular dysrhythmias that should be controlled with medication. If, however, the shunt is substantial, resulting in many years of increased pulmonary blood flow, pulmonary hypertension and right heart failure can develop, and the shunt reverses. The combination of pulmonary hypertension and right-to-left shunt through any communication between the systemic and pulmonary circulation is known as Eisenmenger syndrome. This condition is life threatening in the pregnant patient, with a maternal mortality of 40% to 60%. Death is due to congestive heart failure and thromboembolic phenomena. The outcome for the fetus is also exceptionally poor, with a perinatal mortality exceeding 28% and a 55% incidence of preterm birth. Women with Eisenmenger syndrome should be strongly discouraged from becoming pregnant or carrying a pregnancy. Management of the gravid patient with this condition includes hospitalization, oxygen therapy, prophylactic anticoagulation, and treatment of heart failure with digoxin and diuretics. Delivery usually requires pulmonary artery catheterization, intrathecal morphine provides excellent analgesia without significant motor or autonomic effects, and shortening of the second stage of labor with forceps delivery is common. SBE prophylaxis is routine and many consider minidose heparinization postpartum.

Tetralogy of Fallot Right-to-left shunting is seen also in tetralogy of Fallot. This term describes the combination of VSD, right ventricular outflow tract obstruction, right ventricular hypertrophy, and overriding aorta. The amount of right-to-left shunting is determined by both the size of the VSD and the degree of right ventricular outflow tract obstruction. Uncorrected tetralogy of Fallot is a cyanotic condition characterized by decreased arterial oxygen saturation and polycythemia. Pregnancy can cause further decompensation, because the decreased systemic vascular resistance increases the right-to-left shunt; shunting is increased also by a rise in the pulmonary vascular resistance resulting from the stress of labor. With uncorrected tetralogy of Fallot, 40% of women develop heart failure during pregnancy, and 12% die; the fetal mortality rate is 36%. Pregnancy is discouraged in those with uncorrected tetralogy. Poor prognosis is associated with several factors, including a prepregnancy hematocrit of over 65%, a history of syncope or congestive heart failure, electrocardiographic evidence of right ventricular strain, and a peripheral oxygen saturation of less than 80%. Pregnancy management includes bed rest, oxygen therapy, and isotopic support as necessary. Because any decrease in systemic vascular resistance can be life threatening, epidural or spinal anesthesia should be avoided. Intravenous medication and pudendal block can be used, and the second stage of labor should be shortened.

Congenital Aortic Stenosis Congenital AS accounts for 5% of all congenital heart disease, with bicuspid aortic valve being the most common malformation. Many patients with bicuspid aortic valve are completely asymptomatic and tolerate pregnancy, labor, and delivery well. For those who are symptomatic, management considerations are the same as for AS resulting from rheumatic heart disease.

Coarctation of the Aorta Coarctation of the aorta rarely complicates pregnancy because most affected women undergo surgical correction as children. During pregnancy, patients with uncorrected coarctation face an increased risk of aortic dissection and rupture, and thus an increased risk of maternal (up to 9%) and fetal (20%) death, as well as bacterial endocarditis and cerebral hemorrhage (associated with intracranial aneurysms). Because the coarctation results in a fixed stroke volume, management is similar to that for AS.

Pulmonic Stenosis Pulmonic stenosis can be either valvular, which usually does not progress until late in life, or subvalvular, which can become steadily worse during the reproductive years. The right ventricle becomes hypertrophic to maintain output but eventually decompensates, leading to left ventricular failure, as well. Right ventricular output is dependent on preload and heart rate, and systemic vascular resistance typically increases to compensate for any reduction in left ventricular output. During labor and delivery, fluids must be managed carefully so that preload is neither increased nor decreased, and bradycardia must be avoided. Because increased systemic vascular resistance is an important compensatory mechanism, epidural or spinal anesthesia should be used very cautiously, if at all.

Other Cardiac Abnormalities

Primary Pulmonary Hypertension Primary pulmonary hypertension leads to right ventricular hypertrophy and eventually to right ventricular and then left ventricular failure. Pregnancy exacerbates this condition, resulting in a maternal mortality rate as high as 50%. Management is similar to that for Eisenmenger syndrome.

Hypertrophic Cardiomyopathy and Asymmetric Septal Hypertrophy Hypertrophic cardiomyopathy and asymmetric septal hypertrophy are relatively well tolerated in pregnancy. The increased intravascular volume of pregnancy tends to distend the left ventricle and reduce the degree of outflow obstruction. However, decreased systemic vascular resistance may increase the left ventricular ejection force and thus increase outflow obstruction. Management goals include avoiding significant increases or decreases in intravascular volume, avoiding tachycardia, avoiding any decrease in systemic vascular resistance, and avoiding anything that increases myocardial contractility. Pain relief during labor can best be provided with intravenous medication or pudendal block or both.

Peripartum Cardiomyopathy Peripartum cardiomyopathy is a global congestive heart failure characterized by dilation of all four chambers of the heart, low cardiac output, and pulmonary edema. Arrhythmias may develop, along with pulmonary or systemic embolism. By definition, peripartum cardiomyopathy arises in the last month of pregnancy or in the first 5 months postpartum, and there is no other discernible etiology. The patient may complain of orthopnea, dyspnea, edema, weakness, and palpitations. The chest radiograph, echocardiogram, and electrocardiogram (ECG) are all consistent with cardiomegaly. The left ventricle and left atrium are enlarged, the ejection fraction is markedly reduced, and pulmonary congestion is often present. Up to 50% show evidence of pulmonary or systemic embolic phenomena. Management consists of aggressive treatment of heart failure with digitalis, diuretics, and vasodilators as necessary, strict bed rest, and full anticoagulation. The prognosis is poor. If heart size and function do not return to normal within 6 months, the mortality rate is high (up to 85% in some series), and survivors often are left with a dilated cardiomyopathy that imposes significant morbidity. A proportion of patients experience a complete normalization of heart size and function within 6 months of the onset of disease and then remain at NYHA cardiac functional class I or II status. These patients should be counseled that the risk of recurrence of cardiomyopathy in future pregnancies approaches 50% and that complete recovery from a second episode cannot be assured.

Myocardial Infarction The risk of myocardial infarction (MI) in a reproductive-age woman is low (1 in 10,000). Contributing factors include atherosclerosis, thrombosis, and vasospastic disease. The risk of death is highest at the time of the MI and is gestational-age dependent; maternal morality is approximately 23% in the first and second trimesters but 50% in the third. The risk of death is also high if delivery occurs within 2 weeks of the infarction. In the event of a cardiac arrest in a pregnant patient, cardiopulmonary resuscitation (CPR) should be administered. Uterine displacement toward the left, maintenance of PaO_2 greater than 70 mm Hg, cardioversion (having removed all metal monitoring devices from mother and fetus), and consideration of a cesarean section to increase the effectiveness of resuscitative efforts are appropriate. Management of a pregnant woman with an MI includes bed rest to minimize cardiac workload and myocardial oxygen consumption. Nitrates, aspirin, ß blockers, and calcium channel blockers have been used successfully. Epidural anesthesia should be provided during labor and delivery, along with supplemental oxygen and left lateral tilt position. Troponin should be used to document an MI, because myoglobin, creatine kinase, and creatine kinase myocardial bands are increased two-fold after delivery. Patients should be advised not to become pregnant for at least 1 year after an MI, and then only if normal ventricular function is confirmed by echocardiography, coronary angiography, or radionuclide studies.

Thromboembolic Disease

Venous thromboembolism occurs in 1 in 1,000 to 2,000 pregnancies and is a leading cause of maternal mortality in the United States. Venous stasis, which is aggravated by uterine compression of the pelvic veins, is a major predisposing factor. Levels of coagulation proteins are also altered unfavorably in pregnancy. Factors II, VII, and X and fibrin increase, levels of protein S decrease, and the fibrinolytic system is inhibited. Years ago, when postpartum ambulation was discouraged, the majority of thromboses occurred after delivery. Now, however, 50% or more of all thromboses occur during the antepartum period, making diagnosis and therapy a

challenge.

Superficial Thrombophlebitis Superficial thrombophlebitis involves only the superficial saphenous veins and is a relatively benign condition, often associated with varicosities. It is treated symptomatically with analgesia, rest, and elastic support.
Deep Venous Thrombosis Deep venous thrombosis (DVT) is a pathologic condition that can be life threatening, with an absolute risk of symptomatic DVT during pregnancy of 0.5 to 3.0 per 1,000 women. It occurs most commonly in the iliofemoral region or in the veins of the calf and is characterized by edema and lower extremity aching and limb discoloration. Most DVT in pregnancy occurs on the left side, can complicate an otherwise unremarkable pregnancy, with diagnosis requiring a search for predisposing factors and a high index of suspicion. Most DVTs can be accurately diagnosed noninvasively. Impedance plethysmography is both highly sensitive and specific for identifying obstruction of the proximal veins (iliac, femoral, and popliteal). Likewise, real-time sonography and duplex Doppler sonography reliably detect proximal vein thrombosis, although they may fail to identify calf vein obstruction. During any examination after the late second trimester, the uterus should be displaced off the vena cava to prevent lower extremity engorgement leading to false-positive results. If ultrasonography is performed properly, however, a positive result after any of these three tests should be considered confirmatory and sufficient to warrant the initiation of therapy. If these studies are equivocal or negative and suspicion is high, venography can be performed and findings are considered highly accurate. The amount of fetal radiation exposure associated with unilateral venography without an abdominal shield is 0.3 rad (0.003 Gy); a limited venogram requires less than 0.05 rad (0.0005 Gy).
Pulmonary Thromboembolism Pulmonary thromboembolism (PTE) is characterized by dyspnea, tachypnea, tachycardia, pleuritic chest pain, cough, and anxiety. In pregnancy, PTE usually is caused by emboli from a DVT and appears to occur more frequently in the postpartum period. Arterial blood gases confirm hypoxemia and hypocapnia, the ECG shows tachycardia with right heart strain, and the chest radiograph reveals subsegmental atelectasis. If there is a strong clinical suspicion of PTE, intravenous heparin therapy should be initiated immediately. The patient is thus protected from further compromise while awaiting confirmation of the diagnosis with a ventilation-perfusion (V/Q) scan. Perfusion defects that are unmatched by ventilation defects indicate a high probability of PTE, while a normal V/Q scan excludes the diagnosis. Intermediate results, however, do not rule out a PTE and must be resolved by pulmonary angiography. Pulmonary angiography can be performed while the patient is receiving heparin. As with DVT, necessary diagnostic procedures should not be withheld because the patient is pregnant. The combination of chest radiograph, V/Q scan, and pulmonary angiography exposes the fetus to a radiation dose of only 0.5 rad (0.005 Gy). Risk factors for a thromboembolic event include a history of DVT, a mechanical heart valve, atrial fibrillation, trauma, prolonged immobilization, major surgery, the antiphospholipid antibody syndrome, and several hereditary thrombophilias. Some individuals carry a gene mutation that predisposes them to a thromboembolic event. Women who are heterozygotes for protein C or protein S deficiency have an approximately 3% to 10% risk of antepartum thromboembolism and an 7% to 19% risk postpartum. The risk for heterozygotes for antithrombin III deficiency is 12% to 60% during pregnancy and 11% to 33% during the puerperium. A mutation in the gene for factor V—the factor V Leiden mutation—produces a single amino acid substitution that prevents factor V destruction and causes activated protein C resistance. Women carrying this mutation have a 28% incidence of pregnancy-associated thromboembolism. These mutations are all dominant with variable expressivity. Most carriers have affected family members who display varying degrees of pathology. Laboratory tests to diagnose all these deficiencies are available and should be considered in the workup of a patient with a history of thromboembolism, especially if there is a strong family history and no clear predisposing factors. Tests for protein C, protein S, and antithrombin III deficiencies cannot be performed while the patient is anticoagulated. Factor V Leiden mutation is identified by molecular analysis, however, and can be diagnosed at any time. Although knowledge of such mutations would not affect management of an acute thromboembolic event, it would have a profound effect on the patient's future medical management. Many authorities recommend continued anticoagulative prophylaxis once such mutations have been identified. As noted previously, antiphospholipid antibody syndrome also imposes an increased risk of thromboembolism and should be considered in the workup for hromboembolic disease. Treatment for PTE with unfractionated heparin consists of intravenous administration for 5 to 10 days, followed by subcutaneous heparin every 12 hours or 3 times a day for the remainder of the pregnancy. Heparin is a large molecule that does not cross the placenta and has few reported side effects (mild thrombocytopenia or reversible osteoporosis after long-term therapy). The dosage should be titrated to achieve a midinterval activated partial thromboplastin time (aPTT) 1.5 to 2.5 times normal or a plasma heparin level of 0.1 to 0.2 IU/mL within 24 hours of the acute event; failure to do so increases the risk of recurrent thromboembolism by a factor of 15. Most patients require a minimum of 24,000 IU per 24 hours (Table 17.5). Unfractionated heparin also can be administered by continuous subcutaneous pump. Fractionated or low-molecular-weight heparin has a longer half-life than ordinary heparin and thus can be administered once daily, and it is associated with reduced bleeding, osteoporosis, and thrombocytopenia that can complicate standard heparin administration. Low-molecular-weight heparin does not cross the placenta, and experience in pregnant patients is increasing. It is necessary to monitor peak antifactor Xa levels periodically when twice-daily dosing is used, because the aPTT does not correlate well with the anticoagulant effect of low-molecular-weight heparin. Warfarin sodium derivatives are not recommended during pregnancy, because they readily cross the placenta and have pathologic effects on the fetus. First-trimester exposure imposes the highest risk, resulting in some or all of the features of warfarin sodium embryopathy, including midfacial hypoplasia, central nervous system (CNS) abnormalities (e.g., microcephaly, hydrocephalus, or agenesis of the corpus callosum), optic atrophy, epiphyseal stippling, low birth weight, mental retardation, and seizures. Exposure beyond the first trimester may cause hemorrhage and secondary disruption of CNS and skeletal structures.

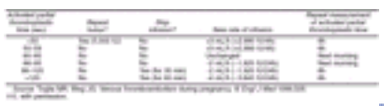

TABLE 17.5. *Protocol for adjustment of intravenous heparin dose*

Unfractionated heparin has a short half-life (60 to 90 minutes) and can be reversed with protamine sulfate. Because the half-life of low-molecular-weight heparin is much longer, most practitioners convert their anticoagulated patients to unfractionated heparin therapy in the last month of pregnancy. When delivery is planned or the patient enters labor, heparin should be discontinued and the aPTT checked. Most patients can undergo epidural anesthesia or cesarean section within 4 to 6 hours of their last unfractionated heparin dose, and protamine can be administered if reversal of anticoagulation is required sooner. Heparin should be resumed 6 to 12 hours postpartum, depending on the type of delivery and the occurrence of any complications, with warfarin sodium administered simultaneously. Once a therapeutic level is reached, warfarin alone should be continued for at least 6 weeks. The recurrence risk of PTE in a subsequent pregnancy is 4% to 15%; the risk is much higher if the patient has a predisposing gene mutation or other risk factor. Prophylactic heparin therapy should, therefore, be provided in subsequent pregnancies, although the ideal heparin dosage and duration of treatment remain to be determined. Some authors recommend a dosage of 5,000 to 10,000 IU every 12 hours, increasing as the pregnancy progresses, while others believe the dosage should be adjusted to maintain a plasma heparin level of 0.1 to 0.2 IU/mL. Prophylactic heparin therapy usually is initiated in the midtrimester or earlier if the patient has a thrombophilic gene mutation.
Mechanical Heart Valves Women with mechanical heart valves require therapeutic anticoagulation during pregnancy. As noted above, coumarin derivatives should be avoided during embryogenesis. Women with mechanical valves can be switched to therapeutic subcutaneous heparin before attempting conception or can be switched immediately after conception is verified (i.e., 1 to 2 weeks after the first missed period). The optimal agent for anticoagulation from 14 to 39 weeks is controversial. The advantages of heparin include its inability to cross the placenta and its rapid reversibility. Disadvantages include difficulty in maintaining a therapeutic dosage and failure to prevent all valve thromboses. Although coumarin may provide more consistent anticoagulation, its effects cannot be readily reversed and extend to the fetus. Consultation with the patient's cardiologist may be helpful.

PULMONARY DISEASE

Asthma

Asthma manifests as a spectrum of illness from infrequent, spontaneously resolving symptoms to repetitive, severe, life-threatening attacks. Symptomatic asthma involves fluctuating degrees of wheezing, dyspnea, chest tightness, and cough associated with reversible obstructive airway disease or bronchial hyperreactivity. Reversibility is defined objectively as an increase in forced expiratory volume in 1 second (FEV_1) of 12% and at least 200 mL after inhalation of a short-acting $ß_2$ agonist.

Pathophysiologic mechanisms suspected as causal in asthma include genetic predisposition and airway hyperreactivity with a tendency toward bronchoconstriction, airway inflammation, and abnormal mucociliary function. Triggering factors include allergen exposure, respiratory infections, exercise, aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and environmental irritants (e.g., tobacco smoke, pollutants).

Asthma may improve, worsen, or remain unchanged during pregnancy. Typically, the more severe the disease, the more likely it is to worsen. The course of asthma in a previous pregnancy is fairly predictive of the course in a subsequent pregnancy in about 60% of women. The peak incidence of asthma exacerbations is 24 to 36 weeks gestation, with relative improvement during the last month of pregnancy. Severe or uncontrolled asthma is associated with an increased risk of preeclampsia and maternal mortality, as well as IUGR, preterm delivery, and perinatal mortality. Potential mechanisms may include hypoxia and medication exposure. It is apparent that perinatal outcome is much improved when optimal control is achieved.

Therapy of this chronic disease characterized by acute exacerbations should include education in the use of a peak flow meter, the importance of compliance with medications, and the avoidance of known triggers. Mild intermittent disease, with symptoms fewer than 2 times per week, is treated with an inhaled $ß_2$ agonist such as albuterol, two puffs every 4 hours, when needed. Use of a spacer improves drug delivery. Mild persistent asthma, with symptoms more than 2 times per week, is treated with an inhaled glucocorticoid, such as triamcinolone (100 µg/puff) 2 puffs t.i.d. to q.i.d. or 4 puffs b.i.d. A long-acting $ß_2$ agonist or a leukotriene antagonist are second-line additive therapies to inhaled glucocorticoids for moderate and severe persistent asthma with daily or continuous symptoms. Systemic glucocorticoids for refractory severe exacerbations in the form of oral prednisone, 40 to 60 mg per day, is recommended until acute symptoms resolve, followed by tapering for 10 to 14 days.

Acute asthma attacks in pregnancy should prompt a thorough evaluation. Blood gas analysis in the normal pregnant woman typically reveals a pH of 7.35 and a higher PO_2 (102 to 106 mm Hg) and lower PCO_2 (28 to 30 mm Hg) than in nonpregnant patients. During the early stages of an asthma attack, the blood gas results are often consistent with hyperventilation, with an even lower PCO_2 and an elevated pH. After a prolonged attack, the patient will tire and may eventually hypoventilate. Therefore, a PCO_2 greater than 35 mm Hg or a PO_2 less than 70 mm Hg indicates severe respiratory compromise.

In addition to arterial blood gas analysis, the evaluation should include a complete blood cell count, electrolyte levels, spirometry, and a chest radiograph (Table 17.6). A respiratory therapist should be involved. Initial management consists of intravenous hydration and inhaled oxygen to maintain a PO_2 greater than 70 mm Hg and adequate urine output (in the face of alkalosis), followed by a nebulized ß $_2$ agonist, such as albuterol, up to three doses in the first 60 to 90 minutes and then 1 to 2 hours thereafter. Next, intravenous methylprednisolone 1 mg/kg every 6 to 8 hours is added, with tapering as clinical improvement occurs. Some clinicians also give intravenous aminophylline, a 6 mg/kg loading dose and 0.5 mg/kg per hour maintenance dose, to keep blood levels between 8 and 12 mg/mL. Patients should receive intravenous antibiotics in the event that an infection is confounding. Finally, terbutaline, 0.25 mg per hour subcutaneously for three doses, is offered. In the absence of clinical response, transfer to an intensive care setting is considered, because respiratory support may become necessary.

1. Arterial blood gas, complete blood cell count, electrolytes, peak flow meter, chest radiograph
2. Call respiratory therapy
3. Intravenous hydration, supplemental oxygen therapy to maintain PO_2 >70 mm Hg; monitor urine output
4. Albuterol, nebulized, 3 doses in initial 60–90 min
5. Methylprednisolone 1 mg/kg i.v. q6h
6. Aminophylline 6 mg/kg i.v. loading dose, then 0.5 mg/kg/h maintenance
7. Antibiotic i.v.
8. Terbutaline 0.25 mg s.c.
9. Transfer to intensive care for respiratory support in absence of improvement

TABLE 17.6. *Treatment of acute asthma attack*

Antepartum management in patients with well-controlled mild to moderate asthma should be like that of an uncomplicated pregnant patient. In those patients with poorly controlled severe asthma, however, the pregnancy should be monitored for IUGR and preeclampsia, and weekly tests of fetal well-being should be instituted if these complications occur. Of treated asthmatic women, 10% experience pulmonary symptoms in labor, in which case they are treated as outlined above. For those patients on a maintenance glucocorticoid or those who received a steroid course during the pregnancy, supplemental hydrocortisone, 100 mg intravenously every 8 hours for three doses, is recommended to avoid the unlikely occurrence of an Addisonian crisis.

Medications to be avoided in the asthmatic patient include ß blockers and prostaglandins. NSAIDs should be avoided in aspirin-sensitive patients. Magnesium sulfate and calcium channel blockers are well tolerated. Epidural anesthesia is preferred to general anesthesia.

Tuberculosis

Pregnancy does not worsen the course of tuberculosis (TB), and TB does not alter the overall outcome of pregnancy. However, it is important to diagnose and treat infected patients aggressively, because congenital TB can develop if a tubercular infection and bacteremia develop in a pregnant patient.

TB screening consists of the purified protein derivative (PPD) tuberculin test or Mantoux test. Forty-eight to 72 hours following intradermal injection, the presence or absence of induration at the injection site is determined. In patients with immunologic dysfunction (e.g., HIV infection), no reaction may be elicited. Therefore, a control skin test, such as for *Candida*, is placed, also. Most women have been exposed, and those who are not anergic will react. Reaction at the site of the control, and not at the site of the PPD test, indicates a negative PPD result. Induration greater than or equal to 5 mm is considered positive in an HIV-positive patient, in anyone in recent contact with an active TB case, or in anyone with clinical or radiologic evidence of TB. Induration greater than or equal to 10 mm is considered positive in health care workers, chronic alcoholics, or institutionalized individuals. Finally, induration greater than or equal to 15 mm on the PPD test is considered positive in all low-risk patients. When a skin test is positive, a chest radiograph should be done; with shielding, this procedure involves minimal fetal radiation exposure. If the chest radiograph result is normal, or abnormal but inconsistent with TB, the patient is offered treatment to prevent disease development: isoniazid (INH) 300 mg every day for 6 months. Pyridoxine (vitamin B_6) at 50 mg daily is recommended, also, to decrease the incidence of peripheral neuropathy and to protect the fetus from the neurotoxic effects of INH. Liver function tests are checked at baseline and then monthly to detect INH-induced hepatitis. If values increase two-fold, the medication is discontinued. Patients on INH are instructed to avoid alcohol and acetaminophen. If the chest radiograph is consistent with old TB and further evaluation fails to reveal active TB, the patient should receive INH 300 mg every day for 12 months after delivery.

If the chest radiograph findings are consistent with TB (adenopathy, multinodular infiltrates, upward medial retraction of hilar markings), further workup to confirm the diagnosis is necessary. The workup should include a thorough history, physical examination, drug sensitivity testing, and a sputum smear and culture. The sputum test results confirm the diagnosis. Treatment for 6 to 9 months with two or more drugs is required, as in nonpregnant patients. INH and rifampin are the drugs of choice. If there is suspicion of drug resistance, ethambutol and pyrazinamide are considered. Household contacts of any patient with active TB should be identified, evaluated, and treated as necessary.

Maternal treatment does not treat the infant. Recognition of congenital TB can be difficult, and unrecognized active disease has significant mortality. Treatment in infants is similar to that in adults. Isolation of the uninfected infant from any potential close infectious contact is recommended until effective treatment is underway, although the infant may breast-feed.

Viral Pneumonia

Influenza Pneumonia Influenza pneumonia is the most commonly occurring viral pneumonia, with type A being the most common antigenic type. Previous reports of increased mortality in the pregnant population have not been substantiated in more recent studies. Treatment is supportive, because antiviral agents are not well studied in this population. Influenza is not associated with an increased incidence of congenital anomalies, and there is no indication for influenza vaccine in the low-risk population.
Varicella Pneumonia Varicella pneumonia can complicate 0.3% to 50% of all primary varicella infections in adults. Pregnant women are at increased risk of this complication, which has a mortality of up to 40%. Respiratory symptoms typically develop 2 to 5 days after the onset of fever, rash, and malaise. The physical examination findings can be unimpressive. Any pregnant woman with varicella and respiratory symptoms should be thoroughly evaluated and hospitalized if pneumonia is suspected. Aggressive treatment with intravenous acyclovir (Zovirax), a DNA polymerase inhibitor, has decreased mortality in the pregnant population by 50%, without an increase in fetal anomalies. Two to five percent of primary varicella infections occurring at less than 20 weeks gestation are associated with congenital varicella syndrome. This syndrome includes microphthalmia, hypoplastic limbs, nasal hypoplasia, and skin lesions. Infants born within 5 days of the development of maternal rash can develop disseminated neonatal varicella, with a 60% to 70% morbidity rate and a 5% to 20% mortality rate. In such cases, delivery should be delayed, if possible, to allow maternal antibodies to reach the fetus.

Cystic Fibrosis

Experience with pregnant patients with cystic fibrosis (CF) is increasing, because the median age of survival is now 27 to 28 years. Most patients with CF have chronic obstructive pulmonary disease and pancreatic insufficiency, but this heritable, autosomal recessive disorder has a broad spectrum of clinical manifestations. Progressive bronchopulmonary disease is the predominant cause of morbidity and mortality in CF. It is characterized by exacerbations of chronic endobronchial infection, bronchiectasis, and airway obstruction. *Pseudomonas* is the most common organism to colonize the respiratory tracts of patients with CF.

Prospective controlled studies of CF in pregnancy are lacking. Counseling regarding the effects of pregnancy on the disease process is therefore difficult. In general, progressive pulmonary deterioration with hypercapnia-hypoxemia with or without cor pulmonale or pulmonary hypertension contraindicate pregnancy. Several reports indicate that patients with good nutritional status and pancreatic sufficiency tolerate pregnancy well. The perinatal mortality rate is increased in patients with CF secondary to preterm delivery reported at 5.9% to 35%. This increased rate is felt to be due to poor weight gain, low maternal prepregnancy weight, and chronic hypoxia. Management of the pregnant patient with CF stresses nutrition, maintenance of baseline pulmonary and cardiovascular status, and prompt treatment of exacerbations and deterioration. Counseling is essential; the patient with CF should understand that the fetus will carry the gene. Paternal testing will reveal the fetal risk of disease. Unaffected couples also should be counseled regarding the risk of disease according to American College of Obstetricians and Gynecologists guidelines.

Sarcoidosis

Pulmonary sarcoidosis rarely complicates pregnancy. If it changes during pregnancy, it usually improves, although the disease can relapse or exacerbate postpartum. No special management is necessary for the pregnant patient with sarcoidosis. Angiotensin-converting enzyme levels do not vary with disease activity, so following such levels is without benefit. If an exacerbation occurs, such as worsening pulmonary symptoms, deterioration in chest radiograph findings, CNS or ophthalmic involvement, or hypercalcemia, systemic steroids are recommended.

RENAL DISEASE

Urinary tract infections are a common complication in pregnancy, occurring in 10% to 15% of women. Pregnancy-associated urinary stasis, glucosuria, and vesicoureteral reflux are predisposing factors. Responsible organisms include *Escherichia coli* (75% to 90%), *Klebsiella* (10% to 15%), and *Proteus* (5%) species. *Pseudomonas, Streptococcus*, and *Staphylococcus* species are present infrequently.

Renal Infections

Asymptomatic Bacteriuria ASB is defined as greater than 10,000 organisms per milliliter of urine in an asymptomatic woman. The incidence of ASB in the pregnant population is 6%, the same as in nonpregnant, sexually active women. The incidence is twice as high in women with sickle cell disease trait. Failure to identify and treat pregnant women with ASB will result in an incidence of pyelonephritis of 25% to 40%, but treatment reduces this 10-fold. Treatment typically consists of empiric antibiotic therapy, such as 10 to 14 days of ampicillin or nitrofurantoin, or therapy based on in vitro bacterial sensitivities. A culture should be repeated 1 week following therapy completion, because 30% of infections recur.
Cystitis Cystitis is symptomatic bacteriuria without flank pain or fever. Urinary urgency, frequency, and dysuria are the most common complaints. Diagnosis and treatment do not differ from those of ASB. Occasionally, the same symptoms are associated with sterile urine; in this situation, the infecting agent is likely to be *Chlamydia trachomatis* and will respond to erythromycin therapy.
Pyelonephritis Renal parenchymal infection, or pyelonephritis, complicates 1% to 3% of pregnancies. Patients with acute pyelonephritis are typically febrile. Symptoms can include chills, urgency, dysuria, and nausea and vomiting. Other signs include costovertebral angle tenderness, pyuria, and bacteriuria. Most cases of pyelonephritis are right sided or bilateral. Disease limited to only the left side suggests an anatomic abnormality. Bacterial endotoxins and cytokines produced by activated macrophages are responsible for many of these symptoms. Hospitalization is recommended routinely, although outpatient management may be effective and safe in selected pregnant women. The risk of preterm labor is increased with pyelonephritis. Once a urine culture is obtained, intravenous antibiotic therapy and vigorous intravenous hydration are started. The antibiotic of choice is usually a cephalosporin, because a large proportion of *E. coli* strains are ampicillin resistant. If the patient is afebrile within 24 hours, oral antibiotic treatment is started. If she remains afebrile for another 24 hours, she can be discharged home to complete a 10-day antibiotic course. If she remains febrile, changing or adding antibiotics to the regimen must be considered. If the urine culture and sensitivity results are available, they can be used to guide selection of drugs. If the organism is sensitive to the original antibiotic, gentamicin should be added. If no clinical improvement is seen, a renal ultrasonographic examination should be performed to rule out calculi or abscess. Recurrent pyelonephritis occurs in 10% to 18% of patients. To reduce this risk, chronic suppressive therapy consisting of nitrofurantoin 100 mg each night often is recommended. Urine is obtained for culture and sensitivity every month, or with patient complaints. Documented recurrent infection is treated with a 10-day course of antibiotics. For the patient with recurrent or persistent disease, a urologic evaluation, including intravenous pyelogram and voiding cystogram, is recommended 3 months postpartum.

Urinary Calculi

Urinary calculi occur in 1 in 1,000 pregnancies. Pregnancy does not affect the risk or severity of calculi formation. However, calculi do increase the incidence of urinary tract infections to 20% to 45%. Patients with known calculi typically are placed on suppressive nitrofurantoin therapy throughout the pregnancy. Urine cultures are performed every month, and infection is treated aggressively.

Urolithiasis should be suspected if the patient experiences colicky flank pain, tenderness, hematuria, or unresolved bacteriuria. The diagnosis can be confirmed by ultrasonography in 60% of patients and in 96% using a single-view intravenous pyelogram, which exposes the fetus to minimal radiation (about 50 mrad). Acute urolithiasis is treated with analgesia and vigorous intravenous hydration. If infection is documented, antibiotic therapy is instituted. A ureteral stent or percutaneous nephrostomy may be required to relieve persistent obstruction.

Chronic Renal Disease

The effect of pregnancy on chronic renal disease varies with the degree of renal insufficiency. Mild renal insufficiency, defined as a serum creatinine less than 1.4 mg/dL, can be associated with a decline in renal function, increased proteinuria, and hypertension. However, renal function typically returns to prepregnancy levels after delivery (Table 17.7).

TABLE 17.7. *Renal disease prognosis*

Moderate renal insufficiency is defined as a creatinine greater than 1.4 mg/dL but less than 2.5 mg/dL. Several series suggest that 10% of women with moderate renal insufficiency experience accelerated deterioration of renal function during pregnancy; women whose prepregnancy creatinine is greater than 2 mg/dL are at greatest risk. Hypertension typically escalates, and its control is essential for good outcome. Although methyldopa is prescribed frequently, the lag between dose and effect may make it a suboptimal choice. Beta blockers, such as labetalol, and calcium channel blockers, such as nifedipine, have been shown to be effective.

Less information is available regarding pregnant patients with severe renal insufficiency (creatinine greater than 2.5 mg/dL). Thirty to forty percent of these patients experience a decline in renal function to end-stage disease within 12 to 24 months postpartum.

Patients with renal insufficiency are at high risk of perinatal mortality (up to 15%), preeclampsia (more than 50%), preterm delivery (30% to 80%), and IUGR (up to 57%). Monitoring of baseline and subsequent laboratory values, routine urine cultures with prompt treatment for infection, serial ultrasonographic examinations for fetal growth, and formal tests of fetal well-being are indicated.

Acute Renal Failure

Acute renal failure is a rare but potentially devastating complication of pregnancy. It has many causes, including preeclampsia, hemorrhage, and placental abruption. Although typically characterized by persistent oliguria, diuretic therapy is not helpful, because it does not correct the cause of the renal failure. In the presence of azotemia and severe oliguria, dialysis usually is initiated and continued until renal function returns. Fortunately, morbidity and mortality from renal failure have decreased as obstetric recognition and intervention have become more prompt, and intensive supportive therapy has become more widely available.

Dialysis

Although most women with severely impaired renal function are infertile, chronic hemodialysis or peritoneal dialysis may make pregnancy possible. Hemodialysis usually is initiated earlier in the pregnant patient than in the nonpregnant, because the risk for intrauterine fetal demise increases at a blood urea nitrogen (BUN) level above 80 mg/dL. The goal of dialysis is to maintain the BUN at 50 to 60 mg/dL, while limiting volume changes and episodes of hypotension. Peritoneal dialysis may be superior to hemodialysis because it minimizes fluid shifts and does not require maternal anticoagulation, although data to support its preferential use in pregnancy are limited. Because dialysis often is accompanied by contractions, magnesium sulfate can be added to the dialysate to maintain a serum level of 5 mEq/L. Increased numbers of hours on hemodialysis and increased frequency of treatments are recommended, because these improve management of weight and diet issues.

Renal Transplantation

Most pregnancies after renal transplantation are successful. Patients typically are advised to avoid pregnancy for 2 years following surgery to allow recovery,

stabilization of graft function, and confirmation of graft survival on maintenance doses of immunosuppressive agents (prednisone up to 15 mg/day, azathioprine up to 2 mg/kg per day). Once pregnancy is achieved, maternal–fetal complications can include an increased incidence of preeclampsia, infection (both viral [CMV, herpes, hepatitis] and urinary tract [40%]), parathyroid dysfunction, and preterm birth. The incidence of prematurity is 45% to 60% and, of these babies, about 20% are growth restricted. Preterm premature rupture of the membranes is more common, as well, likely due to long-term steroid therapy. However, pregnancy outcome is considered successful in 80% to 90% of these patients. Pregnancy management can be intense. Suspicion of graft rejection is high in the presence of fever, oliguria, graft enlargement, tenderness, and decline in renal function. Because the differential diagnosis also includes severe preeclampsia, pyelonephritis, and recurrence of glomerulopathy, renal biopsy may be necessary to confirm rejection. The immunosuppressive agents typically prescribed, including prednisone, azathioprine, and cyclosporine, are considered to be safe in pregnancy.

NEUROLOGIC DISORDERS

Neurologic diseases occur frequently in the general population (Table 17.8) and in reproductive-age women, and pregnancy can provoke or exacerbate certain neurologic abnormalities.

Disorder	*Prevalence*
Migraine	2,000
Epilepsy	650
Cerebral palsy	250
Multiple sclerosis	100
Spinal cord injury	50
Subarachnoid hemorrhage	50
Myasthenia gravis	4
Genetic disorders (excluding congenital central nervous system malformations)	<10

Source: Kurtzke JF. The current neurologic burden of illness and injury in the United States. *Neurology* 1982;32:1207, with permission.

TABLE 17.8. *Prevalence of neurologic disorders*

Headache

Headache is a common complaint during pregnancy, and the overwhelming majority are tension headaches. Tension headaches typically persist for hours and are characterized by a tight, sore feeling in the back of the head and neck. The pain usually responds to rest, application of heat or ice packs to the neck, massage, antiinflammatory drugs, or a mild tranquilizer such as chlordiazepoxide. Strategies to relieve stress are important to prevent recurrence. Depression headaches usually occur in association with other symptoms of depression and respond to antidepressant medication and counseling.

Migraine Headache

Migraine headaches are seen commonly in pregnancy, and 15% of women with migraines experience their first one when pregnant. However, 64% of women with a history of menstrual migraine headaches experience a dramatic improvement in symptoms during pregnancy. Migraines are noteworthy for cerebral artery vasoconstriction and decreased blood flow. There is a 3-fold to 6-fold increased incidence of ischemic stroke in the population with migraines, which is increased to 10-fold to 14-fold with tobacco abuse.

There are at least four types of migraine headaches. Common migraine is characterized by a frequently unilateral headache lasting several hours, nausea and vomiting, and scalp tenderness. There is often a family history of similar headaches. Classic migraine has the same symptoms but is preceded by premonitory sensory phenomena, such as visual scotomata or hallucinations. Basilar migraine includes symptoms of vertigo, dysarthria, or diplopia, while complicated migraine involves more serious neurologic symptoms, mimicking an ischemic event.

The diagnosis of new-onset migraine headaches during pregnancy is usually one of exclusion. Other disorders such as brain tumor, stroke, and epilepsy need to be ruled out. The patient can undergo the same evaluation as a nonpregnant individual, usually consisting of a thorough history and neurologic examination and sometimes including computed tomography (CT) or magnetic resonance (MR) imaging or awake and asleep electroencephalograms. Immediate treatment is also very similar in the pregnant patient and can include aspirin or acetaminophen, with or without caffeine or butalbital, narcotics, phenothiazine antiemetics, or sumatriptan succinate (Imitrex). Ergotamine should not be given during pregnancy, because it is a potent vasoconstrictor that can adversely affect uterine and placental blood flow. NSAIDs should be avoided in the third trimester. If headaches are chronic, the patient may benefit from suppressive amitriptyline or nortriptyline, propranolol, or verapamil. Valproic acid (Depakene) may be prescribed after the first trimester, when the fetal neural tube is completely formed.

Epilepsy

Epilepsy affects 0.5% to 2.0% of the population and complicates 1 in 200 pregnancies. Seizures usually are classified according to whether they are idiopathic or acquired (e.g., trauma, infection, space-occupying lesion, metabolic disorder), are partial or generalized, as well as by a description of the seizure itself. Absent seizures, or petit mal, involve loss of consciousness without any accompanying motor activity. Although both progesterone and estrogen have been shown to influence seizure activity, the relationship of pregnancy and seizure activity is unclear; 46% of women experience no change in seizure frequency, 20% experience a reduction, and 34% experience an increase in seizure activity during gestation. Factors that increase the frequency of seizures during pregnancy include discontinuation of antiepileptic medication in the belief that it harms the fetus, subtherapeutic drug levels because the dosage was not adjusted to compensate for expanding maternal vascular volume, inability to ingest medication because of nausea and vomiting, and lowering of the seizure threshold by sleep deprivation and stress.

The new onset of seizures during pregnancy is concerning. Although gestational epilepsy is probably a distinct entity, it is a diagnosis of exclusion. A complete workup should be performed as for a nonpregnant individual. Status epilepticus is a medical emergency, and the pregnant woman should be treated in the same manner as a nonpregnant individual. The airway must be secured and protected, and intravenous fluids, along with a glucose bolus and thiamine 100 mg, should be given. Intravenous phenytoin, phenobarbital, or diazepam should be administered. If possible, a wedge should be placed under one hip to displace the uterus off the vena cava. Although fetal heart rate abnormalities may be present during the seizure, the mother should be stabilized before any fetal intervention is contemplated. In most cases, resuscitation of the mother resuscitates the fetus. A thorough workup, including a toxicology screen and anticonvulsant drug levels, should be initiated following maternal stabilization.

Most epileptic women require seizure medication to remain seizure free. For many anticonvulsant drugs, the benefit of preventing seizures outweighs any potential risks to the fetus. Other medications are clearly teratogenic and should be avoided, if possible; these include valproic acid before 8 weeks gestation and trimethadione (Tridione). However, women with epilepsy are at increased risk for fetal malformations, whether or not they ingest anticonvulsant medication. Although women taking multiple medications are at highest risk, it is not clear whether the increased risk is due to fetal drug exposure or whether it correlates with severity of maternal disease. Fetal factors play a role, as well. For example, fetuses with epoxide hydrolase deficiency are at high risk for fetal hydantoin syndrome. The epileptic gravida should be counseled that her disease increases the risk of birth defects from the background rate of 3% to approximately 7%.

The lowest medication dosage associated with seizure prevention should be prescribed. Stressors should be minimized, and the patient should ingest a multivitamin with folate. Some authors advocate prescribing oral vitamin K in the last month of pregnancy to women taking phenytoin, although this is controversial, because it is not clear that vitamin K crosses the placenta, and exposed fetuses usually are given vitamin K neonatally. A second-trimester targeted ultrasonographic examination, with other ultrasonographic examinations as needed to assess fetal growth, is warranted. During labor, antiseizure medications should be continued, and pain relief should be excellent, so that hyperventilation with pain does not lead to a respiratory alkalosis that could lower the seizure threshold. The patient may breast-feed. The anticonvulsant content of breast milk is inversely proportional to the degree of protein binding. However, even drugs that are not highly protein bound (e.g., carbamazepine, phenobarbital, primidone [Mysoline]) are present at low levels, so that the total dosage ingested by the infant is usually negligible.

Subarachnoid Hemorrhage

Intracranial vascular anomalies can become symptomatic during pregnancy. Rupture of such malformations, resulting in subarachnoid hemorrhage, occurs in 1 in 75,000 pregnancies. Subarachnoid hemorrhage is heralded by sudden intense headache, visual changes or cranial nerve abnormalities, focal neurologic deficits, or an altered level of consciousness. In addition, the patient often complains of nausea, vomiting, and photophobia. The examination reveals signs of meningeal irritation, tachycardia, hypertension, slight fever, and mild leukocytosis and proteinuria. Subarachnoid hemorrhage may result from a ruptured cerebral angioma, saccular aneurysm, or arteriovenous malformation (AVM); aneurysm rupture reportedly occurs 3 times more often than rupture of an AVM. The mortality rate is reported to be as high as 35%.

If intracranial hemorrhage is suspected during pregnancy, the patient should undergo a CT scan to confirm the hemorrhage and localize the bleeding. If the CT scan is normal but hemorrhage is strongly suspected, examination of the cerebrospinal fluid to confirm the presence of blood followed by angiography to locate the lesion may be indicated. Treatment consists of bed rest, sedation, and analgesia; surgical correction often is recommended. Aneurysms that have bled once are very likely to bleed again within weeks of the first bleed, and 5% to 7% of AVMs bleed again during the first year. Therapy should not be withheld from the patient because she is pregnant. Hypothermia during neurosurgery usually is well tolerated by the fetus, although hypotension should be avoided if at all possible. If the patient requires neurosurgery near term, cesarean section just prior to the craniotomy may avoid fetal compromise if the fetus is mature. Otherwise, there is usually no maternal benefit to terminating the pregnancy. Patients who experience an intracranial hemorrhage within 2 months of delivery or who have an unrepaired aneurysm should not perform the Valsalva maneuver during labor. Epidural anesthesia and assisted vaginal delivery are indicated.

Ischemic or Thrombotic Stroke

Ischemic (thrombotic) stroke is uncommon in reproductive-age women, occurring in 1 in 7,000 to 11,000 pregnancies; however, it can occur in association with hypertension, diabetes, hyperlipidemia, antiphospholipid antibody syndrome, sickle cell disease, rheumatic heart disease, septicemia, and tobacco abuse. Cerebral artery thrombosis most often is associated with atherosclerosis and may be preceded by transient ischemic attacks. Cerebral artery embolism usually is associated with cardiac arrhythmia. In either case, the affected patient experiences the sudden onset of severe headache, hemiplegia or other neurologic deficits, or new-onset seizures. A thorough workup should be performed, including complete blood cell count, sedimentation rate, serum lipid profile, ECG or echocardiogram, and head CT scan or cerebral angiography, as necessary. Therapy includes rest, analgesia, aspirin, and heparin. Heparin may be discontinued prior to vaginal delivery and restarted postpartum. Cesarean section should be for obstetric indications.

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis is usually a puerperal complication, occurring in association with preeclampsia, sepsis, or a coagulation defect. The patient complains of severe headache, drowsiness, and confusion, and may have convulsions, focal neurologic deficits, hypertension, or papilledema. The diagnosis is made by CT scan or angiography. Treatment consists of mannitol or dexamethasone to reduce intracranial edema, along with antiepileptic medication if seizures have occurred. Heparin may be given if hemorrhage has been ruled out. If sepsis is a cofactor, the source must be identified and the infection treated aggressively. The mortality rate can be as high as 30%; poor prognostic factors include obtundation, coma, accompanying subarachnoid hemorrhage, or rapid deterioration. However, the prognosis for survivors is excellent.

Primary CNS malignancies occur in 3 to 5 per 100,000 people per year. Although pregnancy does not alter this incidence, intracranial malignancies account for 10% of all maternal deaths. The malignancy may arise during pregnancy, or the physiologic changes of pregnancy may induce symptoms in a previously asymptomatic tumor. Symptoms typically include headache, vomiting, altered levels of consciousness, seizures, and hypertension. The presence of papilledema helps to distinguish intracranial pathology from other entities such as preeclampsia. Diagnosis is by CT or MR imaging. If an operable tumor of high malignant potential is suspected (e.g., high-grade gliomas, choroid plexus papillomas, posterior fossa tumors) or if there are significant neurologic complications such as seizures or progressive hydrocephalus, surgery should be performed without delay. Intraoperative hypothermia usually is well tolerated by the fetus, although hypotension should be avoided, if possible. In contrast, minimally symptomatic lesions of low malignant potential (e.g., meningioma) may be followed and treated definitively postpartum.

It should be kept in mind that a proportion of intracranial malignancies are metastatic from other sites, primarily breast, lung, or gastrointestinal or genitourinary tracts. A complete history and physical examination is, therefore, crucial. Choriocarcinoma may manifest intracranial findings, and pituitary tumors may become symptomatic in pregnancy.

If intracranial malignancy is diagnosed early in pregnancy, pregnancy termination is not indicated routinely but might be appropriate in patients with uncontrollable seizures or progressive loss of consciousness. Patients who have undergone craniotomy within 2 months of delivery should not perform the Valsalva maneuver during labor. Epidural anesthesia and assisted vaginal delivery are indicated. Cesarean section should be for obstetric indications only.

Pseudotumor Cerebri

Pseudotumor cerebri is defined by increased intracranial pressure, papilledema, and headache without focal neurologic abnormalities. The etiology is unknown. Although pregnancy does not increase the incidence, the majority of cases occur in obese women of reproductive age. Pregnancy complications experienced by such women are likely to be related to their obesity and not their neurologic diagnosis. Women with pseudotumor cerebri should be followed with serial visual field and acuity testing. Treatment typically consists of repeated lumbar punctures, shunting, glucocorticoids, or acetazolamide (Diamox); all can be safely used in pregnancy. Although weight loss and diuretics may also be helpful, they should be deferred until postpartum.

Multiple Sclerosis

Multiple sclerosis (MS) is a multifocal demyelinating disease of CNS white matter, characterized by chronic inflammation, selective demyelination, and scarring. The etiology is unknown but may involve a virus-triggered autoimmune phenomenon in a genetically susceptible individual. There are three forms of MS: relapsing MS, which is defined by recurrent attacks of neurologic abnormality followed by greater or lesser degrees of recovery; chronic progressive MS, which gradually worsens from the onset without remission; and inactive MS, in which patients have fixed neurologic deficits that neither progress nor resolve. Because it is most commonly seen in 20- to 40-year-old white women and does not impair fertility, MS can first manifest coincidentally with pregnancy. Symptoms and signs include weakness, hyperreflexia, paresthesia, hypesthesia, ataxia, visual loss resulting from optic neuritis, diplopia, facial nerve palsy, vertigo, urinary urgency, or incontinence. None of the symptoms or signs can be explained by a single anatomic lesion. The diagnosis is one of exclusion, with MS confirmed by cerebrospinal fluid abnormalities and MR imaging. In many patients, MS has been diagnosed before conception, and medical therapy in the form of corticotropin and glucocorticoids was initiated. Patients with chronic progressive MS or severe relapsing MS may require more aggressive therapy with immunosuppressive drugs such as cyclosporine, azathioprine, or cyclophosphamide. All of these drugs may be continued during pregnancy if there is clear maternal benefit. Affected patients may also require an antispasmodic agent, urinary tract infection prophylaxis, and physical therapy.

Women with MS should be counseled that pregnancy increases the likelihood of urinary tract infections and constipation and may exacerbate fatigue and mobility problems. Women with paraplegia or quadriplegia are at risk for unmonitored, precipitous delivery. Women with a lesion at or above T6 are at risk for autonomic dysreflexia. Although some women experience relatively little symptomatic progression during pregnancy, flares are common during the first 3 postpartum months. Flares may preclude breast-feeding, and the patient may require assistance with infant care.

Myasthenia Gravis

Myasthenia gravis is a chronic autoimmune neuromuscular disease characterized by easy fatigability of facial, oropharyngeal, extraocular, and limb muscles. The primary defect is immunoglobulin G (IgG)-mediated destruction of striated muscle acetylcholine receptors. The diagnosis is made with the edrophonium chloride test (edrophonium inhibits acetylcholinesterase, which allows acetylcholine levels to increase and improves strength in myasthenic muscles), nerve stimulation tests, and measurement of acetylcholine receptor antibodies. The incidence of myasthenia gravis is 1 in 10,000. Women are affected more often than men and experience a peak occurrence in their 20s and 30s. Symptoms typically wax and wane and are not altered by pregnancy, although postpartum exacerbation is common. Thymectomy usually is performed shortly after diagnosis, because it results in symptomatic improvement and may ultimately eliminate the need for medical therapy.

Pregnant women with mild disease usually require only adequate rest and the avoidance of strenuous activities. More seriously affected women require medical therapy in the form of pyridostigmine bromide or neostigmine bromide, glucocorticoids, or immunosuppressive drugs. Plasmapheresis can relieve acute symptoms by mechanically removing the pathologic antibodies and can be performed during pregnancy, if care is taken to avoid maternal hypotension or hypovolemia. Because the disease does not affect smooth muscle, labor and delivery proceed normally. The patient may receive oxytocin and analgesics, but care should be taken to avoid extensive regional blocks that could compromise maternal respiration. Certain drugs are tolerated poorly and should be avoided. These include magnesium sulfate, aminoglycosides, certain antiarrhythmic agents (e.g., quinine, quinidine, and procaine), procaine anesthetics, curare, succinylcholine, and large doses of narcotics. Because the antireceptor IgG antibody easily crosses the placenta, the neonate will be transiently symptomatic in approximately 10% of cases and will require tertiary care.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant, multisystem disease characterized by muscle stiffness (myotonia), progressive dystrophic changes in muscles of the face, neck, and distal limbs, and posterior subcapsular cataracts. It occurs in 3 to 5 per 100,000 individuals and usually is diagnosed in late childhood or early adulthood, with the development of progressive muscle weakness and atrophy. Affected patients have characteristic facies (drooping eyelids, bitemporal wasting, and weakness, with diminished expressivity of the mouth known as a *flattened smile*), weakness and atrophy of small hand muscles, and respiratory and gastrointestinal

difficulties. Although menstrual irregularities and infertility are common, affected patients can become pregnant. Such pregnancies can be complicated by polyhydramnios, preterm labor, dysfunctional labor, and postpartum hemorrhage. Maternal deaths related to aspiration pneumonia or cardiac failure have been reported. Symptoms are usually worse in the last half of pregnancy and often improve after delivery.

The molecular defect is a region of CTG trinucleotide repeats in the myotonin gene on the long arm of chromosome 19. The number of repeats in this region determines the severity of the symptoms; expansion of the region, along with an increase in symptom severity, can occur with each generation. The fetus of an affected mother is thus at risk of inheriting an expanded form of the gene and having the severe congenital form of the disease. Infants with congenital myotonia are floppy at birth, have diminished suck and cry reflexes, and have serious respiratory compromise. Prenatal diagnosis is available. Severely affected women and their affected infants usually require tertiary care.

Spinal Cord Injury

Spinal cord injury resulting in paraplegia or quadriplegia occurs in 1 in 10,000 individuals per year in the United States. Reproductive-age women with spinal cord injuries generally tolerate pregnancy well, although pregnancy may exacerbate bowel dysfunction or pressure necrosis of the skin and may increase the incidence of urinary tract infections. Women with lesions below T10 to T12 feel uterine contractions normally. Women with lesions above this level, however, usually do not feel their contractions and are at risk for a precipitous, unattended delivery. Such women should be taught to palpate their uterus for contractions on a regular basis during the third trimester.

Women whose lesion is above T6 are at risk for autonomic hyperreflexia. In this condition, any number of stimuli (labor, urethral catheterization, cervical or rectal examination) can provoke afferent nerve impulses that enter the cord and initiate focal segmental reflexes that are not modulated or inhibited by higher centers, resulting in stimulation of the sympathetic nervous system. Symptoms include pilomotor erection, excessive sweating, facial flushing, dilated pupils, severe headache, paroxysmal hypertension, and bradycardia. Epidural anesthesia can prevent or control such sympathetic stimulation and is, therefore, a crucial component of planned labor management. Vaginal delivery is possible for some patients with spinal cord injury, because the expulsive forces of the uterus are sufficient to bring down the fetal head for an assisted vaginal delivery. If cesarean section is required, regional anesthesia is ideal.

ENDOCRINOLOGY

Pituitary Tumors

The pituitary gland normally enlarges by 30% during pregnancy, and compression of the optic chiasm infrequently results in bitemporal hemianopsia. Pituitary secretions are altered by pregnancy: follicle-stimulating hormone and luteinizing hormone levels are decreased, and corticotropin and prolactin are increased. Thyroid-stimulating hormone (TSH) concentrations, however, vary with gestational timing.

Pituitary adenomas are benign neoplasms of anterior pituitary cells. Adenomas can secrete hormones, such as prolactin or ACTH, and cause hypopituitarism or headache or visual problems. They are classified by size as microadenomas or macroadenomas, with the former being less than 10 mm. They also can be classified by the hormone they secrete, with prolactin-secreting adenomas being the most prevalent at 26%. Diagnosis is confirmed by MR imaging or CT scan. Hyperprolactinemia can manifest as galactorrhea, menstrual disorders, infertility, hirsutism, headache, and visual field defects.

Treatment options include medical, surgical, or radiation therapy. Medical treatment is with the dopamine agonist bromocriptine, which decreases prolactin levels to normal in up to 90% of treated patients. Bromocriptine is not known to be teratogenic, but treatment during pregnancy typically is discontinued. As the normal pituitary enlarges during pregnancy, the potential for enlargement of an adenoma exists, as well. Pregnant women should be educated about and monitored for the symptoms of expansion, such as headaches and visual field changes. This occurs infrequently, because only 2% of microadenomas and 15% of macroadenomas show signs or symptoms of tumor growth during pregnancy. An initial visual field examination early in the pregnancy is routine, but serial exams typically are not useful because visual field losses are acute. Instead, the patient should be made aware of the possibility of visual field loss, with the recommendation made to seek prompt evaluation if it occurs. Surgery and radiation are alternative treatment modalities for adenomas, with surgery reserved for patients with very large tumors in whom medical therapy fails. Breast-feeding is unaffected by hyperprolactinemia. Bromocriptine is reinstituted at its completion.

Diabetes Insipidus

Diabetes insipidus (DI) involves water loss secondary to inadequate renal tubule reabsorption. Polyuria, polydipsia, and excessive thirst are characteristic. There are three causes of DI (Table 17.9). Hypothalamic (central) DI results from inadequate arginine vasopressin (AVP) secretion in response to stimuli and can be genetic (rare) or acquired. Acquired central DI occurs as the result of tumor, trauma, infection, Sheehan syndrome, or autoimmune disease. Nephrogenic DI results from decreased renal sensitivity to normal or elevated AVP levels and can be familial or acquired. Lithium also causes this type. Primary polydipsia, typically psychogenic in origin, involves excessive fluid intake and AVP suppression.

Hypothalamic
Genetic
Acquired
Nephrogenic
Primary polydipsia

TABLE 17.9. *Causes of diabetes insipidus*

DI is diagnosed with a water deprivation test. In a pregnant patient with a viable fetus, this test is performed with continuous fetal monitoring. Dehydration in DI will be accompanied by rising serum osmolality and an inability to concentrate the urine. Intranasal administration of desmopressin acetate prompts urine concentration and confirms the diagnosis. Its use is not associated with maternal or fetal complications.

Thyroid Disease

Maternal Thyroid Function During Normal Pregnancy Normal pregnancy results in modest thyroid enlargement, detectable on physical examination. Serum levels of TSH and thyroid-releasing hormone (TRH) are the same in the pregnant patient as in the nonpregnant, while levels of thyroid-binding globulin (TBG) increase due to estrogen-enhanced hepatic production. Because total thyroxine (T_4) and triiodothyronine (T_3) are increased, also, free biologically active T_3 and T_4 concentrations are unchanged in normal pregnant women. Human chorionic gonadotropin has the same a chain as TSH, so there is an inverse relationship between these hormone levels during pregnancy.
Maternal Hypothyroidism Most pregnant patients treated for hypothyroidism during pregnancy are diagnosed before pregnancy and are already on replacement therapy. In these patients, the dosage should be maintained initially. A patient may also develop hypothyroidism during pregnancy. The most common cause of hypothyroidism is Hashimoto thyroiditis, which is confirmed by demonstrating the presence of circulating antithyroglobulin and antimicrosomal antibodies. Women who have undergone thyroid ablation for Graves disease and are receiving inadequate replacement may also be hypothyroid. Symptoms include excessive fatigue, dry skin, cold intolerance, constipation, bradycardia, and irritability. Myxedema is rare. Laboratory evaluation reveals low free T_4 and high TSH levels. The goal of therapy is to provide enough T_4 to normalize the TSH and the pulse rate, which should be checked every 2 to 3 weeks. A typical replacement dosage is 150 µg of levothyroxine per day. At least 75% of all hypothyroid patients will require a higher dosage during pregnancy. The dosage typically is increased in 50 µg increments. Unrecognized or inadequately treated hypothyroidism is associated with an increased risk of miscarriage, preeclampsia, intrauterine fetal demise, and postpartum hemorrhage.
Maternal Hyperthyroidism Hyperthyroidism complicates 1 in 500 pregnancies. Causes include Graves disease, acute or subacute thyroiditis, toxic nodular goiter, toxic adenoma, and gestational trophoblastic disease (Table 17.10). Patients with Hashimoto thyroiditis also may exhibit signs of hyperthyroidism if they make antithyroid antibodies (a combination of Graves disease and Hashimoto thyroiditis, or Hashitoxicosis) or if they make anti-TSH receptor antibodies.

Graves disease
Acute (subacute) thyroiditis
Hashimoto disease
Toxic nodular goiter
Toxic adenoma
Gestational trophoblastic disease

TABLE 17.10. *Causes of hyperthyroidism*

The most common cause of hyperthyroidism in pregnancy is Graves disease. The diagnosis is based on a triad of manifestations, including hyperthyroidism with diffuse goiter, ophthalmopathy (particularly exophthalmos), and dermopathy. Graves disease is an autoimmune disorder in which circulating thyroid-stimulating

immunoglobulins (TSIs) bind to thyroid follicular cell TSH receptors, stimulating excess thyroid hormone synthesis and secretion. The patient may have other autoimmune diseases, including systemic lupus erythematosus, myasthenia gravis, and immune thrombocytopenia. The diagnosis of hyperthyroidism can be difficult, because the patient may report symptoms that are seen commonly in a normal pregnancy. These include shortness of breath, palpitations, and heat intolerance. Signs and symptoms of hyperthyroidism that are not typical of pregnancy, and thus aid in its diagnosis, include weight loss or poor weight gain and increased bowel frequency. Laboratory evaluation confirms the diagnosis. Free T_4 level is high in hyperthyroid patients. Rarely (in 3% to 5%), T_4 level may be normal and free T_3 elevated. TSH is suppressed. Autoantibodies confirm the autoimmune nature of the disease and may have fetal implications. Hyperthyroidism can be treated with antithyroid medications, surgery, or radioactive sodium iodine (^{131}I). All medications have some contraindications in pregnancy. Propylthiouracil (PTU) and methimazole (Tapazole) are thioamides that inhibit thyroid hormone biosynthesis. PTU lowers T_4 levels faster than methimazole, giving it an advantage for therapy. The recommended dose of PTU is 300 to 450 mg initially, followed by a 50- to 300-mg daily maintenance dose, usually divided into a 3-times-a-day dosage regimen. Both PTU and methimazole cross the placenta and can have inhibitory effects on fetal thyroid function. Once a high-normal free T_4 level has been achieved, the PTU dosage should be reduced to the smallest amount that maintains this level, thus decreasing the risk of fetal hypothyroidism. During therapy, maternal thyroid function should be evaluated every 3 to 4 weeks to guide dosage adjustments. Before initiation of therapy, a baseline white blood cell count and differential should be obtained. Adverse reactions to PTU include skin rash (2% to 8%), bronchospasm, drug fever, hepatitis, oral ulcers, and idiopathic agranulocytopenia. Idiopathic agranulocytopenia usually occurs during the first 3 months of therapy (1 in 500 patients) and is reversible after stopping the PTU. An adverse reaction to one thioamide does not necessarily predict a similar reaction to another. Both PTU and methimazole are taken up by the fetal thyroid gland after the first trimester. At PTU dosages of 300 mg or greater daily, fetal goiter and hypothyroidism have been reported; at dosages lower than 300 mg daily, fetal clinical outcome is usually improved; and at dosages lower than 200 mg daily, fetal T_4 levels can be normal. Aplasia cutis has been described in some fetuses exposed to methimazole, which may make PTU preferable during pregnancy. After birth, women taking these antithyroid medications may pass physiologically significant dosages of the medication into their milk. However, PTU is more strongly plasma protein bound, and therefore preferable for the patient who desires to breast-feed. The patient should be reminded to take the medication after feeding or pumping and to notify their pediatrician that she is taking the medication. The infant's thyroid function should be checked eriodically to prevent undiagnosed neonatal hypothyroidism. Beta blockers may be useful in decreasing the sympathetic-like symptoms of hyperthyroidism, while thyroid hormone levels are being reduced by other forms of therapy. In addition, propranolol has an inhibitory effect on the peripheral conversion of T_4 to T_3 and thus lowers circulating thyroid hormone levels. This action is additive to the effects of the thioamides. The recommended propranolol dose for this indication is 20 to 40 mg orally 3 to 4 times a day. Surgical thyroid ablation, or thyroidectomy, may be necessary during pregnancy if very high dosages of PTU (greater than 300 mg daily) are needed long term to control maternal hyperthyroidism. Medical thyroid ablation with ^{131}I should not be considered during pregnancy because of the possibility of simultaneous fetal thyroid ablation. Antenatal treatment with ^{131}I at the usual dosage results in 0.75 to 1.5 rad (0.0075 to 0.015 Gy) of fetal radiation exposure. Patients with inadvertent first-trimester exposure can be reassured that the fetal thyroid gland does not begin concentrating iodine until 10 to 12 weeks gestation, and maternal thyroid ablation before this time would not be expected to affect the fetus. Exposure after 12 weeks gestation, however, may result in congenital hypothyroidism. Theoretically, 10 days of maternal PTU administration after accidental exposure may benefit the fetus by decreasing uptake of ^{131}I iodine into the fetal thyroid gland. Adequate treatment of hyperthyroidism is important to decrease the risk of preeclampsia and preterm delivery, as well as that of fetal demise, growth restriction, and fetal or neonatal thyroid dysfunction. The patient with a very serious complication of Graves disease, thyroid storm or crisis, can experience tachycardia, hyperpyrexia, circulatory collapse, and death. Thyroid storm involves a massive release of thyroid hormones and often is recipitated by a stressor, such as infection (e.g., pyelonephritis), thyroid gland palpation, or labor and delivery. Thyroid storm is an emergency and must be treated aggressively to prevent maternal decompensation. Treatment may require the administration of multiple agents for up to 1 to 2 weeks (Table 17.11). PTU should be given in large doses: 600 mg orally initially followed by 300 mg orally every 6 hours. The thioamides can be administered through a nasogastric tube if the patient cannot tolerate oral medications. In addition, sodium iodide, 1 g in 500 mL of fluid, should be given daily to inhibit the release of stored hormone. Propranolol may be added for control of tachycardia and other sympathetic-like symptoms if there is no evidence of cardiac failure. The initial propranolol dosage is 40 to 80 mg orally every 4 to 6 hours, or 1 mg per minute intravenously for 2 to 10 minutes with concurrent maternal cardiac monitoring. The dosage may be adjusted, depending on the patient's cardiac response. Dexamethasone, 1 mg orally or intramuscularly every 6 hours, or hydrocortisone, 100 mg intravenously every 8 hours, can further inhibit peripheral T_4 to T_3 conversion. Oxygen, digitalis, fluid replacement, and acetaminophen (as an antipyretic) should be given as needed.

Propylthiouracil: 600 mg p.o. (n.g.), then 300 mg q6h
Sodium iodide: 1 g/500 empc i.v. q.d.
Propranolol: 40–60 mg p.o. q4–6h
Dexamethasone: 1 mg p.o. i.m. q6h
Oxygen, acetaminophen, fluid replacement

n.g., nasogastric tube administration.

TABLE 17.11. *Treatment of thyroid storm*

Thyroid Nodules and Cancer Evaluation of thyroid nodules discovered during pregnancy should begin with a complete physical exam, evaluation of thyroid function tests, and ultrasonography to document the nodule's presence and size. This is followed by a fine-needle aspiration, and if elected, surgical removal, preferably in the mid-second trimester. Thyroid cancer is suspected if there is rapid growth unaccompanied by tenderness or hoarseness. Thyroid function test results are usually normal. Thyroid cancer is more likely in a population irradiated in childhood; in this group, 30% of those with a thyroid nodule will have thyroid cancer at the time of surgery. In the pregnant patient, papillary cancer predominates and is no more aggressive than in the nonpregnant patient. Importantly, a delay in surgery does not alter outcome. In the presence of either a hyperfunctioning benign nodule or documented papillary carcinoma, thyroid function typically is suppressed with levothyroxine until definitively treated. In the presence of a more malignant cell type, such as medullary or undifferentiated carcinoma, or lymphoma, some practitioners recommend pregnancy termination to pursue aggressive management with surgery, adjuvant radiation, and chemotherapy. There is no evidence that pregnancy affects the progression of thyroid cancer or that thyroid cancer affects the outcome of pregnancy. As a result, thyroid cancer or a history of it is not an absolute contraindication to pregnancy. Although pregnancy is not a contraindication to thyroid surgery, it is a contraindication to ^{131}I treatment.

Fetal Thyroid Function The fetal thyroid gland is first capable of hormonal activity by the end of the first trimester, and there is normally a gradual increase in fetal T_4 concentrations during pregnancy. This increase represents fetal production rather than transplacental transfer, because both T_3 and T_4 cross the placenta only minimally. However, iodides, antithyroid medications, and TSIs cross the placenta easily. Thyroid hormone deficiency during fetal development or during the first 2 years of life can cause irreversible brain damage, with the degree of disease related to the severity, duration, and gestational age at which the hypothyroidism occurs. Although neonatal hypothyroidism is not common (1 in 4,000 live births in the United States), it is a potentially treatable cause of mental retardation and thus is now included in most newborn blood screening programs. Fetal hypothyroidism can be treated antenatally by direct hormone injection of the fetus via amniocentesis. Fetal hyperthyroidism can also be diagnosed before birth and may respond to prenatal treatment. Fetal or neonatal thyrotoxicosis occurs in 1 of 70 thyrotoxic mothers. It results from the transplacental transfer of TSIs and is a potentially serious disease, with mortality rates of 10% to 16% due to prematurity and congestive heart failure. Hyperthyroid pregnant patients should be evaluated frequently for fetal tachycardia, and appropriate interval fetal growth should be confirmed. Fetal goiter may be identified on ultrasonographic examination, and fetal thyroid function can be assessed with fetal blood sampling. Because PTU and methimazole cross the placenta, maternal dosage can be adjusted to correct the fetal hyperthyroidism; replacement T_4 can then be given to the mother, if necessary. The diagnosis of neonatal thyrotoxicosis is usually clinically apparent, because the infant may have a goiter, exophthalmos, tachycardia, irritability, and growth restriction. The mother likely has a history of hyperthyroidism and may have had previous infants affected by this disease. Mild cases of neonatal thyrotoxicosis require no treatment; the symptoms resolve as maternal TSIs are cleared from the infant's system. Severely symptomatic babies are treated with propranolol and PTU.

Parathyroid Conditions The parathyroid glands function to maintain maternal calcium and phosphate homeostasis. Total calcium levels decline during pregnancy because the binding protein albumin declines, but the level of ionized, biologically active calcium is unchanged. The fetus contains approximately 30 mg of calcium, which is transported actively across the placenta. Maternal calcium requirements increase from 0.5 mg per day to 1.5 mg per day at term. Serum parathyroid hormone (PTH) levels gradually increase during pregnancy, reflecting the increased calcium transfer to the fetus plus the increases in extracellular fluid volume and glomerular filtration rate.

Hyperparathyroidism Hyperparathyroidism is a condition caused by excessive PTH production, often due to a clinically inapparent parathyroid adenoma. Hypercalcemia results and causes symptoms of fatigue, weakness, polyuria, polydipsia, nausea, anorexia, and constipation. During pregnancy, affected women may have prolonged nausea and vomiting. Increased renal excretion of calcium may predispose to nephrocalcinosis, renal calculi, and symptomatic bony resorption. Although serum calcium measurements remain the best single diagnostic test, the physiologic changes of pregnancy may make the diagnosis of hyperparathyroidism difficult. A total calcium concentration of 10.5 mg/dL or greater in late pregnancy must be considered suspicious, and a total calcium concentration of 12.0 mg/dL or greater is definite evidence of hyperparathyroidism. Palpable parathyroid adenomas are extremely uncommon. Hyperparathyroidism is associated with an increased incidence of perinatal morbidity and mortality; therapy is recommended. Up to 50% of infants of untreated mothers will develop hypocalcemia and tetany, which may be the first indicator of maternal disease. If the diagnosis is first established during pregnancy, surgical resection of the adenoma generally is indicated, although oral phosphate therapy (1 to 1.5 g daily in divided doses) may occasionally be attempted. Pregnancy termination need not be considered except in the rare case of advanced renal involvement.

Hypoparathyroidism Hypoparathyroidism results from inadequate production of PTH and is characterized by weakness, fatigue, mental status changes, numbness and paresthesias of the extremities, muscle cramps, and tetany. It must be distinguished from pseudohypoparathyroidism, in which parathyroid function is normal but end organs do not respond to PTH. The signs and symptoms of hypoparathyroidism are the result of a decreased serum ionized calcium level and increased neuromuscular irritability. It occurs most commonly as the result of parathyroid gland injury or removal in association with thyroid surgery or irradiation, but it can be idiopathic. The increased calcium requirements of pregnancy may make patients with hypoparathyroidism more symptomatic. In addition, relative unavailability of calcium for the fetus may lead to secondary neonatal hyperparathyroidism. Symptomatic hypocalcemia can be prevented with calcitriol (1,25-dihydroxyvitamin D_3), dihydrotachysterol, large doses of vitamin D, and calcium gluconate or lactate. The patient should be on a low-phosphate diet and might benefit from consultation with an endocrinologist and a dietitian.

Adrenal Disease

In normal pregnancy, plasma concentrations of adrenal steroid hormones typically increase with advancing gestation. Because the amount of cortisol bound to nuclear receptors actually is decreased slightly (due to competition by progesterone), both total plasma cortisol and cortisol-binding globulin levels increase. Free cortisol levels are increased, and a diurnal variation is maintained. Aldosterone levels also rise, although the factor(s) responsible remain unclear; no consistent correlations exist with observed elevations in angiotensin II or progesterone. Adrenal function tests are unaltered. As with other endocrine disorders, abnormalities in adrenal function are usually associated with infertility. However, adrenal insufficiency and hyperfunction can complicate pregnancy.

Adrenal Insufficiency Inadequate production of adrenal corticosteroids can be either chronic or acute. Although most cases of adrenal insufficiency are diagnosed outside of pregnancy, the disease may first occur during pregnancy and present a diagnostic challenge. The chronic form may become apparent with numerous nonspecific signs and symptoms, whereas the acute form may manifest as vascular collapse. The signs and symptoms of chronic adrenocortical insufficiency during pregnancy are identical to those in the nonpregnant state and include fatigue, hyperpigmentation, weakness, anorexia, nausea, vomiting, and weight loss. Because all of these problems may be encountered during the course of an otherwise normal gestation, the clinical diagnosis of adrenocortical insufficiency in pregnancy may be difficult. However, persistent weight loss or nausea and vomiting beyond the first trimester, particularly in association with any of the aforementioned signs or symptoms, should raise suspicions. The diagnosis and appropriate treatment of adrenocortical insufficiency during pregnancy are important because of the risks associated with the added stress of pregnancy and delivery and because of the increased likelihood of adrenal crisis, particularly during the puerperium. Adrenal insufficiency can be primary (Addison disease), due to autoimmune adrenal destruction or tuberculosis, or secondary, due most often to exogenous glucocorticoid intake (Table 17.12). When Addison disease is suspected, a blood sample for plasma cortisol and ACTH levels should be obtained (Table 17.13). A cortisol level less than 20 µg/dL is consistent with Addison disease. Treatment should be started promptly, consisting of intravenous hydrocortisone 100 mg every 6 hours. When chronic adrenal insufficiency is suspected or confirmation of the diagnosis of acute adrenal insufficiency is needed, an ACTH challenge test can be performed and a 24-hour urinary free cortisol level determined. Long-term replacement thereafter consists of hydrocortisone 12 to 15 mg/m ^{2} per day and, if necessary (as guided by serum potassium), fludrocortisone acetate (Florinef) 100 g per day for mineralocorticoid activity.

Primary (Addison Disease)
Autoimmune
Tuberculosis
Secondary
Exogenous glucocorticoids

TABLE 17.12. *Causes of adrenal insufficiency*

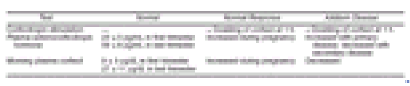

TABLE 17.13. *Laboratory diagnosis of adrenocortical insufficiency*

Additional cortisol replacement is recommended during periods of major stress, with criteria being fairly vague and liberal (e.g., injury, fever, surgery). In these instances, the dosage is increased to at least 200 mg per day until the stress has passed. For periods of minor stress (e.g., nausea, vomiting, low-grade fever), the routine daily dosage is doubled. Because glucocorticoids cross the placenta, transient suppression of the newborn hypothalamic-pituitary-adrenal axis may be observed, and the neonate may require cortisol replacement and treatment of hypoglycemia. Neonatal outcome is otherwise unaffected.

Cushing Syndrome or Hypercortisolism Elevated levels of glucocorticoids can result from bilateral adrenal hyperplasia, benign or malignant adrenal adenomas, or exogenous corticosteroid therapy. If adrenal hyperplasia occurs in response to an ACTH-producing pituitary tumor, the diagnosis is Cushing disease. Affected individuals are obese, hypertensive, and hirsute, with common complaints of weakness, easy bruising, and emotional lability. Classically described features of Cushing syndrome include round faces and full cheeks, with increased centripetal fat distribution. Glucose intolerance, acne, and osteoporosis are also common in untreated patients. The diagnosis of Cushing syndrome in pregnancy may be difficult, because many of the previously mentioned signs and symptoms may be seen in normal pregnancy. However, hirsutism and acne tend to be particularly prominent. These patients have elevated plasma cortisol levels, without diurnal variation, that are not suppressed with dexamethasone (Table 17.14). Because of the possibility of adrenal carcinoma, any such patient must be evaluated carefully by appropriate laboratory and radiographic means. With Cushing symptomatology, adrenal cancers are typically very large (6 cm) and easily detectable on CT scan.

TABLE 17.14. *Laboratory diagnosis of hypercortisolism*

Cushing syndrome in pregnancy is associated with an increased incidence of miscarriage, premature labor, diabetes, hypertension, and stillbirth. Consequently, careful fetal surveillance is mandatory.

Congenital Adrenal Hyperplasia Congenital adrenal hyperplasia (CAH) is the result of one of several enzyme defects in cortisol biosynthesis. The majority of patients have 21-hydroxylase deficiency, although 11ß-hydroxylase deficiency or 18-hydroxysteroid dehydrogenase deficiency may be encountered rarely. Because these enzyme deficiencies are autosomal recessive, the patient with this diagnosis has a negligible chance to have an affected child, unless she is related to the child's father. Approximately 90% of patients with CAH during pregnancy have a partial or complete deficiency of the 21-hydroxylase enzyme. The resultant decrease in cortisol production leads to increased ACTH stimulation, which then results in both increased production of androgenic cortisol precursors (e.g., 17ß-hydroxyprogesterone) and decreased production of aldosterone. Because these androgenic steroids readily cross the placenta, pregnancies complicated by significant maternal 21-hydroxylase deficiency are at increased risk for fetal virilization. Such virilization is most apparent in female infants, although male infants also may have somewhat enlarged external genitalia. The risk of fetal virilization is reduced if pregnant patients with CAH receive adequate basal glucocorticoid replacement, together with additional glucocorticoid in times of stress. Mineralocorticoid replacement should be continued, as well. Sometimes the pregnant patient, herself, does not have CAH but has had a previous child with the disorder. The diagnosis of CAH in the fetus historically has been made on the basis of amniotic fluid measurement of 17ß-hydroxyprogesterone. However, molecular genetic techniques are available for evaluation of fetuses at risk by sampling of chorionic villus cells or amniocytes. The affected fetus will produce high levels of androgenic steroids that can cause virilization. Fetal treatment consisting of maternal oral dexamethasone twice daily, beginning at 6 to 7 weeks, may prevent this. The treatment is discontinued if CVS or amniocyte analysis confirms that the fetus does not carry the enzymatic defect. A newborn with ambiguous genitalia requires rapid diagnosis, treatment, and gender assignment. The karyotype, electrolytes, 17ß-hydroxyprogesterone, and urinary 17-ketosteroids should be evaluated expeditiously. The clinical manifestations of cortisol and aldosterone deficiency can include hypoglycemia, hyperpigmentation, apneic episodes, seizures, emesis, hyperkalemia, dehydration, hypotension, vascular collapse, and shock. Resuscitation requires hydrocortisone administration and saline-glucose hydration. Elevated plasma renin activity indicates the need for mineralocorticoid replacement, as well. Eventually, maintenance therapy with hydrocortisone (glucocorticoid) and fludrocortisone (mineralocorticoid) is guided by 17ß-hydroxyprogesterone and plasma renin activity measurements, respectively. Under-treatment is accompanied by premature skeletal maturation, whereas over-treatment leads to slowing of skeletal maturation. It is hoped that using clinical variables such as height velocity and weight to guide replacement therapy will improve the mean adult height in patients with this disorder (i.e., 4th percentile for men and 25th percentile for women).

Pheochromocytoma Pheochromocytoma is a rare, but extremely serious, complication of pregnancy, with increased maternal and perinatal morbidity and mortality rates. Hypertension is present in the majority of patients and may be either paroxysmal or sustained. Only a minority of patients have classic pheochromocytoma episodes, characterized by extreme hypertension, headache, diaphoresis, weakness, tremor, and palpitations. Such patients often are initially considered to have hyperthyroidism. The diagnosis of pheochromocytoma is best made by measurement of 24-hour urinary catecholamine levels; normal values are unaffected by pregnancy. If the diagnosis is established by laboratory criteria, the tumor should be localized, using whatever combination of abdominal CT scan and selective venous sampling is clinically indicated. Eighty percent of these tumors are located in one adrenal gland, 10% to 15% are bilateral, and 10% are found in other locations, including the renal hilus, the organ of Zuckerkandl, and the periaortic sympathetic chain. Because of the high morbidity and mortality associated with this condition, surgical removal during pregnancy is indicated when the diagnosis is established. The patient should be pretreated with a and ß blockers, usually phenoxybenzamine and propranolol, for 1 to 2 weeks before surgery to increase the likelihood of intraoperative symptomatic control. Multidisciplinary management is essential to maximize maternal and fetal outcomes.

DERMATOLOGIC DISEASE

Physiologic Changes During Pregnancy

The systemic changes of pregnancy affect the skin in many ways. Effects can be transient or permanent. Striae gravidarum, or stretch marks, develop in the majority of women and, although they may fade postpartum, they seldom disappear. Ninety percent of all pregnant women experience some degree of hyperpigmentation, the cause of which is unknown. It may involve melanocyte-stimulating hormone and estrogens, or other factors. Hyperpigmentation is more marked in darker skinned women, more often permanent in lighter skinned women, and involves the nipples, perineum, umbilicus, and the linea alba (nigra). Facial pigmentation, or melasma, is seen in at least 50% of pregnant women. It is melanin related and aggravated by sunlight. Benign or melanocytic nevi commonly enlarge and darken and can be

confused with malignant melanoma. Vascular changes are prominent and may manifest as spider angiomas, palmar erythema, and venous varicosities. Finally, scalp hair growth is altered, with an increased proportion of growing hairs to resting hairs. This is reversed after delivery with the onset of telogen effluvium, an abrupt hair loss 1 to 4 months postpartum. By 6 to 12 months, normal hair growth is restored.

Pregnancy-specific Dermatologic Disease

Intrahepatic Cholestasis of Pregnancy Intrahepatic cholestasis of pregnancy is the second most common cause of jaundice in pregnant women (hepatitis is the most common cause) and can produce intense pruritus (Table 17.15). There may be a several-fold increase in maternal serum bile salts, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic-pyruvic transaminase), and bilirubin. Treatment is symptomatic but not always effective. Topical antipruritics, antihistamines, dexamethasone, cholestyramine, and ursodeoxycholic acid have been used with variable success. The pruritus and laboratory abnormalities typically resolve promptly after delivery, but one half of patients will experience recurrence in subsequent pregnancies or with oral contraceptive use. Cholestasis is associated with an increased risk of adverse fetal outcome. Antepartum tests of fetal well-being and consideration of delivery upon documentation of fetal lung maturity are recommended.

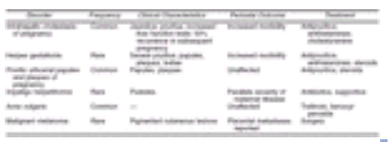

TABLE 17.15. *Dermatologic diseases in pregnancy*

Herpes Gestationis Herpes gestationis, or pemphigoid gestationis, is a rare, serious, autoimmune dermatologic disease seen in pregnancy. The onset is typically in mid to late pregnancy but occasionally occurs postpartum. It is characterized by severe pruritus, with urticarial papules, plaques, erythema, and vesicles and bullae involving the abdomen and extremities. It is occasionally generalized, and exacerbations and remissions are common. Treatment for these pruritic lesions typically includes antihistamines and topical steroids, with oral steroids considered in severe cases. Biopsy with histologic examination reveals subepidermal edema with inflammatory infiltrate, and immunofluorescent staining confirms complement and IgG deposition at the basement membrane. This complement-fixing IgG can cross the placenta and cause dermatologic manifestations in about 5% of newborns; these typically resolve within several weeks. Herpes gestationis has been associated with adverse fetal outcome, so fetal well-being testing is appropriate. Recurrence is seen in subsequent pregnancies, and it is often more severe and occurs earlier in gestation.

Pruritic Urticarial Papules and Plaques of Pregnancy Pruritic urticarial papules and plaques (PUPP) of pregnancy is the most common pruritic dermatosis of pregnancy. An intensely pruritic disorder, PUPP appears late in pregnancy, with a frequency as high as 1%. It is more common in nulliparas and is not known to recur. The papules and plaques can be generalized or patchy, involving the abdomen, buttocks, thighs, and arms. On biopsy and immunofluorescent staining, the absence of antibody or complement deposition distinguishes PUPP from herpes gestationis; instead, there is a nonspecific lymphocytic perivasculitis. Treatment consists of antipruritics and topical steroids. In severe cases, oral steroids may be considered. There is no associated increase in perinatal morbidity.

Impetigo Herpetiformis Impetigo herpetiformis, which some consider to be pustular psoriasis, is a rare disease with an onset late in pregnancy. It initially involves intertriginous surfaces but can extend to involve the entire skin surface and mucous membranes. It classically appears as erythematous patches surrounded by sterile pustules that can become secondarily infected. Systemic symptoms and signs include fever, malaise, gastrointestinal distress, and hypocalcemia. Maternal sepsis is not uncommon. Treatment is supportive, with maintenance of fluid and electrolyte balance, correction of hypocalcemia, and antibiotic therapy, as needed. The utility of steroids is uncertain. Delivery is not necessarily accompanied by resolution. Perinatal morbidity and mortality parallel the severity of maternal disease and tests of fetal well-being are warranted in severe cases.

Non–pregnancy-specific Dermatologic Disease

Acne Vulgaris Some, but not all, women will note that their acne vulgaris improves with pregnancy. Topical treatments, such as tretinoin (Retin-A) and benzoyl peroxide, as well as oral erythromycin, can be useful for the pregnant patient. Isotretinoin (Accutane), prescribed for severe cystic acne, and etretinate (Tegison), prescribed for psoriasis, are contraindicated, because they are teratogenic.

Malignant Melanoma Malignant melanoma, a relatively common disease of women of childbearing age, complicates about 3 in 1,000 births. Melanoma should be considered if a skin lesion is enlarging and unusually colored, with bleeding or irregular borders. The most significant risk factor is sun exposure. Diagnosis is by biopsy. Pregnancy is not thought to affect survival and, as in the nonpregnant population, tumor size and thickness are the most important qualifiers for prognosis. Placental metastases have been reported. Treatment is primarily surgical, with adjuvant chemotherapy or immunotherapy. Because the majority of recurrences manifest within 5 years, most experts recommend a delay in future pregnancies.

ACUTE ABDOMEN AND SURGICAL DISEASE IN PREGNANCY

Excluding ectopic pregnancy, pregnancy does not increase the risk of surgical illness or malignancy and does not increase the risk of adverse outcome after an uncomplicated surgical procedure. Surgical diseases in the pregnant woman can be life threatening, however, because the physiologic changes of pregnancy and the presence of a gravid uterus may delay accurate diagnosis and can make many surgical procedures more technically difficult. Although elective surgery should be postponed until after delivery if at all possible, a surgical emergency in a pregnant woman should prompt the same aggressive treatment considered for the nonpregnant individual.

Appendicitis

Laparotomy is required during 1 in 500 to 1,000 pregnancies; appendicitis is the most common diagnosis. Pregnancy does not increase the risk of appendicitis. It occurs with equal frequency in all three trimesters, and appendectomy can be performed safely throughout pregnancy. However, acute appendicitis has been associated with a maternal mortality rate as high as 5% and an increased risk of preterm labor and fetal loss. These complications most often result from a delay in diagnosis.

Intraabdominal pathology can be difficult to diagnose in the gravid woman. Bowel is progressively displaced upward and backward as the gravid uterus grows during pregnancy. Because bowel sounds normally are heard only in the upper abdomen, the absence of bowel sounds may not be appreciated. The appendix also assumes an increasingly more cephalad position, and associated inflammation and pain are therefore not typically localized to the right lower quadrant after the first trimester. Anorexia, nausea and vomiting, a change in bowel habits, and even epigastric or abdominal pain can be part of normal pregnancy and thus may not suggest pathology. Laboratory evaluation may not be helpful, because a mild leukocytosis is common in pregnancy. Nevertheless, it is in the patient's best interest to have a high index of suspicion, because delayed diagnosis and therapy can be catastrophic.

The patient typically has periumbilical or right flank pain that is increased by uterine manipulation. Placing the patient on her left side allows the uterus to fall away from the right flank and may facilitate examination. Thirty percent of appendices are retrocecal in location; in this situation, the initial complaint may be right flank or leg pain or pain on rectal examination, and the patient may have psoas or obturator muscle symptoms. Anorexia, nausea, and vomiting usually are increased relative to normal pregnancy. The white blood cell count may be elevated significantly, and the patient may be febrile, especially if rupture or generalized peritonitis is present. Sonographic examination can help rule out other diagnoses but generally cannot confirm appendicitis itself, because ultrasound waves penetrate gas-filled structures poorly. A plain radiograph to identify air-fluid levels or free air in the abdomen can be very helpful and generally exposes the fetus to less than 300 mrad (0.0003 Gy) of radiation. Once appendicitis is suspected, laparotomy should be performed. A right paramedian vertical incision provides ideal visualization.

Intestinal Obstruction

The second most common nonobstetric indication for abdominal surgery is intestinal obstruction, which complicates 3 in 10,000 pregnancies. Risk factors include previous pelvic inflammatory disease and previous intraabdominal surgery. The incidence of intestinal obstruction increases as pregnancy advances because the enlarging uterus displaces the bowel upward and backward, placing preexisting adhesions on tension and increasing the risk of volvulus. As stated above, pregnancy makes assessment of bowel function difficult and may contribute to a delay in diagnosis. Maternal mortality as high as 10% to 20% has been reported, due primarily to maternal shock associated with unrecognized bowel infarction. As with appendicitis, once bowel obstruction unresponsive to conservative management has been diagnosed, surgical intervention should not be delayed.

Cholecystitis

Acute abdomen may be due to cholecystitis. Cholecystitis occurs in 1 in 1,000 to 1,600 pregnancies; over 90% of cases are caused by cholelithiasis. Patients typically seek treatment for nausea, vomiting, and the acute onset of colicky midepigastric pain. Laboratory evaluation and ultrasonographic examination are helpful in making the diagnosis. The treatment is primarily medical, especially in the first and third trimesters. Surgery is considered for the patient with repeated severe episodes of

cholecystitis and unremitting pain, systemic toxicity, or persistent or recurring pancreatitis. The second trimester is preferable for elective surgery, because the risks of surgery-associated fetal loss, preterm labor, or fetal compromise are lowest at this time. Further, although the pregnancy is well established, the uterus is still small enough to allow adequate visualization of the operative site without extensive uterine manipulation. Open laparoscopic second-trimester cholecystectomy has been reported with good results. Maternal mortality is minimal, and fetal mortality is usually less than 5%.

Pancreatitis

Pancreatitis can result in acute abdomen. In pregnancy, the most common cause of pancreatitis is cholecystitis, with alcohol abuse, viral infection, and hyperlipidemia accounting for a small proportion of cases. Treatment is primarily medical, as outlined earlier, with surgery considered only if symptoms do not improve rapidly (1 to 2 days) or an abscess or pseudocyst develops. As with cholecystitis, ultrasonographic examination may be helpful in making the diagnosis and ruling out other entities. The patient should be followed closely, with careful attention given to fluid management. Fetal loss can occur in complicated cases as a result of acidosis, hypovolemia, and hypoxia.

Liver Disease

Abdominal pain, particularly right upper quadrant pain, may be due to liver disease. Most commonly, liver pathology in pregnancy is due to preeclampsia, hepatitis, or acute fatty liver. Very rarely, pregnancy is complicated by cirrhosis or portal hypertension. Because pregnancy increases the risk of bleeding from esophageal varices, such patients may require endoscopic sclerotherapy during pregnancy.

Peptic Ulcer Disease

Although PUD can cause symptoms of acute abdomen, it is rare in gravid women because the hormonal milieu and other physiologic changes of pregnancy confer a protective effect. Endoscopy can be performed to confirm the diagnosis. Management is primarily medical.

MATERNAL TRAUMA

Physiologic Changes in Pregnancy

Accurate assessment of the pregnant trauma victim requires knowledge of the physiologic changes that normally occur during gestation. No organ system is unaffected, but the functions of the cardiovascular and respiratory systems are altered most dramatically. Plasma volume increases by 50%, while red blood cell mass increases by 25%, resulting in a physiologic anemia. Leukocytosis normally occurs, peaking in the third trimester with a white blood cell count of 12,000 to 18,000/mm^3 and 25,000/mm^3 in labor. Cardiac output increases by 4.5 to 6.0 liters per minute (30% to 50%), primarily as a result of a gradual increase in stroke volume to 50% above nonpregnant levels. The majority of pregnant women have a widely split first heart sound, a third heart sound, and a systolic ejection murmur. Over 10% of cardiac output goes to the uterus at term, and veins in the pelvis and lower extremities are engorged. Renal blood flow increases by 30%, leading to a 30% to 50% increase in the glomerular filtration rate. As a result, the BUN and creatinine fall and should not be higher than 13 mg/dL and 0.8 mg/dL, respectively, during pregnancy. A hormonally mediated decrease in vascular resistance leads to a midtrimester decrease in both systolic and diastolic blood pressure. All these changes are affected by maternal position. In the supine position, the uterus compresses the vena cava, resulting in decreased venous return, decreased cardiac output, a drop in blood pressure, bradycardia, and syncope.

Hyperventilation begins as early as the first trimester, probably in response to increased progesterone levels. Because of gradual elevation of the diaphragm by the enlarging uterus, functional residual capacity, residual volume, and expiratory reserve volume all decrease, while inspiratory reserve volume increases. The normal gravida at term has a chronic respiratory alkalosis with a resting carbon dioxide tension below 30 mm Hg. Seventy-five percent of gravidas experience dyspnea in the third trimester. Although arterial oxygen tension generally rises toward term, a moderate hypoxemia can occur in the supine position. Thus, the midtrimester gravida lying supine in the emergency room may be hypotensive, bradycardic, relatively hypoxemic, and anemic, all because of normal physiologic changes.

The ABCs

Taking into consideration the physiology of pregnancy, the pregnant trauma patient should be assessed initially as any trauma victim is assessed, according to the ABCs: airway, breathing, and circulation. In a rapid assessment of the patient's status, airway patency and adequacy of respirations should be established. Supplemental oxygen should be administered to all patients; the patient who is not breathing spontaneously should be intubated and mechanically ventilated. A wedge should be placed under the right hip to displace the uterus off the vena cava. Pregnancy significantly slows gastrointestinal motility, so all pregnant women should be assumed to have a full stomach. The conscious patient should be given sodium citrate or a similar antacid, while the airway of the unconscious patient should be protected.

If cardiac function is adequate, attention should be turned to maintaining adequate circulating volume. One or two large-bore intravenous lines should be established and Ringer's lactate solution given. Infusion of large volumes of sodium chloride should be avoided, because it can lead to hyperchloremic acidosis that would exacerbate lactic acidosis caused by poor perfusion. If the patient is bleeding, packed red blood cells should be ordered and administered as soon as possible.

If cardiac arrest has occurred, full resuscitation should be initiated as for any other patient. CPR at most generates only 30% of the normal cardiac output; CPR of a pregnant woman in left lateral tilt will be even less effective. The patient must therefore remain supine, and someone must be assigned to elevate the uterus manually off the vena cava. It can be assumed that perfusion to the uterus will be negligible during CPR. The general consensus is that a fetus can survive total asphyxia for at most 4 to 6 minutes. If cardiac function has not been restored within 4 minutes of arrest and the fetus is still alive, an emergent, nonsterile, classic cesarean section should be performed without anesthesia at the bedside, and the uterus and abdominal incisions closed as rapidly as possible. If cardiac arrest has persisted for more than 6 minutes but fetal cardiac activity continues, delivery should still be performed. In addition to possibly saving the fetus, evacuation of the uterus will facilitate CPR by improving cardiovascular dynamics.

The American College of Obstetricians and Gynecologists recommends that any pregnant woman sustaining trauma beyond 22 to 24 weeks gestation undergo fetal monitoring for a minimum of 4 hours. If more than four contractions per hour are observed, if rupture of membranes, bleeding, fetal arrhythmia, or fetal heart rate decelerations occur, or if the mother is seriously injured, the patient should be admitted with continuous fetal monitoring for at least 24 hours.

Abdominal Trauma

Motor vehicle accidents are the leading cause of blunt abdominal trauma (especially if the woman is unrestrained or is not wearing her lap belt as low as possible under her uterus), followed by falls and direct assaults. Placental abruption is the most common severe complication of blunt trauma, occurring with 1% to 5% of minor injuries and 20% to 50% of major injuries. Findings may include vaginal bleeding, uterine tenderness or contractions, as well as fetal tachycardia, decelerations, acidosis, and death. Direct fetal injury is less common but most often involves fetal skull and brain injury as a result of maternal pelvic fracture. Rupture of the liver or spleen can accompany blunt trauma, and rupture of the uterus occurs in less then 1% of cases. Bladder injury or rupture is more common after 20 weeks, when the bladder assumes an intraabdominal position and no longer is protected by the pelvis. Bladder injury may also result from pelvic fracture.

A patient with any signs of shock or peritoneal irritation is appropriately suspected to have major intraabdominal injury. Intraabdominal bleeding can be detected with intraperitoneal lavage, just as in the nonpregnant patient. Bladder injury is suspected when a urinary catheter cannot be passed, fails to return urine, or returns grossly bloody fluid. Bowel injury is uncommon, except at points of fixation. Uterine rupture usually results in vaginal bleeding, hypotension, absent fetal heart tones, and hematuria if the rupture involves the anterior uterine wall. If significant injury is suspected, the patient should be stabilized and a laparotomy performed as rapidly as possible. Extent of injuries, gestational age, and assessment of fetal well being are considerations for fetal delivery. Appropriate counseling should be provided regarding the possibility of hysterectomy, and blood products should obviously be available.

However, if the patient is stable and a CT scan or other radiologic studies are necessary for diagnostic purposes, they should be performed. If at all possible, the patient should be positioned with a wedge under one hip to deflect the uterus off the vena cava. The amount of radiation exposure resulting from standard radiologic procedures is less than the minimum dose associated with fetal teratogenicity or growth effects. The fetus is most susceptible before 15 weeks gestation, when radiation doses of 10 rad (0.1 Gy) or greater can cause mental retardation. At 16 to 25 weeks, the risk is considerably less, and radiologic procedures at 25 weeks or beyond pose minimal to no risk. Most authorities recommend limiting fetal exposure to less than 5 rad (0.05 Gy). Most plain radiographs entail doses of less than 1 rad (0.01 Gy); an abdominal CT scan exposes the fetus to 2 to 2.6 mrad (0.02 to 0.026 Gy). MR imaging does not require ionizing radiation and thus does not entail risk at any gestational age. Medical and surgical care should not be compromised in any way because the patient is pregnant. If the woman is Rh negative and unsensitized, Rh_0(D) immune globulin will protect her if there was fetal-maternal bleeding.

Penetrating Abdominal Trauma

Gunshot and knife wounds are responsible for most cases of penetrating abdominal trauma in pregnancy. As the uterus grows out of the pelvis, it becomes more likely that the uterus will be a site of injury. Penetration of the uterus results in maternal mortality in less than 5% of cases, but in fetal injury in 59% to 89% of cases, with fetal death in 41% to 71%. After penetrating abdominal trauma, the pregnant patient should be assessed as above and attempts made to determine the exact site(s) of injury and associated organ damage. The initial evaluation and subsequent surgical management should be the same as for the nonpregnant patient. If the uterus is the primary site of injury, exploratory laparotomy will likely be required. Bullet wounds must be explored surgically, because deflection of the bullet off intraabdominal structures can cause extensive damage and make it impossible to determine the projectile path. Knife wounds may require exploration, because the enlarged uterus compresses other intraabdominal organs and prevents structures underlying the stab wound from sliding away from the blade, as they would in the nonpregnant state. Ultrasonographic examination of the fetus to determine age and assess viability is essential.

Decisions about whether or not to empty the uterus should be individualized. If there is extensive intrauterine damage, if the pregnancy is near term, if there is a strong suspicion of fetal hemorrhage, or if uteroplacental insufficiency is present, the fetus should be delivered and the uterus thoroughly explored. If the uterus is uninjured or the injury can be repaired without entering the uterine cavity, if the fetus is previable or dead, and if uterine size does not preclude adequate exploration of the abdominal cavity, hysterotomy may be avoided as long as hemostasis is achieved.

Intraabdominal organs are compressed into the upper abdomen as pregnancy advances. Penetrating wounds in this area are especially traumatic, because multiple organs are injured. In decreasing order of frequency, small bowel, liver, colon, and stomach are damaged most often. For this reason, many authorities recommend that upper abdominal wounds be explored by laparotomy in all pregnant patients. Broad-spectrum antibiotics should be administered, and tocolytic therapy can be used with caution during the postoperative period. Beta mimetic agents have maternal and fetal cardiovascular effects that may confuse postoperative assessment, while magnesium sulfate is associated with maternal nausea, vomiting, and dizziness. Maintenance of normal intravascular volume and close attention to fluid balance are crucial.

Head Trauma

The gravida with head trauma should be evaluated and treated in the same way as the nonpregnant patient. Assessment begins with the ABCs. The head and neck should be immobilized as a unit in case there is cervical spine injury. In the stable patient, gestational age and viability should be assessed. Unless precluded by vertebral fractures, the uterus should be rolled off the vena cava by placing a wedge under the backboard. Mannitol, steroids, and other medications should be given, as necessary. Because fluid restriction, osmotic diuresis, maternal hypotension, and hypothermia induced during neurosurgery may reduce uteroplacental blood flow, the viable fetus should be monitored and therapeutic adjustments made as required.

Burns

Burns are described as being partial or full thickness and quantitated according to the percentage of surface area affected. Extensive full-thickness burns result in severe thermal instability and dramatic fluid loss. Hypovolemic shock can occur, especially within the first 36 hours. Airway management and treatment of the burn, itself, should be the same for pregnant and nonpregnant patients. The pregnant burn victim, however, requires meticulous attention to fluid management, with consideration of the expanded intravascular volume and altered cardiovascular dynamics associated with pregnancy (see above). Fetal status is related directly to the adequacy of uteroplacental perfusion; poor outcome is associated with inadequate fluid resuscitation. If more than 50% of the patient's surface area is affected, immediate delivery of the viable fetus should be considered. However, in some cases, aggressive fluid resuscitation and close fetal monitoring may allow delivery to be deferred.

Thermal injury causes elevated prostaglandin levels and increased susceptibility to infection. These factors often contribute to preterm labor. Because complications typically associated with tocolytic therapy may not be tolerated by the gravid burn victim, tocolytics should be used cautiously, if at all. Indomethacin (Indocin) may be the safest agent for use before 32 weeks. If fetal surveillance (24 or more weeks gestation) indicates fetal compromise despite optimal maternal resuscitation, the fetus should be delivered.

Electrical Injury

There are very few reports of electrical injury during pregnancy. Because the uterus and amniotic fluid offer low resistance, current entering an upper xtremity and exiting a lower extremity may traverse the uterus and fetus. Maternal cardiac and respiratory status should be assessed and treated as in any injured patient. Ultrasonographic examination and fetal monitoring should guide pregnancy management. Fetal survival without specific intervention has been reported, although immediate fetal death is also possible.

SUMMARY POINTS

- The obstetrician-gynecologist must be thoroughly familiar with the normal physiologic changes of pregnancy, because these changes affect the clinical pictures of many diseases, as well as their management.
- Although many disease processes are unchanged by pregnancy, the course of some diseases is altered. This alteration often affects diagnosis and therapy.
- Necessary radiologic procedures can be performed during pregnancy.
- Very few medications need to be restricted in pregnancy.
- In general, pregnant and nonpregnant women with a medical or surgical disease should receive comparable care, although fetal well-being must be kept in mind if fetal viability has been reached.

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Chapter 18

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Immunologic Disorders in Pregnancy

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REPRODUCTIVE IMMUNOLOGY

The physiologic mechanisms that protect the fetus and its placenta from attack by the maternal immune system are complex, and many remain poorly understood. Nevertheless, the practicing obstetrician should be familiar with the immunologic aspects of the maternal–fetal relationship, as well as the profound impact that aberrations in immunologic function have on pregnancy outcome.

Fundamental Immunobiology

The primary function of the immune system is to protect against foreign pathogens, primarily by distinguishing biologic “self” from “nonself” (the clonal selection model of immunity). In the early stages of development, immune cell precursors are educated to recognize self. T cells that recognize self-antigens are killed or rendered inactive while T cells with specific receptor types against foreign pathogens continue to develop.

The immune system has two primary effector mechanisms classified as either innate or adaptive. Although they function through different mechanisms, they work together to defend the body from foreign pathogens. The innate immune response, also known as cellular immunity, is a continuous, nonspecific process that recognizes all foreign material as nonself. Components of the innate system include physical and biochemical barriers, primary effector cells such as mononuclear phagocytes, natural killer (NK) cells, and polymorphonuclear leukocytes, and circulating biochemical factors such as the complement system. Recognition of foreign pathogens by membrane receptors on effector cells is followed by phagocytic destruction and induction of apoptosis by NK cells (Fig. 18.1). One family of pathogen recognition receptors, called Toll-like receptors (Tlr), appears to play an important role in mediating the inflammatory responses in the reproductive tract. As membrane receptors on inflammatory cells, they initiate a nonspecific response to bacterial antigens and may also function to facilitate adhesion of immune cells on endothelium.

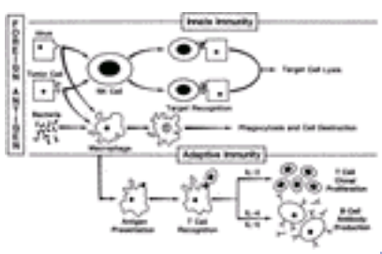

FIG. 18.1. Schematic view of innate and adaptive immune systems. Phagocytic cells of the innate immune system recognize foreign antigen. The foreign antigen can be a microbial pathogen, viral antigen, or tumor antigen. Innate immune responses result in direct cytotoxicity or destruction of the pathogen. Activation of the adaptive immune system depends on interaction with processed antigen provided by cells of the innate immune system. T-cell and B-cell activation results in T-cell clonal proliferation and B-cell antibody production, respectively. *IL*, interleukin; *NK*, natural killer. (From Dudley DJ. The immune system in health and disease. *Balliere's Clin Obstet Gynaecol* 1992;6:393.)

As proliferating T cells mature, they differentiate into an array of subtypes that have diverse functions. CD4+ helper cells help other cells proliferate and help B cells produce antibodies. CD4+ inducer cells control the subsequent development of other T cells. CD8+ cytotoxic cells lyse foreign or virus-infected cells, and CD8+ suppressor cells prevent uncontrolled proliferation. T-cell subsets destroy and remove foreign tissues and organisms by direct binding and secretion of cytokines that recruit and activate macrophages. Cytokines are a means of communication between immune cells. Interleukin (IL)-1 is produced by macrophages and monocytes and promotes multiplication and activation of lymphocytes. IL-2, produced in response to lymphocyte activation, is the major T-cell growth factor for the proliferation of activated T cells.

The hallmark of adaptive immunity is precise specificity of antigen recognition and memory so that repeated exposures to a specific antigen elicit an enhanced immune

response. The adaptive response includes several stepwise processes that occur in the lymphatic system (see Fig. 18.1). The primary adaptive effector cells are B cells, precursors of plasma cells that secrete specific antibodies that circulate through the bloodstream and destroy target cells in concert with complement or antibody-dependent cellular cytotoxic cells. Antibodies are heterogeneous proteins produced by gene rearrangement, a process that creates myriad possible immunoglobulin antigen-recognition sites. The first antibody to respond is immunoglobulin M (IgM), which is soon superseded by a predominantly immunoglobulin G (IgG) response.

Cells of the innate immune system act as secondary effector cells in the adaptive response through T-cell recognition of HLA antigens, which are products of the major histocompatibility complex (MHC) located on the short arm of chromosome 6 (Fig. 18.2). Class I MHC antigens are expressed by nearly all nucleated cells and are identified by cytotoxic T cells. Class II MHC antigen expression is restricted to B cells, monocytes, macrophages, and activated T cells but is important for presenting antigen to helper T cells.

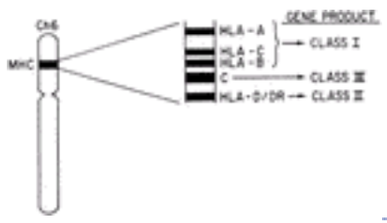

FIG. 18.2. Chromosomal location of the major histocompatibility complex. Within the complex are genes that encode as follows: for class I antigens (HLA-A, HLA-B, and HLA-C); for several components of the complement cascade, including complement components 2 and 4 and factor B, some of which are located at position C; and for class II antigens. (From Scott JR, Rote NS, eds. *Immunology in obstetrics and gynecology.* Norwalk, CT: Appleton-Century-Crofts, 1985:35.)

Embryologic Development of the Immune System

The development of the immune system begins at conception and continues throughout pregnancy and into the newborn period. During weeks 2 and 3 of gestation, pluripotential yolk sac stem cells form the precursors for all the blood cell series. The thymus develops in the human embryo at 6 weeks gestation, and lymphocyte differentiation proceeds in the absence of foreign antigens. Small lymphocytes appear in the peripheral blood at week 7 and around lymphocyte plexuses by week 8. As early as 13 weeks gestation, T cells that can respond to mitogens and recognize histoincompatible cells begin to appear. By 20 weeks gestation, the human fetus has the ability to respond to congenital infections by producing plasma cells and antibodies.

The presence of an intact trophoblastic cellular barrier prevents the movement of large numbers of immunocompetent cells into or out of the fetus during pregnancy. In contrast, maternal IgG, by virtue of its Fc fragment, is specifically selected for placental transfer (Fig. 18.3). Fetal IgG concentrations are about 10% of adult levels by the middle of the first trimester (Fig. 18.4). Adequate humoral immunity in the neonatal period depends on the circulating immunoglobulins that have crossed the placenta, and fetal blood levels of IgG reflect maternal levels. The specific antibody protection depends on the mother's own antigenic experience. The primary role of maternal antibodies is to protect the neonate from infections. However, several maternal autoimmune disorders are characterized by production of IgG antibodies and can be harmful to the infant.

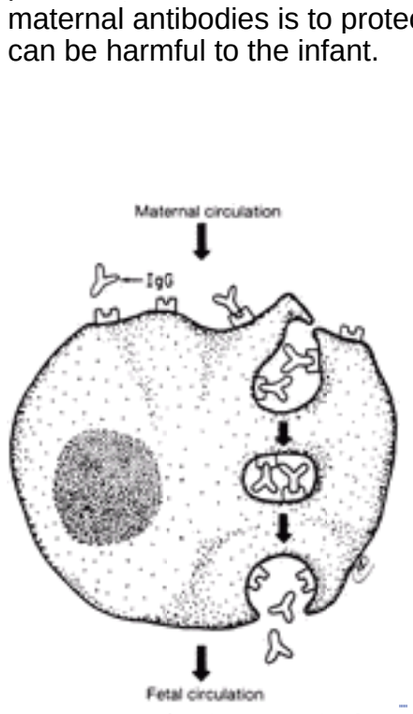

FIG. 18.3. The transport of maternal immunoglobulin G (IgG) across the trophoblast and into the fetal circulation is an active process. Maternal IgG binds to Fc receptors on the surface of the trophoblast and is internalized into vacuoles. These receptors are specific for the Fc portion of IgG and do not bind other classes of immunoglobulins. The interaction of IgG with the receptors probably protects the antibody from digestion during the transport of the vacuole across the cell. On the fetal side, IgG is released into the fetal circulation. (From Scott JR, Rote NS, eds. *Immunology in obstetrics and gynecology.* Norwalk, CT: Appleton-Century-Crofts, 1985:70.)

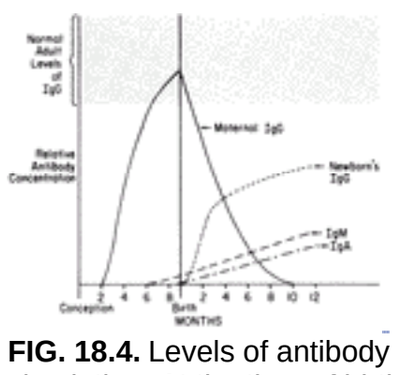

FIG. 18.4. Levels of antibody in the cord blood and neonatal circulation. Early in gestation, maternal immunoglobulin G (IgG) crosses the placenta and enters the fetal circulation. At the time of birth, the fetal circulation normally contains a near-adult level of IgG, which is almost exclusively maternal, and small amounts of fetal immunoglobulin M and immunoglobulin A. After delivery of the child, maternal IgG is rapidly catabolized, whereas neonatal IgG production increases. (From Scott JR, Rote NS, eds. *Immunology in obstetrics and gynecology.* Norwalk, CT: Appleton-Century-Crofts, 1985:69.)

Pathogenesis of Autoimmune Disease

The immune system is normally regulated so that cells capable of producing an immune response to self-antigens are suppressed. Activation of innate immunity requires two separate signals from a presenting antigen to T cells. The first signal is produced through the recognition of the MHC antigen on presenting cells. The second signal is through CD28 expressed on the T cell and CD80 or CD86, which are expressed on the activated antigen-presenting cell. If only one signal is received, the T cell is rendered anergic or unresponsive to further activation even if both signals are given at a later time.

Autoimmune diseases result from a breakdown in normal regulatory mechanisms that lead to an inability to discriminate between self and nonself. Autoimmunity is characterized by persistent activation of immunologic mechanisms that affect the function and integrity of certain cells and organs. The process may be initiated by environmental agents but is probably sustained by persistent T-cell activation that overrides normal tolerance of self-antigens. Autoimmune diseases have a predilection for women of reproductive age and are often encountered during pregnancy. The effects of pregnancy on autoimmunity appear to depend on whether the autoimmune disease is innate (cellular) or adaptive (humoral) in nature. Diseases with strong cellular pathophysiology, such as rheumatoid arthritis and multiple sclerosis, are associated with remission during pregnancy whereas diseases characterized by autoantibody production, such as lupus and Graves disease, are more

severe in pregnancy.

Maternal–Fetal Immunology

Maternal immunologic reaction to the genetically dissimilar cells of the conceptus begins at fertilization and continues throughout pregnancy as differentiated fetal trophoblast cells interact with maternal uterine tissue and blood. The normal relationship between mother and fetus appears to be healthy and growth-promoting rather than the usual allogeneic model of destruction.

Several mechanisms likely play a role in protection of the fetus from immunologic damage. Circulating blocking factors have been theorized to attenuate maternal immunologic reaction. One progesterone-induced blocking factor suppresses production of lymphocytes and pro-inflammatory cytokines. In addition, so-called blocking antibodies may prevent lymphocytic destruction by binding to receptors on fetoplacental tissues. Alternatively, blocking antibodies may be directed against antigen-specific combining sites (idiotypes) on maternally produced antibodies that prevent them from assisting lymphocytes in targeting cells on the conceptus. While the concept is appealing, the relevance of blocking antibodies and other alleged circulating pregnancy-maintaining factors remains unsettled. Not only do agammaglobulinemic women without antibody production have normal pregnancies, antibodies do not frequently appear until late in the first or second trimester of the first pregnancy.

Immunotolerance during pregnancy probably results from interactions at the local maternal–fetal interface rather than from generalized maternal immunosuppression. Before conception, endometrial stromal cells transform into decidual cells that contain T-cell subtypes with immunosuppressive activity. One T-helper cell subset secretes cytokines that are beneficial or neutral to the presence of the fetus. Another is thought to prevent colonization with microbial pathogens. Additional evidence suggests that some subsets of the decidual T cells promote growth of the placenta through the secretion of cytokines that suppress inflammation. Hormones, enzymes, growth factors, and endometrial proteins within maternal decidual tissue also have potent immunomodulatory properties that promote a favorable interaction between the conceptus and the mother.

The presence of large granular lymphocytes in luteal phase and early to mid-pregnancy deciduas has generated considerable interest among reproductive immunologists. Under normal circumstances, these nonspecific innate immune effector cells, similar to NK cells, kill standard NK cell targets with the notable exception of trophoblastic cells. Their absence or alteration has been associated with pregnancy loss.

The placenta also plays an active role in protection of the fetus from maternal immune responses. Villous cytotrophoblasts and syncytiotrophoblasts escape destruction because both express nonclassic MHC antigens that prevent trophoblast destruction through inhibition of lysis by activated NK cells, limitation of leukocyte cytotoxic activity, suppression of pro-inflammatory cytokine production, and induction of T-cell death. Nonclassic MHC antigens also promote trophoblast proliferation and invasion. Altered expression of nonclassic MHC antigens has been linked to recurrent miscarriage and preeclampsia.

Placental expression of a protein known as the Fas ligand may also play a role in pregnancy success through selective deletion of antifetal T-cell clones. In animal studies, binding to the Fas ligand causes death and removal of autoreactive T cells.

The placenta may also inhibit T-cell proliferation by sequestering nutrients. Placental indolamine 2,3-dioxidase (IDO) inactivates the amino acid tryptophan that is essential for the proliferation of T cells. The role of IDO in recurrent pregnancy loss in humans has not yet been widely investigated.

ERYTHROBLASTOSIS FETALIS

Though the first description of erythroblastosis fetalis (hemolytic disease of the newborn) dates back to the 1609, it was not until the early 1900s that the role of alloimmunization in the pathogenesis of erythroblastosis was established. The early investigators determined that an Rh–negative mother becomes alloimmunized by exposure to Rh–positive fetal erythrocytes during pregnancy or delivery. Maternally produced anti-erythrocyte antibodies pass through the placenta to the fetus where they react with the Rh–positive fetal erythrocytes, causing their destruction. In the past, Rh alloimmunization has also been referred to as sensitization and immunization. The terms *alloimmunization* and *sensitization* will be used interchangeable in this text.

Many other erythrocyte antigens have been described since the discovery of the Rh antigen but only a few are clinically important causes of maternal alloimmunization. However, with the widespread use of Rh–immunoglobulin prophylaxis and the decline in Rh-D alloimmunization, the overall importance of the “minor antigens” in red cell alloimmunization has increased.

Genetics of the Rh Antigen

The Rh blood group was so named because rabbits immunized with rhesus monkey erythrocytes produced an antibody that agglutinated erythrocytes from 85% of whites. The so-called Rh factor is actually an antibody directed against an erythrocyte surface antigen of the rhesus blood group system. The Rh blood group system has a high degree of polymorphism, with five major antigens and many variant minor antigens. While three systems of nomenclature have been suggested, the Fisher-Race system is probably best suited to understanding the inheritance of the Rh antigen and the clinical management of Rh alloimmunization. It assumes the presence of three genetic loci, each with two major alleles, lettered C, c, D, E, and e. No antiserum specific for a ?d? antigen has been found.

The Rh gene complex is described by the three appropriate letters with eight possible combinations (listed in decreasing order of frequency among whites): CDe, cde, cDE, cDe, Cde, cdE, CDE, and CdE. Genotypes are indicated as pairs of gene complexes, such as CDe/cde. Certain genotypes, and thus certain phenotypes, are more prevalent than others. Although the alleles are always written in the order C(c), D, E (e), the actual order on chromosome one is of the genes coding for the antigens D, C(c), E (e). Anti–C, anti–c, anti–D, anti–E, and anti–e designate specific antibodies directed against the respective antigens. Because the majority of Rh alloimmunization resulting in overt clinical disease results from incompatibility with respect to the D antigen, common convention holds that *Rh-positive* indicates the presence of the D antigen and *Rh-negative* indicates the absence of D antigen on erythrocytes.

Unique Rh antibodies have been used to identify more than 30 antigenic variants in the Rh blood group system, the most common of which is the D^u antigen, now commonly referred to as *weak D*. This heterogeneous group of clinically important D-antigen variants is most often found in blacks. At least some weak D–positive patients are capable of producing anti–D, which could presumably result in a weak D–positive mother becoming sensitized to her D–positive fetus, but such an occurrence is exceedingly rare.

The Rh-D antigen appears very early in embryonic life and has been demonstrated on the red blood cells of a 38-day-old fetus. Its precise function is unknown, though it may play a role in maintaining red cell membrane integrity or regulate the asymmetric distribution of different phospholipids through the red cell membrane.

Pathophysiology of Rh Alloimmunization

Rh alloimmunization can only occur in the presence of three conditions:

1. The fetus must have Rh–positive erythrocytes, and the mother must have Rh–negative erythrocytes.
2. The mother must have the immunogenic capacity to produce antibody directed against the D antigen.
3. A sufficient number of fetal erythrocytes must gain access to the maternal circulation.

Incidence of Rh-D Incompatibility and Subsequent Alloimmunization About 15% of whites, 5% to 8% of blacks, and 1% to 2% of Asians and Native Americans are Rh-D–negative. In terms of risk, an Rh–negative woman has about an 85% chance of mating with an Rh–positive man, 60% of whom are heterozygous and 40% of whom are homozygous at the D locus. Assuming that one-half of the conceptions of heterozygous men will be Rh-D–positive, the chance of an Rh–positive man producing an Rh–positive fetus is about 70%. An Rh–negative woman has about a 60% chance of bearing an Rh–positive fetus (0.85 × 0.70). About 10% of pregnancies are Rh-incompatible (0.15 × 0.60). However, fewer than 20% of Rh–incompatible pregnancies result in alloimmunization because fetomaternal hemorrhage sufficient to trigger a maternal antibody response does not occur in every case. About 16% of untreated Rh–negative women become alloimmunized in their first Rh–incompatible (ABO–compatible) pregnancy. Half produce detectable anti–D antibody within 6 months of delivery while the rest have undetectable amounts until early in the next incompatible pregnancy. Overall, even before the introduction of Rh–immunoglobulin prophylaxis, only about 1% of pregnant women had anti–D antibody.
Maternal Immunologic Response The probability and severity of Rh-D alloimmunization varies depending on individual patient characteristics. As many as 30% of Rh–negative individuals appear to be immunologic “nonresponders” who will not become sensitized. In addition, ABO incompatibility diminishes the risk of alloimmunization to about 1.5% to 2.0% after the delivery of an Rh–positive fetus. This is possibly due to rapid clearance of ABO–incompatible fetal cells from the maternal circulation or alteration or damage to the fetal Rh antigen so that it is no longer immunogenic. The effect is most pronounced if the mother is type O and the father is type A, B, or AB.

Fetomaternal Hemorrhage Fetal red cells may gain access to the maternal circulation during pregnancy, delivery, and the immediate postpartum period. Fetomaternal hemorrhage in a volume sufficient to cause alloimmunization is most common at delivery, occurring in 15% to 50% of births. The amount of fetal blood entering the maternal circulation is usually less than 0.1 mL but may be greater than 30 mL in 0.2% to 1% of cases. Risk factors for excessive postpartum fetomaternal hemorrhage include cesarean delivery, multiple gestations, bleeding placenta previa or abruption, manual removal of the placenta, and intrauterine manipulation. However, the majority of cases of excessive fetomaternal hemorrhage occur after uncomplicated vaginal delivery. Antepartum events can also result fetomaternal hemorrhage in sufficient volume to cause in alloimmunization in 1% to 2% of cases, even without obvious disruption of the choriodecidual junction (Table 18.1). Fortunately, asymptomatic antepartum sensitization rarely occurs before the third trimester.

Event or procedure	*Dosage of Rh Immune globulin*
First trimester miscarriage	50 µg
Ectopic pregnancy	50 µg
Threatened first trimester miscarriage[a]	50 µg
Molar pregnancy	50 µg
Induced first trimester abortion	50 µg
Induced second trimester abortion[b]	300 µg
Fetal death (>10 wks of gestation)[b]	300 µg
Amniocentesis	300 µg
Chorionic villus sampling	50 µg
External cephalic version[b]	300 µg
Abruption/previa[b]	300 µg
Abdominal trauma[b]	300 µg
Vaginal bleeding in the second and third trimester of unknown origin[b]	300 µg

[a]The risk of fetomaternal hemorrhage and alloimmunization is uncertain and the benefit of prophylaxis is uncertain in this situation.
[b]A test for the presence and volume of fetomaternal hemorrhage should be performed to determine the dosage of Rh immune globulin.

TABLE 18.1. *Antepartum events associated with fetomaternal hemorrhage*

Rh-D Immunoglobulin

The prevention of alloimmunization to a specific antigen by the passive administration of antibody is termed *antibody-mediated immune suppression*. In the case of Rh-D alloimmunization, a high degree of protection was first achieved by administering anti–D immunoglobulin (Rh-D immunoglobulin) to Rh–negative male volunteers who had been infused with Rh–positive red cells. It was later established that the amount of Rh-D immunoglobulin necessary to prevent alloimmunization varies according to the size of fetomaternal hemorrhage:

- 300 g of Rh-D immunoglobulin for exposure to 10 mL of fetal blood
- 20 g of Rh-D immunoglobulin for exposure to 1 mL of fetal erythrocytes
- 10 g of Rh-D immunoglobulin for 1 mL of whole fetal blood.

Postpartum Alloimmunization Prophylaxis The early Rh-D alloimmunization prevention trials found that administration of Rh-D immunoglobulin within 72 hours of delivery reduced alloimmunization to less than 1.5% in Rh–negative women, a seven- to ten-fold decrease in alloimmunization compared with untreated controls. Although 300 g of Rh immunoglobulin was used (and continues to be the standard in the United States), it has subsequently been shown that a dose of 100 g to 150 g is probably adequate for routine use. Rh-D immunoglobulin must be given as soon as possible after exposure to Rh-D–positive blood (delivery or other event associated with fetomaternal hemorrhage) before the primary immune response is established. While 72 hours is the standard recommendation, it is an artifact from the early studies performed using inmates, during which prison officials would allow visits only at 3-day intervals. Prophylaxis beyond 3 days has never been extensively studied but if for some reason Rh–immune prophylaxis does not occur within 72 hours after exposure, susceptible Rh-D–negative women should be treated up to 14 to 28 days. Further, if the neonatal Rh status is unknown 3 days after delivery, Rh immunoglobulin should be given rather than waiting for the neonatal results.
Antepartum Alloimmunization Prophylaxis One to two percent of susceptible Rh-D–negative women become sensitized during pregnancy in spite of postpartum Rh-D–immune prophylaxis. Most failures can be attributed to antepartum fetomaternal hemorrhage that is often not clinically apparent. Prophylactic administration of Rh-D immunoglobulin at 28 weeks gestation reduces the incidence of alloimmunization from 1.8% to 0.1%. Initial concerns about potential adverse effects of antenatal Rh-D–immune prophylaxis have been refuted by decades of experience with Rh-D immunoglobulin without reports of maternal or fetal complications. Further, routine antepartum prophylaxis is much less expensive than the neonatal intensive care required for severely anemic infants.

Management of the Unsensitized Rh–Negative Pregnant Woman

Prenatal care for Rh-D–negative women, without evidence of alloimmunization is straightforward (Table 18.2). Every woman should have her ABO blood group, Rh type, and antibody screen checked at the first prenatal visit of all pregnancies. If she is Rh-negative or weak D–negative and has no demonstrable antibody, she is a candidate for 300 g Rh–immunoglobulin prophylaxis at around 28 weeks gestation and again immediately postpartum. The American Association of Blood Banks recommends obtaining another antibody screen before administration of Rh immunoglobulin, including antepartum prophylaxis.

TABLE 18.2. *Evaluation and management of an unsensitized Rh-negative, pregnant woman*

After delivery, another antibody screen is routinely performed. If negative and the newborn is Rh-D–positive or weak D–positive, alloimmunized women should be given 300 g of Rh-D immunoglobulin. In addition, because up to 1% of deliveries result in a fetomaternal hemorrhage greater than 30 mL (the largest volume of fetal blood adequately covered by a standard 300-g dose of Rh immunoglobulin), a screen for “excessive” fetomaternal hemorrhage should be performed. Most laboratories use the erythrocyte rosette test, a simple and sensitive method for detecting fetomaternal bleeding. If the rosette test is positive, the volume of fetal red cells in the maternal circulation can be calculated using the Kleihauer-Betke test. If the volume of fetomaternal hemorrhage is greater than 30 mL whole blood, an additional 10g of Rh immunoglobulin should be administered for each additional milliliter of fetal blood.

A weak D–positive mother who delivers an Rh–positive infant is not at significant risk of Rh sensitization, probably because the weak D antigen is actually an incompletely expressed D antigen. Therefore, weak D–positive mothers usually do not require Rh immunoglobulin. Occasionally a woman previously typed as Rh-negative is unexpectedly found to be weak D–positive during pregnancy or after delivery. In this situation, the clinician should be suspicious that the patient's “new” weak D–positive status is actually due to a large number of Rh–positive fetal cells in the maternal circulation. Appropriate diagnostic studies should be performed, and if fetomaternal hemorrhage is found, the mother should be treated with Rh immunoglobulin.

Several antepartum complications and procedures may also result in fetomaternal hemorrhage (see Table 18.1). First trimester complications, including spontaneous miscarriage, elective abortion, and ectopic abortion, may result in fetomaternal hemorrhage sufficient to result in alloimmunization.

Fetomaternal hemorrhage has also been demonstrated in up to half of women with *threatened* first trimester miscarriage but is only occasionally associated with alloimmunization. Management is controversial with no clear consensus or evidence-based recommendation on use of Rh immunoglobulin.

An Rh–negative, unsensitized patient who has antepartum bleeding or suffers an unexplained second or third trimester fetal death should receive Rh–immunoglobulin prophylaxis and be evaluated for the possibility of massive fetomaternal hemorrhage. Several procedures may also result in fetomaternal hemorrhage sufficient to cause alloimmunization including chorionic villus sampling, amniocentesis, and external cephalic version.

For first trimester pregnancy complications and procedures, 50 g of Rh immunoglobulin is protective. Beyond 12 weeks, a full 300-g dose is indicated even if in the absence of detectable hemorrhage. In addition, because excessive fetomaternal hemorrhage may occur with any complication or procedures performed in the second and third trimester, an assessment of the volume of fetal whole blood should be performed and the appropriate amount of Rh-D immunoglobulin should be given.

Failure to administer Rh immunoglobulin when indicated is responsible for one-fourth of new cases of alloimmunization. This inexcusable oversight may be due to:

- failure to type the patient's blood at the first prenatal visit or to order Rh-D immunoglobulin when indicated
- error in transmitting the proper blood type to the mother's chart and to the physician
- error in typing the mother's, father's, or baby's blood

- failure to administer Rh-D immunoglobulin when ordered
- unrecognized fetomaternal hemorrhage during pregnancy
- inadequate Rh-D-immunoglobulin for the volume of fetomaternal hemorrhage
- patient refusal.

Management of the Rh-D–Alloimmunized Pregnancy

Obstetric History A well-documented obstetric history is essential to guide management of alloimmunized pregnancy. Fetal hemolytic disease tends to become more severe in subsequent pregnancies. If hydrops occurred in a previous pregnancy, the next Rh–incompatible fetus has an 80% to 90% chance of becoming hydropic as well. With this in mind, patients are grouped into one of three categories:

- mildly affected fetuses, which can be allowed to remain in utero until they have achieved pulmonary maturation
- moderately affected fetuses, which may need to be delivered before pulmonary maturity but who do not need fetal treatment
- severely affected fetuses, which require active intervention to reach a gestational age at which the risks of delivery and neonatal intensive care are less than the risks of in utero therapy.

In general, hemolysis and hydrops develop at about the same time or somewhat earlier in subsequent pregnancies; this can be used as a rough guide for timing initial fetal studies and transfusions. Fetal hydrops seldom develops in a first sensitized pregnancy.
Maternal Antibody Titers Severe erythroblastosis or perinatal death does not occur if antibody levels remain below 1:16. Some centers use an anti–D titer of 1:8 because of variations in reliability and methods of titration. In general, women with anti–D titers of 1:8 or less, and no history of a previously affected infant, can be safely followed with anti–D titers every 2 to 4 weeks and serial fetal ultrasound assessment. Those with anti–D titers of 1:16 or greater should be referred for amniocentesis. Once the critical anti–D antibody titer has been reached in a sensitized pregnancy, more antibody titers are not useful in the current pregnancy or subsequent pregnancies. Titers may remain stable in up to 80% of severely affected pregnancies. Variability between maternal antibody levels and severity of fetal disease is explained by the fact that antibody concentration is only one factor influencing the degree of anemia. Other factors include antibody subclass and degree of glycosylation, placental transfer of antibody, antigen expression on fetal erythrocytes, functional maturity of the fetal reticuloendothelial system, and the presence of HLA-related antibodies that inhibit fetal erythrocyte destruction.
Determination of the Fetal Antigen Status The possibility that the fetus is Rh-negative (not at risk) should always be considered. A reasonable first step in this process is to determine paternal Rh–antigen status and zygosity:

- If the father is Rh-negative, the fetus must also be Rh-negative and no further testing is necessary.
- If the father is Rh-positive, but has previously fathered Rh–negative children, he is heterozygous and the probability that this fetus is Rh-negative is 50%.
- If the father is Rh-positive without other Rh–negative children, zygosity can be established using either DNA analysis or Rh antisera. If the father is homozygous, this fetus is Rh-positive and no other testing is necessary.

In the past, determination of fetal blood type required direct analysis of fetal blood obtained by umbilical cord blood sampling with its attendant risks of fetal loss and fetomaternal hemorrhage. The development of DNA tests that use polymerase chain reaction (PCR) has made it possible to determine fetal Rh status from uncultured amniocytes obtained from as little as 2 mL of amniotic fluid or 5 mg of chorionic villi. Though highly accurate, DNA testing for fetal Rh status is equivocal in about 1% of cases, probably because of the presence of gene rearrangements near the Rh-D locus that can be missed by standard DNA primers used for PCR. Most laboratories recommend simultaneous testing of paternal blood and amniotic fluid. Fetal antigen testing from amniocytes has become routine at most centers in the United States. Most alloimmunized women have fetal antigen typing at the time of the first amniocentesis for amniotic fluid bilirubin analysis. Alloimmunized women having chorionic villus sampling (CVS) or second trimester amniocentesis for other unrelated conditions can have fetal antigen typing earlier. However, except for patients with severe Rh sensitization who would consider termination of an Rh–positive pregnancy, CVS and amniocentesis are not usually offered for detection of Rh-D fetal antigen status alone. If the DNA test indicates an Rh–negative fetus, the small likelihood of misdiagnosis should be discussed and the patients offered standard antenatal surveillance. In the future, fetal Rh–antigen status will likely be performed on fetal cells obtained from the maternal circulation or by preimplantation genetics.
Amniotic Fluid Optical Density Analysis Assessment of amniotic fluid in Rh alloimmunization is based on the original observations that spectrophotometric determinations of amniotic fluid bilirubin correlated with the severity of fetal hemolysis. A by-product of fetal hemolysis, bilirubin is excreted into the amniotic fluid through fetal pulmonary and tracheal secretions and by diffusion across the fetal membranes and the umbilical cord. Using a semilogarithmic plot, the curve of optical density of normal amniotic fluid is approximately linear between wavelengths of 525 and 375 nm. Bilirubin causes a shift in the spectrophotometric density with a peak at a wavelength of 450 nm. The amount of shift in optical density from linearity at 450 nm (the ?OD450) is used to estimate the degree of fetal red cell hemolysis (Fig. 18.5).

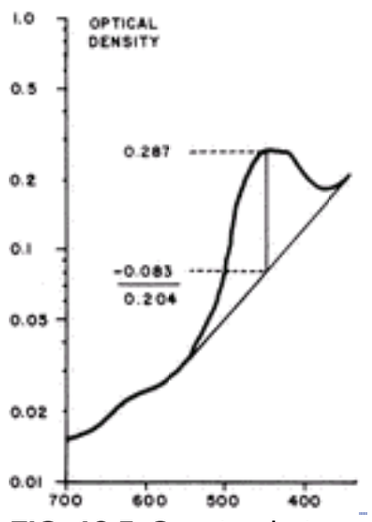

FIG. 18.5. Spectrophotometric scan of amniotic fluid containing bilirubin. An arbitrary line (*thick line*) has been drawn to show where the scan would have been traced if there had been no increase in bilirubin. The peak absorption of bilirubin occurs at 450 µm. The difference between the peak and the arbitrary line equals 0.204.

Liley was the first to correlate amniotic fluid ?OD450 values with newborn outcome by dividing a semilogarithmic graph of gestational age versus ?OD450 into three zones (Fig. 18.6). Unaffected fetuses and those with mild anemia had ?OD450 values in zone I (the lowest zone), while severely affected fetuses had ?OD450 values in zone III (the highest zone). Fetuses with zone II values (the middle zone) had disease ranging from mild to severe, indicated primarily by the trend of the determinations of amniotic fluid bilirubin. Because there is a tendency for amniotic fluid bilirubin to decrease as pregnancy advances, the boundaries of the zones slope downward as gestational age increases. Implementation of Liley's method reduced perinatal mortality from 22% to 9% over a 5-year period.

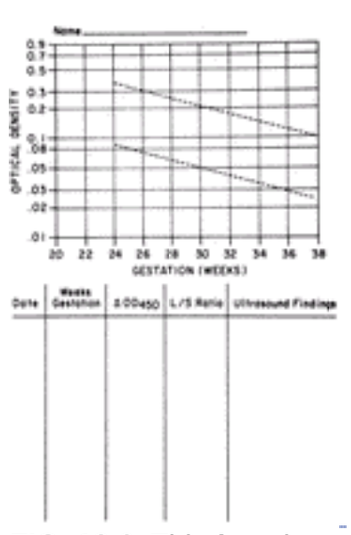

FIG. 18.6. This form is used to record serial data on each Rh-immunized patient. The modified Liley graph is divided into three zones to predict the outcome of the pregnancy in terms of umbilical cord blood hemoglobin, intrauterine deaths, or unaffected fetuses.

A single ?OD450 measurement is seldom helpful in the management of alloimmunized pregnancies unless it is very high or very low. Instead, serial amniocenteses should be performed to determine the trend of ?OD450 values over time. Amniotic fluid ?OD450 values trend downward in unaffected and mildly affected infants while values from severely affected fetuses show a mixed pattern of higher values. A horizontal or rising trend is ominous and indicates the need for intervention either by

intrauterine transfusion (IUT) or delivery. The usefulness of third trimester measurements of amniotic fluid bilirubin using ?OD450 determinations has been confirmed by decades of clinical experience. There have also been attempts to extrapolate Liley's original graph backward to assess fetal status before 27 weeks gestation. However, ?OD450 measurements in the second trimester tend to be less reliable predictors of true fetal anemia because of wide physiologic variation in concentrations of amniotic fluid bilirubin. Laboratory techniques, including chloroform extraction to remove blood and meconium from amniotic fluid, appear to improve the accuracy of second trimester ?OD450 measurements. Still, umbilical cord blood sampling remains the most accurate method of fetal assessment during the second trimester in severely alloimmunized pregnancies. Unfortunately, it is often impractical because of the technical expertise and clinical support required to avoid an unacceptably high rate of pregnancy loss. Enthusiasm for second trimester measurement of concentrations of amniotic fluid bilirubin has grown in recent years. One approach uses a curve developed by Queenan (Fig. 18.7), which, like Liley's original curve, plots ?OD450 measurements against gestational age. The Queenan curve has four outcome zones which predict the degree of fetal anemia and guide management. Alternatively, others have simply extended Liley's original zones backward with some success. Recognizing that this issue is not completely settled, one reasonable approach is to use the standard semilogarithmic Liley curve for amniotic fluid assessment, extrapolated linearly back to 24 weeks gestational age (see Fig. 18.6). Clinical management is then based on trends rather than single ?OD450 values, taking history and gestational age into consideration.

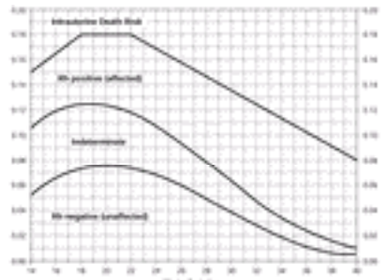

FIG. 18.7. The Queenan curve plots ?OD450 measurements against gestational age, dividing them into four zones of fetal risk. This curve allows prediction of the degree of fetal hemolysis from 14 weeks gestation until term. (Adapted from Queenan JT, Tomai TP, Ural SH, et al. *Am J Obstet Gynecol* 1993;168:1370–1376.)

Fetal Blood Analysis Ultrasound-guided umbilical cord sampling (cordocentesis) should be performed to assess the degree of fetal anemia in severely alloimmunized pregnancies. The procedure is successful in greater than 95% of cases with fetal loss rates between 0.5% and 2% per procedure. Fetomaternal bleeding may occur at the time of cordocentesis resulting in worsened maternal alloimmunization. Traversing an anterior placenta with the sampling needle is thought to result in increased sensitization in as many as 50% of cases. Other complications have also been described including acute refractory fetal distress, umbilical cord hematoma, amnionitis with maternal adult respiratory distress syndrome, and placental abruption. The role of cordocentesis in the management of alloimmunization is limited to assessment of those fetuses already known to be antigen-positive and who are suspected of having moderate to severe anemia. Because of the technical difficulty and increased hazard (both immediate and remote) associated with the procedure, umbilical cord blood sampling should be used with caution and performed only by properly trained personnel.
Ultrasound and Doppler Studies Ultrasonographic examination of the fetus has become an extremely important adjunct in the management of the Rh–alloimmunized pregnancy, primarily as a guide for amniocentesis, cordocentesis, and IUT. Sonographic fetal findings have also been studied in an effort to identify those with severe anemia and reduce the need for invasive procedures. However, other than identifying frank hydrops, ultrasound is not sufficiently reliable in distinguishing mild from severe hemolytic disease. Doppler flow velocity waveforms of fetal cardiac output and red cell flow in numerous fetal blood vessels have been extensively investigated as noninvasive predictors of fetal anemia. Doppler flow waveforms of the fetal middle cerebral artery (MCA) have shown the most promise in the management of Rh–alloimmunized pregnancies. Several investigators have reported that fetal MCA peak systolic velocity waveforms consistently identify fetuses with moderate or severe anemia when velocities are greater than 1.5 times the median of values derived from normal controls (Fig. 18.8). New protocols are emerging at many centers that use fetal MCA peak systolic velocity values to guide management of alloimmunized pregnancies in a manner similar to traditional amniotic fluid protocols using amniotic fluid ?OD450 values. As more clinical experience is gained, it seems likely that this noninvasive tool may become routinely employed to direct fetal management.

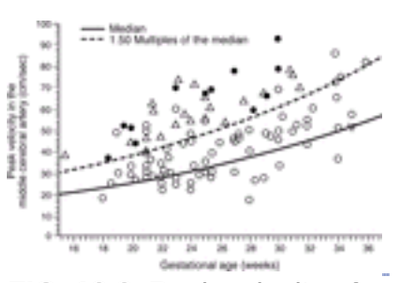

FIG. 18.8. Peak velocity of systolic blood flow in the middle cerebral artery in 111 fetuses at risk for anemia due to maternal red-cell alloimmunization. *Open circles* indicate fetuses with either no anemia or mild anemia (0.65 multiples of the median hemoglobin concentration). *Triangles* indicate fetuses with moderate or severe anemia (<0.65 multiples of the median hemoglobin concentration). The *solid circles* indicate the fetuses with hydrops. The *solid curve* indicates the median peak systolic velocity in the middle cerebral artery, and the *dotted curve* indicates 1.5 multiples of the median. (From Mari G, Deter RL, Carpenter RL, et al. *N Engl J Med* 2000;342:9–14.)

Intrauterine Transfusion in Rh–Alloimmunized Pregnancies

Determining the Need for Transfusion The goals of IUT are to correct fetal anemia in an effort to improve fetal oxygenation and to reduce extramedullary hematopoietic demand which, in turn, should result in a fall in portal venous pressure and improved hepatic function. The need for cordocentesis and IUT should be determined by obstetric history, clinical findings, and the experience and expertise of the management team. About one-half of susceptible infants of Rh–immunized pregnancies have mild to moderate hemolytic disease and do not require IUT or extensive extrauterine therapy. Reasonable management for these patients includes serial ultrasound examinations of the fetus every 2 to 4 weeks from 20 weeks gestation until delivery and serial amniotic fluid ?OD450 determinations, with the first amniocentesis at 24 to 28 weeks gestation. The timing of the next amniocenteses or need for IUT or delivery depends on the trend in ?OD450 values (Fig. 18.9). If ?OD450 values fall within the low zone or the lower half of the middle zone on the Liley graph, amniocentesis is repeated every 2 to 4 weeks. Severe anemia is suspected when the ?OD450 values rise into the upper fourth of the middle zone or into zone III, especially before 30 weeks gestation. Depending on the clinical situation, a single ?OD450 value in zone III may also be an indication of severe anemia. If ultrasound reveals any evidence of fetal hydrops, severe fetal anemia (hematocrit <15%) can be assumed and cordocentesis and IUT should be arranged immediately.

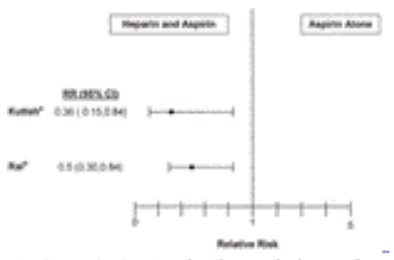

FIG. 18.9. Relative risks of pregnancy loss in women with antiphospholipid syndrome after treatment. *Closed circles* represent the relative risk of pregnancy loss after treatment with heparin and low-dose aspirin. *Horizontal lines* represent range of 95% confidence interval.

A history of severe alloimmunization with early hemolysis and fetal hydrops is predictive of a similarly bad outcome in the current pregnancy. Fetal survival may depend on identifying severe anemia earlier than 24 weeks gestation. Either the Queenan curve or extrapolation of the Liley curve can be used to guide management, understanding that single ?OD450 values between 18 and 24 weeks are difficult to interpret and that trends in ?OD450 determinations are more accurate indicators of fetal anemia. In general, ?OD450 values below 0.09 suggest an unaffected or mildly affected fetus while those greater than 0.15 suggest fetal anemia. In the occasional patient with a particularly ominous history of early second trimester disease or previous severe disease with misleading ?OD450 values, cordocentesis to determine the fetal hematocrit is a reasonable first step. At any gestational age, fetal hydrops should be considered evidence of severe fetal anemia and cordocentesis with immediate intravascular transfusion is indicated.
Intraperitoneal Intrauterine Transfusion Intraperitoneal transfusions were the mainstay of IUT therapy until the mid-1980s. Placement of erythrocytes in the fetal peritoneal cavity was found to reduce fetal anemia by gradual uptake of transfused red cells into the fetal circulatory system via subdiaphragmatic lymphatics. Success depended on the gestational age and the severity of fetal disease, particularly with regard to fetal hydrops (Table 18.3).

TABLE 18.3. *Neonatal survival of infants with severe Rh alloimmunization treated with intrauterine transfusions*

The routine use of ultrasound for needle guidance has dramatically reduced the procedure-related morbidity and mortality associated with intraperitoneal transfusion. Confirmation of appropriate needle placement is usually straightforward, but inadvertent transfusion into the bowel, liver, abdominal wall, and retroperitoneum may occur. Infection, premature rupture of the membranes, refractory preterm labor, and fetal distress necessitating immediate delivery are potential hazards of intraperitoneal IUT. The procedure should be performed only in well-equipped centers with appropriately trained personnel.

Intrauterine Intravascular Transfusion Direct access to the fetal circulation for transfusion offers several advantages over the intraperitoneal approach. The initial fetal hematocrit can be measured, allowing a more precise calculation of the volume of blood required for transfusion. In some cases, the fetus will have a higher hematocrit than expected and transfusion can be delayed. A post-transfusion hematocrit can also be obtained to determine whether the transfusion was adequate and when the next one should be scheduled. Further, transfusion into the fetal vascular system ensures complete uptake with a more rapid correction of fetal anemia, especially important for hydropic fetuses that often do not adequately absorb intraperitoneally transfused erythrocytes. Disadvantages of intravascular fetal transfusion include the rare possibility of volume overload in the compromised fetus, procedure-related complications, and the risk of increasing the severity of maternal sensitization due to fetomaternal hemorrhage. The perinatal survival of nonhydropic fetuses exceeds 90%, and approximately 75% of hydropic fetuses survive with intravascular transfusion (see Table 18.3). Several different methods of estimating the volume of blood needed for transfusion have been reported with a goal of keeping the post-transfusion hematocrit at 40% to 45%. Following intravascular transfusion, the decline in the donor hematocrit is most dependent on the life span of the donor erythrocytes, the rate of fetal growth (and increased vascular volume), and the ratio of fetal to donor erythrocytes (since the fetal erythrocytes are subject to continued hemolysis). The latter is most influential between the first and second intravascular transfusions, when the ratio of fetal cells to donor cells is greatest. On average, the decline in the fetal hematocrit following the first transfusion is about 1.5% per day; following subsequent transfusions, the decline in fetal hematocrit is about 1% to 2% per day. Follow-up intravascular transfusions are scheduled to keep the fetal hematocrit above 20% to 25%. Morbidity and mortality associated with intravascular transfusion are related to the technique of vascular access and transfusion. Fetal bradycardia is the most common problem, occurring in 8% to 12% of cases, though only rarely requires immediate delivery. Postprocedure infection and premature rupture of the membranes have also been reported. Overall, it appears that intravascular transfusion in experienced hands seems to have a procedure-related complication rate of around 10% to 15% and a perinatal mortality rate of 1% to 5%.

Other Therapies

A number of noninvasive alternatives to IUT have been investigated for the treatment of fetal hemolysis. Most have been aimed at modifying the maternal immune response. High-dose intravenous immunoglobulin (IVIG) has been used to treat women with severe Rh alloimmunization refractory to traditional treatment. Experience is limited to case reports and small case series, all with different dosing regimens. The mechanism of action is uncertain, but is most likely at the maternal or placental level since direct fetal administration is not effective. Plasmapheresis has also been tried in refractory Rh alloimmunization and has been associated with a transient reduction in the anti–D titer during or immediately after treatment. However, no long-term, clinically significant reduction in antibody titer has been achieved.

Timing of Delivery

The timing of delivery should be based on individual case circumstances, including obstetric history and severity of Rh-D alloimmunization. In mildly affected pregnancies, induction of labor at 37 to 38 weeks gestation is reasonable, unless fetal pulmonary maturity is documented earlier by amniocentesis. In severely sensitized pregnancies, the risks of continued cord blood sampling and transfusions must be weighed against the potential neonatal morbidity and mortality associated with preterm delivery. This has traditionally led to scheduling the last procedures around 30 to 32 weeks gestation, with delivery between 32 to 34 weeks after maternal steroid administration to enhance fetal pulmonary maturity. In an effort to limit neonatal morbidity, IUT can be continued up to 36 weeks gestation with delivery between 37 and 38 weeks. At the University of Utah, we generally time the last procedure so that delivery can be carried out at about 34 to 36 weeks. Using this approach, neonatal survival in our nursery approaches 100% and long-term morbidity from prematurity is exceedingly low.

Alloimmunization Caused by Minor Antigens

The reduction in Rh disease brought about by Rh–immunoglobulin prophylaxis has led to a relative increase in the number of cases of alloimmunization caused by other red blood cell surface antigens, known as “minor,” “atypical,” or “irregular” antigens (Table 18.4). Overall, alloimmunization due to minor antigens occurs in about 1.5% to 2.5% of obstetric patients though the frequency depends on ethnicity of the population under study. Most cases result from incompatible blood transfusion because blood banks do not routinely assess donor–recipient compatibility for antigens other than ABO and Rh-D. Some of the most common antibodies (i.e., anti–Lea, anti–Leb, and anti–I), do not cause fetal or neonatal hemolysis. However, other commonly encountered atypical antibodies (i.e., anti–E, anti–Kell, anti–c, anti-c + E, and anti–Fya [Duffy A]) may cause erythroblastosis fetalis and hydrops.

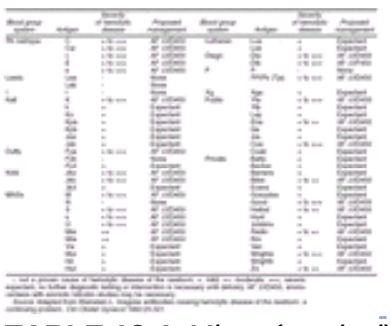

TABLE 18.4. *Minor (atypical) red blood cell antigens, their risk of hemolytic disease, and proposed management*

In general, management of pregnancies complicated by alloimmunization to one of the minor red cell antigens is similar to management of pregnancies complicated by Rh-D alloimmunization. An exception to this rule is alloimmunization to the Kell antigen, which requires special vigilance because of its unpredictability and potential for severe fetal anemia, hydrops, and death. Its virulence may be related to its ability to suppress fetal erythropoiesis and activate the complement cascade in addition to hemolysis. Fortunately, only 9% of whites are positive for the Kell antigen and only 0.2% of pregnancies are complicated by Kell alloimmunization.

Compared to Rh alloimmunization, maternal antibody titers and amniotic fluid ?OD450 values and trends do not predict the degree of fetal hemolysis in cases of Kell alloimmunization. Severe anemia seems to occur with lower antibody titers and in zones of the Liley curve rather than with Rh-D alloimmunization. Because of this, some authorities suggest routine umbilical cord blood sampling as early as 20 weeks gestation if the father is Kell-positive or of uncertain status. An alternative approach with less likelihood of perinatal morbidity and mortality is to perform early amniocentesis (20 weeks or less) and have a lower threshold to proceed with cordocentesis and IUT. In addition, noninvasive diagnostic modalities that detect fetal anemia, such as Doppler and ultrasound, may be well suited to management of pregnancies complicated by Kell alloimmunization.

ABO INCOMPATIBILITY

A comparison of Rh and ABO incompatibility is important because they are the most frequent causes of immune hemolytic disease in the neonatal period. In about 20% to 25% of pregnancies, ABO incompatibility exists between mother and infant, but a clinically recognizable hemolytic process in the infant occurs in only 10%. ABO hemolytic disease affects the firstborn child in about 50% of ases, and it is not uncommon for multiple siblings to be affected with comparable severity.

The pathophysiology involves the transplacental passage of maternal antibody and its interaction with fetal or neonatal red blood cell antigens, yielding erythrocyte destruction, variable anemia, and hyperbilirubinemia. Clinically, ABO hemolytic problems are confined almost exclusively to the A (specifically A1 rather than A2) or B infants of group O mothers. Anti–A and anti–B “natural” antibodies produced early in life by group A or B individuals are predominantly IgM. In contrast, group O individuals produce anti–A or anti–B that is predominantly IgG and capable of crossing the placenta. Yet, for reasons not completely understood, these antibodies seldom cause harm during pregnancy. There is no relationship between the antibody titer and the severity of hemolytic disease. The discordance between the high frequency of ABO–incompatible pregnancies and the low frequency of hemolytic disease as well as the broad spectrum of the severity has been attributed to such factors as immature, weak, nonspecific, or altered antigens on the fetal red blood cell; absorption of the antibodies by ABO antigens present in all body tissues; and the presence of soluble blood group substances in fetal plasma and tissue fluids that can neutralize maternal antibody. No single test exists that can forewarn the physician

of impending ABO hemolytic disease.

Because this problem does not occur until after birth, amniocentesis and preterm induction of labor are not justified. The most common manifestations of ABO incompatibility in the neonate are early-onset jaundice (i.e., within 24 hours) and a variable elevation of the indirect bilirubin fraction. In contrast to Rh disease, kernicterus and anemia are rare. The cornerstones of management of ABO incompatibility are bilirubin surveillance, phototherapy (required in about 10% of infants), and, occasionally, exchange transfusion.

PLATELET ALLOIMMUNIZATION

Like erythrocytes, platelets have specific surface antigens that occasionally result in maternal alloimmunization when there is an incompatibility between fetus and mother. In a situation analogous to Rh disease, fetal or neonatal alloimmune thrombocytopenia (NAIT) results from maternal production of antiplatelet antibodies followed by placental transfer of antiplatelet antibodies and subsequent platelet destruction. The maternal platelet count is normal but fetal/neonatal thrombocytopenia is often profound.

Several different bi-allelic antigen systems may cause platelet alloimmunization, but most cases (75%) are due to sensitization to the HPA-1a (PlA1) antigen. Approximately 2% of whites, 0.4% of blacks, and less than 0.1% Asians are negative for HPA-1a and thus at risk for NAIT. Though fetomaternal incompatibility to platelet antigens is relatively common, only about 1:1,000 to 1:2,000 births are complicated by NAIT, probably because maternal HLA-antigen class II type influences susceptibility. Clinically, about 90% of affected newborns have diffuse petechiae and 9% to 12% suffer intracranial bleeding with a neonatal mortality of 5% to 13%. Fetal thrombocytopenia has been detected as early as 20 weeks gestation with 50% of intracranial hemorrhages diagnosed at the time of prenatal ultrasound.

Unlike erythrocyte alloimmunization, platelet alloimmunization often occurs during the first pregnancy with diagnosis after delivery of severely affected firstborn children. Maternal platelet antibody titers are not beneficial in predicting the severity of NAIT. Routine testing for HPA-1a antibody status during pregnancy has been proposed but is probably not justified because of the wide variation in the clinical expression of maternal–fetal platelet incompatibility and because 25% of cases of NAIT are due to antigens other than HPA-1a. The incidence of recurrent NAIT following delivery of an affected newborn is approximately 90% to 95% and thrombocytopenia is generally equal or worse in severity.

Obstetric Management of Platelet Alloimmunization

Umbilical cord blood sampling and direct measurement of fetal platelet count is the only method that accurately predicts disease severity. However, serial cordocentesis and IUT are not recommended because of the high risk of procedure-related fetal loss. Based on the effectiveness of IVIG treatment for neonates with NAIT, antenatal protocols using maternally administered high-dose IVIG have been developed and widely accepted. Some centers also add dexamethasone if the response to IVIG treatment is not adequate. The mechanism of IVIG treatment probably involves Fc–receptor saturation in the placenta and blockage of antibody transfer to the fetus. Direct fetal administration has not been successful. The use of high-dose IVIG in pregnancies at risk for NAIT is not without risk. Treatment with IVIG is expensive (over $1,000 per weekly infusion), occasional shortages have occurred, and there have been sporadic reports of acute hepatitis C associated with IVIG use.

The management of pregnancies at risk for NAIT is directed at prevention of hemorrhage in the fetus and newborn. As in erythrocyte alloimmunization, the paternal antigen status can be determined using DNA diagnostic techniques. If the father is homozygous, the fetus is at risk and pregnancy management should proceed accordingly. If the father is heterozygous for the particular antigen, amniocentesis at 16 to 20 weeks can be performed to assess fetal antigen status. If the fetus is antigen-negative, there is no significant risk of thrombocytopenia or intracranial hemorrhage and no fetal blood sampling is performed. If the fetus is antigen-positive, a protocol involving a combination of cordocentesis and IVIG treatments should be offered. In all cases at risk for NAIT, maternal platelets should be available for transfusion after delivery, regardless of the antenatal treatment or previously obtained fetal platelet counts.

MATERNAL THROMBOCYTOPENIA

Maternal thrombocytopenia is one of the most common hematologic disorders in pregnancy. Most cases of maternal thrombocytopenia are immunologically mediated, though thrombocytopenia may also be part of other systemic illnesses as well (Table 18.5). Normal values for platelets are unchanged during pregnancy; the mean platelet count for healthy pregnant women is 246,000 per mL. Platelet counts less than 150,000 per mm ^{3} occur in up to 7.6% of pregnant women and counts less than 100,000 per mm3 occur in less than 1%. Thrombocytopenia may be categorized into mild (100,000–150,000/mL), moderate (50,000–100,000/mL), and severe (<50,000/mL). Clinically significant bleeding does not usually occur until platelet counts drop below 10,000 per mL. Excessive bleeding associated with trauma or surgery is uncommon unless the patient's platelet count is less than 50,000 per mL.

Gestational thrombocytopenia
Pregnancy-induced hypertension
HELLP syndrome
Pseudothrombocytopenia (laboratory artifact)
Human immunodeficiency virus (HIV) infection
Immune thrombocytopenic purpura
Systemic lupus erythematosus
Antiphospholipid syndrome
Hypersplenism
Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Congenital thrombocytopenias
Medications (heparin, quinine, quinidine, zidovudine, sulfonamides)

HELLP, hemolysis, elevated liver enzymes, low platelet count.

TABLE 18.5. *Causes of thrombocytopenia in pregnancy*

Gestational Thrombocytopenia

Gestational thrombocytopenia, also known as essential thrombocytopenia or incidental thrombocytopenia is the most common type of mild thrombocytopenia in pregnancy. It is often diagnosed at the time of routine prenatal screening. Characteristics of gestational thrombocytopenia include the following:

- Thrombocytopenia is mild, usually greater than 70,000 per mL.
- Women with thrombocytopenia are asymptomatic with no history of bleeding diathesis.
- There is no history of thrombocytopenia, except in prior pregnancies.
- Platelet counts return to normal 1 to 2 weeks following delivery.
- There are no serious maternal or fetal consequences.

The mechanism of gestational thrombocytopenia is unknown but may involve accelerated platelet consumption. Many women with gestational thrombocytopenia have antiplatelet antibodies but their presence is probably meaningless. Except for the addition of serial platelets counts, no change in prenatal care is necessary.

Autoimmune Thrombocytopenia

Autoimmune thrombocytopenia (ATP) is the most common autoimmune bleeding disorder encountered during pregnancy, affecting between 1 in 1,000 to 10,000 pregnancies. While acute ATP is a self-limited disorder of childhood, chronic ATP typically presents in the second or third decade of life with a female-to-male ratio of 3:1. Autoimmune thrombocytopenia is characterized by production of IgG antibodies directed against platelet membrane glycoproteins. The IgG antiplatelet antibodies bind to platelets, rendering them more susceptible to sequestration and premature destruction in the reticuloendothelial system. Thrombocytopenia occurs when the rate of destruction exceeds the ability of the bone marrow to produce new platelets. Though other sites are also involved, most antibody production and platelet destruction occur in the spleen.

The diagnosis of ATP should be based on clinical findings, after other causes of thrombocytopenia have been excluded. Characteristics include:

- Thrombocytopenia (platelet count <100,000/mL) is present before and after pregnancy with or without megathrombocytes on the peripheral smear.
- Bone marrow aspirates reveal normal or increased numbers of megakaryocytes.
- Patients usually, but not uniformly, have a history of bleeding, easy bruising, petechiae, menorrhagia, or other bleeding problems.

- Splenomegaly is absent.

The course of ATP is not substantially influenced by pregnancy. However, ATP may lead to complications in pregnancy, the most serious of which is maternal hemorrhage around the time of delivery. No maternal deaths from ATP in pregnancy have been recorded since the early 1980s, but peripartum bleeding may result in serious morbidity. Because the placenta selectively transports maternal IgG antiplatelet antibodies into the fetal circulation, fetal thrombocytopenia may also occur, sometimes leading to purpura, ecchymosis, or melena. Intracranial hemorrhage is only rarely reported and appears to be unrelated to the mode of delivery.

Many women with ATP have elevated levels of platelet-associated antibodies and sometimes circulating antiplatelet antibodies. Assays for these antibodies are commercially available but should not be routinely performed because they are nonspecific, poorly standardized, and subject to a large degree of interlaboratory variation. Furthermore, levels of antiplatelet antibodies do not correlate well with the degree of fetal thrombocytopenia.

Treatment Treatment of pregnant women with ATP are aimed at preventing bleeding by maintenance of the platelet count above 20,000 per mm ^{3} in the antepartum period and over 50,000 per mm ^{3} for delivery.
Glucocorticoids Glucocorticoid drugs are the cornerstones of therapy for ATP in pregnancy. Prednisone (1–2 mg/kg/d in divided doses) for 2 to 3 weeks is the most typical regimen. An increase in platelet count to more than 50,000 per mL, accompanied by a decrease in clinical bleeding, is usually achieved within 21 days. More than 70% of patients have some response and complete remission occurs in up to 25%. The prednisone dose is tapered by 10% to 20% decrements at 2-week intervals to a dose that maintains the platelet count above 50,000 per mm ^{3}. Dexamethasone and betamethasone also cause an increase in platelet count but both readily cross the placenta and have harmful fetal effects. The side effects of glucocorticoids in pregnancy include steroid-induced moon facies, gestational diabetes mellitus, psychosis, adrenocortical insufficiency, osteoporosis, aseptic necrosis, hypertension, and uteroplacental insufficiency.
Intravenous Immunoglobulin Given at high doses (i.e., 400 mg/kg/d for 5 days), IVIG usually induces a peak in platelet count within 7 to 9 days. More than 80% of patients achieve a platelet count greater than 50,000 per mm ^{3}, and the response lasts for more than 30 days in 30% of patients. Only 2 to 3 days of IVIG therapy may be needed in some patients, and doses greater than 800 mg or 1 g per kg may suffice as a single or double infusion. Although expensive, IVIG therapy initiated 1 to 2 weeks before delivery or surgery may be useful in some obstetric patients who must undergo operative procedures or who develop bleeding problems and require emergency treatment. The exact mechanism of action of IVIG is unclear, but may be related to decreased antiplatelet antibody production, interference with antibody attachment to platelets, inhibition of macrophage receptor-mediated immune complex clearance, or interference with platelet receptor mechanisms in the reticuloendothelial system. IgG is selectively transported across the placenta and the amount transferred increases with gestational age and dose so that after 32 weeks of gestation, maternally infused IgG sometimes has a beneficial effect on the fetal platelet count. No cases of human immunodeficiency virus (HIV) transmission have been reported with the use of IVIG, but adverse effects include thrombosis, alopecia, liver function disturbances, transient neutropenia, chills, nausea, flushing, tightness of the chest, wheezing, and anaphylactic reactions in patients with immunoglobulin A (IgA) antibodies.
Splenectomy Splenectomy serves to remove the site of destruction of damaged platelets as well as the major source of antibody production. During pregnancy, it is used only for patients with ATP who are refractory to or cannot tolerate glucocorticoids and IVIG. A complete remission is obtained in 80% of patients. The postsplenectomy platelet count increases rapidly and often is normal within 1 to 2 weeks. The surgery is associated with a modest risk of spontaneous abortion or preterm labor and is technically more difficult late in gestation. If splenectomy is unavoidable, it is best performed in the second trimester; it has also been combined safely with cesarean section at term. Splenectomy does not always protect the fetus from thrombocytopenia because antibodies to platelets are also produced in other lymphoid tissues.
Platelet Transfusions Platelet transfusions are used only as a temporizing measure to control life-threatening hemorrhage or to prepare a patient for splenectomy or cesarean section. The survival of transfused platelets is decreased in patients with ATP because antiplatelet antibodies also bind to donor platelets. In addition, patients with ATP do not respond as well as normal individuals to platelet transfusions but 6 to 10 U is usually sufficient to temporarily control hemostasis.
Other Treatments Other agents have been used with some success in patients who are refractory to glucocorticoids, IVIG, and splenectomy. Those most commonly used, such as azathioprine, cyclophosphamide, Vinca alkaloids, and danazol, are to be avoided in pregnancy because of their toxicity and potential adverse effects on the fetus. Plasmapheresis has also been tried, but the results of this treatment are variable.
Obstetric Management of Autoimmune Thrombocytopenia Management of pregnancies complicated by ATP is controversial largely because of uncertainties regarding the actual risk of fetal thrombocytopenia. In the past, cesarean delivery was advocated in all women with ATP because of anecdotal reports of intracranial hemorrhage associated with vaginal delivery. Prompted by the fact that clinically significant bleeding is extremely unlikely in fetuses with platelet counts more than 50,000 per mL, some authorities recommended cesarean delivery only if the fetal platelet count was less than 50,000 per mL. However, this required measurement of the fetal platelet count. Fetal scalp sampling during labor was the first and most commonly performed method of obtaining the fetal platelet count, allowing 80% of fetuses with acceptable platelet counts to be safely delivered vaginally. Unfortunately, the procedure is technically difficult to perform in early labor and falsely low platelets were sometimes obtained. Cordocentesis often replaced fetal scalp sampling because platelet counts were extremely accurate and the procedure could be performed before the onset of labor. However, cordocentesis is expensive and unavailable in centers without appropriate expertise and equipment. It also has several potentially serious complications including fetal bradycardia, hemorrhage at the puncture site, and cord hematoma. Both fetal scalp sampling and cordocentesis might be useful if there was any evidence that cesarean delivery reliably prevents intracranial hemorrhage in thrombocytopenic fetuses. However, it appears that early reports of ATP in pregnancy overestimated the risk of severe fetal thrombocytopenia and intracranial hemorrhage associated with vaginal delivery. In a recent, large, population-based study of almost 16,000 pregnancies, no infant born to a mother with ATP suffered intracranial hemorrhage, regardless of the route of delivery. Because it appears that fetal scalp sampling, cordocentesis, and cesarean delivery contribute to cost and morbidity without preventing intracranial hemorrhage, many obstetricians have abandoned antenatal measurement of fetal platelet counts and reserved cesarean delivery for the usual obstetric indications. Mothers with ATP do not require substantial alterations in prenatal care. Serial platelet counts should be obtained during the pregnancy. If the platelet count is less than 50,000 per mL in the weeks preceding delivery, patients with ATP should be treated with glucocorticoids or IVIG. Women requiring chronic glucocorticoid therapy during pregnancy should be carefully monitored for the development of gestational diabetes and should have serial ultrasounds to assess fetal growth. Women with prior splenectomy should be monitored for the development of infection. Delivery is best accomplished in a setting in which platelets, fresh frozen plasma, and IVIG are available. A neonatologist or pediatrician familiar with the disorder should be present to promptly treat any hemorrhagic complications in the neonate. In the puerperium, salicylates and nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided. Though breast-feeding may theoretically induce neonatal thrombocytopenia because of the passage of antiplatelet antibodies in the colostrum, it is considered safe and reasonable by most pediatricians.

Other Causes of Thrombocytopenia in Pregnancy

Other than ATP, the most common serious condition associated with maternal thrombocytopenia late in pregnancy is preeclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Other conditions that can result in maternal thrombocytopenia at any gestational age include acute HIV infection, systemic lupus erythematosus, antiphospholipid syndrome (APS), sepsis, cocaine abuse, thrombotic thrombocytopenic purpura, transfusion reaction, blood dyscrasias, or certain medications (see Table 18.5).

Pseudothrombocytopenia can result from laboratory artifacts such as platelet clumping induced by ethylenediaminetetraacetic acid (EDTA) in the collection tube, blood clotting related to techniques of blood withdrawal, and an inadequate amount of anticoagulant. These factors can be confirmed by examining a stained peripheral maternal blood smear. Once the diagnosis of pseudothrombocytopenia is established, no further treatment is needed for mother or infant.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic inflammatory condition affecting virtually every organ system of the body. With a predilection for women of reproductive age, it is the autoimmune disease most commonly encountered during pregnancy. No specific gene mutation for SLE has been identified. However, 5% to 12% of affected individuals have another relative with SLE and 25% to 50% of affected monozygotic twins are concordant for the disease. Several alterations in the HLA-antigen system have been linked to the development of SLE and homozygous carriers of inherited complement deficiency disorders also appear to be predisposed to development of the disease. With an increased awareness of the disease, more sophisticated diagnostic methods, and improved drug therapy, the 10-year survival rate now exceeds 90%.

Diagnosis of Lupus

Lupus may easily be overlooked because it often begins with mild and vague symptoms such as fatigue and is characterized by periods of exacerbation and remission. The presence of autoantibodies, characteristically against nuclear components, is a hallmark of the disorder. The American Rheumatism Association has set criteria for the diagnosis of SLE that incorporate immunologic abnormalities and improve disease classification for purposes of clinical studies (Table 18.6). The most common clinical manifestations include arthralgia or arthritis (90%), dermatologic involvement (70%–80%), renal disease (46%), hematologic abnormalities (50%), and cardiovascular disease (30%–50%). The most frequent laboratory findings are thrombocytopenia, leukopenia, and the presence of autoantibodies.

Finding	Frequency
Malar rash (fixed erythema over malar eminences)	85%
Discoid rash (erythematous, raised patches with scaling	15%
Photosensitivity	Common
Oral or pharyngeal ulcers	50%
Arthritis (nonerosive, involving two or more joints)	90%
Pleuritis or pericarditis	25%–46%
Proteinuria, 0.5 g/d, or cellular casts	50%
Seizures or psychosis	20%
Anemia, leukopenia, thrombocytopenia	>95%
Positive antinuclear antibody titer	>95%
Positive lupus erythematosus preparation, anti-DNA, anti-Sm, or false-positive test results for syphilis	>95%

[a]The presence of any four criteria, serially or simultaneously, in any given period of observation is sufficient to make the diagnosis of systemic lupus erythematosus.

TABLE 18.6. *Diagnostic criteria for systemic lupus erythematosusa*

Lupus should be suspected when a woman in her reproductive years presents with glomerulonephritis, nephrotic syndrome, hemolytic anemia, leukopenia, or thrombocytopenia. A positive antinuclear antibody (ANA) test is confirmatory in virtually all (98%) patients. However, this test does not have high specificity for SLE and many healthy women may test positive for low levels of ANA antibodies. High titers of antibodies to double-stranded DNA and antibodies to the Smith (Sm) antigen are most specific for SLE.

Systemic Lupus Erythematosus and Pregnancy

Lupus Flare During Pregnancy Considerable debate surrounds the incidence and severity of SLE flare during pregnancy. Studying SLE flare in pregnancy is difficult because many of the signs and symptoms typically associated with SLE flare are considered routine during pregnancy. In addition, studies have not consistently used the same criteria for flare or disease severity. Nevertheless, it appears that SLE flare occurs in 35% to 65% of pregnant women with well-controlled SLE. Most flares are mild-to-moderate in nature and easily treated with glucocorticoids. Flares occur with equal frequency in all three trimesters and the puerperium. Women at greatest risk for complications of SLE during pregnancy are undoubtedly those with preexisting lupus nephritis (LN). Approximately half of all SLE patients eventually develop LN as a result of immune complex deposition in the kidney with subsequent complement activation and inflammatory tissue damage. Patients typically present with proteinuria, hematuria, aseptic pyuria, and urinary sediment. Renal biopsy is necessary to confirm the diagnosis. Pregnancy places women with LN at risk for deterioration of renal function and increased proteinuria, especially if active nephritis or renal insufficiency is present at the time of conception. However, the risks of pregnancy may not be so serious for women with stable LN. About one-third of women with LN experience flare during pregnancy, fewer than 25% have worsening renal function, and 10% of have permanent deterioration. The incidence of maternal death attributed to renal failure during pregnancy is less than 2%.
Obstetric Complications in Women with Lupus Women with SLE are at risk for several obstetric complications. Between 20% to 30% of women with SLE have pregnancies complicated by preeclampsia. Women with secondary APS, underlying renal disease, chronic hypertension, or chronic steroid use are at particular risk. Uteroplacental insufficiency resulting in intrauterine growth restriction (IUGR) or neonates who are small for gestational age has been reported in 12% to 40% of pregnancies complicated by SLE. Renal insufficiency or hypertension increases the risk of IUGR. The risk of pregnancy loss for women with SLE is uncertain with reported rates ranging from 10% to 50%. There appears to be a predilection for the second and third trimester. Renal insufficiency increases the risk of fetal loss; live births occur in only 50% of pregnancies complicated by moderate to severe renal insufficiency (serum creatinine >1.5 mg/dL) and in 40% with preexisting proteinuria (>300 mg/24 h or creatinine clearance <100 mL/min). Coexisting APS poses the greatest risk for pregnancy loss in women with SLE. Only 50% of women with SLE and APS have live births; if they have previously experienced a fetal loss, 85% have recurrent loss in subsequent pregnancies.
Lupus Disease Activity and Risks of Pregnancy The degree of disease activity at conception dramatically affects the risk of SLE flare and other complications during pregnancy. The rate of SLE flare is lower for women with SLE in remission prior to conception. Renal deterioration is also less likely and less severe in women with inactive LN in the 6 months prior to conception. Furthermore, nearly 90% of women with inactive SLE at conception have live births compared to 64% of those with active disease. Women with SLE who plan their pregnancies after disease remission have outcomes similar to those of the general population.
Neonatal Lupus Erythematosus Neonatal lupus erythematosus (NLE) is a rare condition of the fetus and neonate, occurring in 1 of 20,000 of all live births and in fewer than 5% of all women with SLE. Dermatologic NLE is most common with lesions described as erythematosus, scaling annular or elliptical plaques occurring on the face or scalp, analogous to the subacute cutaneous lesions in adults. Lesions appear in the first weeks of life, probably induced by exposure of the skin to ultraviolet light, and may last for up to 6 months. Hypopigmentation may persist for up to 2 years. Hematologic NLE is manifest as autoimmune hemolytic anemia, leukopenia, thrombocytopenia, and hepatosplenomegaly. The most well-known form of SLE is congenital complete heart block (CCHB) caused by endomyocardial fibrosis of the conduction system in the area of the atrioventricular node. The diagnosis is usually made in the second trimester when a fixed bradycardia, in the range of 60 to 80 beats per minute, is detected during a routine prenatal visit. Fetal echocardiography confirms complete atrioventricular dissociation with a structurally normal heart. There is no known treatment for prenatally diagnosed CCHB though glucocorticoids, plasmapheresis, intravenous immune globulin, digoxin, or some combination thereof, have been tried. Maternally administered glucocorticoids appear to reduce the risk of recurrence of CCHB in another pregnancy. The prognosis for fetuses with CCHB varies but hydrops fetalis may develop in the most severe cases. Because the endomyocardial damage is permanent, a pacemaker may be necessary for neonatal survival. The manifestations of NLE are probably caused by maternal autoantibodies that cross the placenta and bind to fetal tissue. Anti–Ro/SSA antibodies are found in 75% to 95% mothers who deliver babies with NLE. A smaller percentage of mothers have anti–La/SSB, and some have both. About 15% of infants born to mothers with anti–Ro/SSA antibodies have dermatologic SLE; the incidence of CCHB is much smaller. However, with a previously affected infant, the risk of recurrence increases two- to three-fold. Occasionally, women with no history of SLE give birth to babies with NLE. More than half eventually develop lupus.

Obstetric Management for Women with Lupus

Immunosuppressive Medications

Glucocorticoids Glucocorticoid preparations are the group of drugs most commonly given to pregnant women with SLE, both as maintenance therapy and in “bursts” to treat suspected SLE flares. Dosing regimens in pregnant women are the same as those in nonpregnant patients. Prophylactic treatment with glucocorticoids is not necessary or prudent in women with inactive disease. Maternal side effects of chronic glucocorticoid therapy include weight gain, striae, acne, hirsutism, immunosuppression, osteonecrosis, and gastrointestinal ulceration. Pregnant women are also at risk for preeclampsia, uteroplacental insufficiency, and glucose intolerance. Prednisolone or methylprednisolone should be used as maintenance therapy because of their conversion to relatively inactive forms in the human placenta. Glucocorticoids with fluorine at the 9a position (dexamethasone, betamethasone) are considerably less well metabolized by the placenta and chronic use may lead to undesirable fetal effects.
Antimalarials An accumulating body of evidence suggests that antimalarial drugs may be used safely for the treatment of SLE during pregnancy. Past concerns about teratogenicity including ototoxicity and eye damage appear to be unfounded. In randomized controlled trials, hydroxychloroquine appears to be more efficacious than glucocorticoids for prevention of flare during pregnancy.
Cytotoxic Agents Azathioprine, methotrexate, and cyclophosphamide are used to treat only the most severely affected patients with SLE. Azathioprine, a derivative of 6-mercaptopurine, is not a human teratogen but has been associated with fetal growth impairment and impaired neonatal immunity. Cyclophosphamide is a known teratogen and should be avoided during the first trimester. Thereafter, its use should be limited to women with severe, progressive proliferative glomerulonephritis or SLE-related central nervous system (CNS) disease. Methotrexate is well known to kill chorionic villi and cause fetal death and its use should be scrupulously avoided.
Nonsteroidal Medications The most common types of analgesics used by women with SLE are NSAIDs. Unfortunately, they readily cross the placenta and should be avoided after the first trimester. Although short-term tocolytic therapy with indomethacin appears to be safe, long-term use of any NSAID has been associated with decreased fetal urinary output and oligohydramnios as well as neonatal renal insufficiency.
Other Treatments Several new treatment regimens including cyclosporine, high-dose IVIG, mycophenolate mofetil, and thalidomide have been studied in the treatment of nonpregnant patients with SLE. Only IVIG has been used during pregnancy without reports of adverse fetal effects. Obviously, thalidomide is absolutely contraindicated during pregnancy.
Detection of SLE Exacerbation (Flare) Thorough and frequent clinical assessment remains essential for the timely and accurate detection of SLE flare. The most common presenting symptom in both flare and new-onset disease is extreme fatigue (see Table 18.6). In pregnancy, skin rashes are more frequent than musculoskeletal manifestations. Patients with LN exhibit worsening proteinuria along with pyuria, hematuria, and urinary casts, which can sometimes be confused with the onset of preeclampsia. Laboratory evaluation of SLE activity should be used to confirm flare in confusing cases. Serial evaluation of complement levels has been suggested as a method of predicting SLE flare during pregnancy. However, the predictive value of complement activation has been inconsistent and never been proven to be superior to thorough and frequent clinical assessment. The most specific laboratory test for disease activity is an elevation in the anti–double-stranded DNA (anti–dsDNA) titer that precedes lupus flare in more than 80% of patients and has been shown to correlate with the need for preterm delivery. In combination with anticardiolipin (aCL) antibodies, elevated levels of anti–dsDNA have been shown to predict fetal loss.
Treatment of SLE Flare during Pregnancy Mild to moderate symptomatic exacerbations of SLE without CNS or renal involvement may be treated with initiation or increased dose of glucocorticoids. Relatively small doses of prednisone (e.g., 15–30 mg/d) result in improvement in most cases. For severe exacerbations without CNS or renal involvement, 1.0 to 1.5 mg per kg per day of prednisone in divided doses should be used, and a good clinical response can be expected in 5 to 10 days. Thereafter, glucocorticoids may be tapered by several different approaches (Table 18.7).

1. Consolidate to a single morning dose of prednisone. Reduce the daily dose by 10%/wk, as tolerated. When a dose of 20 to 30 mg/d is reached, reduce by 2.5-mg increments/wk. If the patient remains asymptomatic at a dose of 15 mg/d, reduce the dose by 1-mg increments/wk to a dose of 5 to 10 mg/day.
2. Consolidate to a single morning dose of prednisone. Taper to 50 to 60 mg/d by reducing the dose 10%/wk. Thereafter eliminate the alternate-day dose by tapering it 10%/wk, as tolerated. Thereafter, taper the remaining every other day dose by 10%/wk, as tolerated.

TABLE 18.7. *Suggested methods for tapering prednisone*

Severe exacerbations, especially those involving the CNS or kidneys, are treated more aggressively. Intravenous-pulse glucocorticoid therapy should be given, usually in a dose of methylprednisolone at 10 to 30 mg per kg (about 500–1,000 mg) for 3 to 6 days. Thereafter, the patient is treated with 1.0 to 1.5 mg per kg per day of prednisone in divided doses and rapidly tapered over the course of 1 month. One can expect that 75% of patients will respond favorably to this approach. This regimen may be repeated every 1 to 3 months in severe cases as an alternative to cytotoxic drugs. The use of cytotoxic agents, plasmapheresis, and IVIG should be reserved for severe SLE exacerbations that do not respond to glucocorticoid therapy. Severe proliferative lupus nephritis is often responsive only to cyclophosphamide.
Obstetric Care for Women with Systemic Lupus Erythematosus Clinical precautions in pregnancies associated with SLE are similar to those required for other high-risk pregnancies. Recommended laboratory studies in addition to routine prenatal tests are listed in Table 18.8. The gestational age should be firmly established early in pregnancy. Serial sonography should be performed to assess fetal growth. Antenatal surveillance (e.g., nonstress tests, biophysical profiles, etc.) should be initiated in the third trimester to confirm fetal well-being. Lupus per se is not an indication for cesarean delivery. Instead, the route of delivery should be based on appropriate obstetric indications.

TABLE 18.8. *Management of systemic lupus erythematosus during pregnancy*

ANTIPHOSPHOLIPID SYNDROME IN PREGNANCY

The diagnosis of APS is based on the presence of one or more characteristic thrombotic or obstetric features of the condition in combination with positive serologic testing for antiphospholipid antibodies (aPL). Patients with bona fide APS must manifest at least one of two clinical criteria (vascular thrombosis or pregnancy morbidity) and at least one of two laboratory criteria (positive lupus anticoagulant [LA] or medium to high titers of ß2-glycoprotein I-dependent IgG or IgM isotype aCL antibodies, confirmed on two separate occasions at least 6 weeks apart (Table 18.9). APS may exist as an isolated immunologic derangement (primary APS) or in combination with other autoimmune diseases (secondary APS), most commonly SLE.

Clinical criteria for diagnosis of APS
Pregnancy loss
Recurrent pregnancy loss
Fetal death (>10 wks)
Preterm birth (<34 wks) because of severe preeclampsia or uteroplacental insufficiency
Thromboembolism
Venous
Arterial, including stroke
Clinical features not considered adequate criteria for the diagnosis of APS
Autoimmune thrombocytopenia
Other
Coombs-positive hemolytic anemia
Livedo reticularis
Laboratory criteria for the diagnosis of APS
Lupus anticoagulant
Anticardiolipin antibodies
Immune globulin G, medium- or high-positive
Immune globulin M, medium- or high-positive and lupus anticoagulant

[a] Wilson WA, Gharavi AE, Koike T. International consensus statement on preliminary classification criteria for definite antiphospholiped syndrome: report of an international workshop. *Arthritis Rheum* 1999;42:1309–1311.

TABLE 18.9. *Clinical and laboratory criteria for antiphospholipid syndrome (APS)* [a]

Clinical Features of Antiphospholipid Syndrome during Pregnancy

In the original description of APS, the sole obstetric criterion for diagnosis was fetal loss (>10 menstrual weeks of gestation). At least 40% of pregnancy losses reported by women with LA or medium to high positive IgG aCL occur in the fetal period. More recently, APS-related pregnancy loss has been extended to include women with early recurrent pregnancy loss (RPL) including those occurring in the preembryonic (<6 menstrual weeks of gestation) and embryonic periods (6–9 menstrual weeks of gestation). In addition, APS is associated with other pregnancy complications including gestational hypertension or preeclampsia and uteroplacental insufficiency as manifested by fetal growth restriction, oligohydramnios, and non-reassuring fetal surveillance. Obstetric complications other than pregnancy loss appear to persist in spite of treatment. There have been some attempts to link infertility and failure of in vitro fertilization (IVF) to the presence of aPL antibodies. However, there is no evidence to support such a relationship. Indeed, multiple studies have refuted any association between aPL antibodies and infertility and failed IVF.

Treatment of Antiphospholipid Syndrome during Pregnancy

The goals of APS treatment during pregnancy are two-fold:

1. Improve maternal and fetal–neonatal outcome by preventing pregnancy loss.
2. Reduce or eliminate risk of thromboembolism.

Initial attempts at treating women with APS during pregnancy involved immunosuppression with a glucocorticoid preparation, usually prednisone. Early enthusiasm for treatment of APS with glucocorticoids waned after publication of a small, randomized trial found maternally administered heparin to be as effective as prednisone, without all of the risks associated with chronic glucocorticoid use during pregnancy. At present, maternally administered heparin is considered the treatment of choice, usually initiated in the early first trimester after ultrasonographic demonstration of a live embryo. Daily low-dose aspirin is usually included as well. Live-birth rates among women with APS are generally greater than 70% with regimens including both heparin and aspirin (see Fig. 18.9). However, rates of other obstetric complications associated with APS are not improved, regardless of therapy.

The safe and effective dose of heparin for pregnant women with APS is debated but should probably depend on individual patient history. Women with APS and a history of thromboembolism should receive adjusted-dose anticoagulation with unfractionated heparin or low–molecular-weight heparin during pregnancy (Table 18.10). For women with APS *without* a history of thromboembolic disease, the choice of anticoagulation is less clear. Low-dose heparin prophylaxis may be sufficient for women with recurrent first trimester loss and no history of fetal loss. However, women with a history of fetal death (>10 weeks gestation) may be at higher risk for thromboembolism during pregnancy and should probably receive higher doses of heparin prophylaxis. We treat such women with generous thromboprophylaxis (e.g., 15,000 to 20,000 units of standard heparin or 60 mg of enoxaparin in daily divided doses). Recommendations for postpartum therapy vary but most authorities recommend at least 6 weeks of some regimen of anticoagulation with unfractionated heparin, low–molecular-weight heparin, or warfarin.

Unfractionated Heparin
Low-dose prophylaxis
1. 5,000–7,500 U every 12 h during the first trimester 7,500–10,000 U every 12 h during the second trimester 10,000 U every 12 h during the third trimester unless the aPTT is elevated. The aPTT may be checked near term and the heparin dose reduced if prolonged. or
2. 5,000–10,000 U every 12 h throughout the pregnancy
Adjusted-dose prophylaxis:
≥10,000 U twice a day to three times a day to achieve an aPTT of 1.5–2.5 control
Low–Molecular-Weight Heparin
Low-dose prophylaxis
Dalteparin, 5,000 U once or twice daily, or enoxaparin, 40 mg once or twice daily
Adjusted-dose prophylaxis
Dalteparin, 5,000–10,000 U every 12 h, or enoxaparin, 30–60 mg every 12 h

aPTT, activated partial thromboplastin time.

TABLE 18.10. *Regimens for anticoagulation during pregnancy*

Healthy women with recurrent embryonic and preembryonic loss who have low or negative aPL titers do not require anticoagulation.

Women with APS should be counseled about the potential risks of heparin therapy during pregnancy including heparin-induced osteoporosis (1%–2%) and heparin-induced thrombocytopenia (HIT). Women treated with heparin should be encouraged to take daily supplemental calcium and vitamin D (e.g., prenatal vitamins) and perform daily axial skeleton weight-bearing exercise (e.g., walking). Immune-mediated HIT is much less common but potentially more serious. Most cases have their onset 3 to 21 days after heparin initiation and are relatively mild in nature. A more severe form of HIT paradoxically involves venous and arterial thromboses resulting in limb schemia, cerebrovascular accidents, and myocardial infarctions, as well as venous thromboses. We obtain serial platelet counts for 2 weeks and discontinue heparin if a significant decrease in platelet count occurs.

Postpartum and Catastrophic Antiphospholipid Syndrome

Catastrophic APS is a rare but devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. The diagnosis should be suspected if at least three organ systems are affected and confirmed if there is histopathologic evidence of acute thrombotic microangiopathy affecting small vessels. Renal involvement occurs in 78% of patients. Most patients have hypertension and 25% eventually require dialysis. Other common manifestations include adult respiratory distress syndrome (66%), cerebral microthrombi and microinfarctions (56%), myocardial microthrombi (50%), dermatologic abnormalities (50%), and disseminated intravascular coagulation (25%). Death from multiorgan failure occurs in 50% of patients. The pathophysiology of catastrophic APS is poorly understood. However, the onset may be presaged by several factors including infection, surgical procedures, discontinuation of anticoagulant therapy, and the use of drugs such as oral contraceptives.

Early and aggressive treatment of catastrophic APS is necessary to avoid death. Patients should be transferred to an intensive care unit where supportive care can be provided. Hypertension should be aggressively treated with appropriate antihypertensive medication. While no one treatment has been shown to be superior to another, a combination of anticoagulants (usually heparin) and steroids plus either plasmapheresis or IVIG has been successful in some patients. Streptokinase and urokinase have also been used to treat acute vascular thrombosis. Women suspected of catastrophic APS during pregnancy should probably be delivered.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory process that primarily involves synovial-lined joints resulting in swelling and pain. The following criteria must be met to establish the diagnosis of RA (i.e., seven criteria for classic RA, five criteria for definite RA, three criteria for probable RA, two criteria for possible RA):

- morning stiffness
- pain and tenderness in at least one joint
- swelling of at least one joint
- swelling of at least one other joint
- symmetric joint swelling
- subcutaneous nodules
- x-ray changes typical of RA
- positive test result for rheumatoid factor
- poor mucin precipitate of synovial fluid
- characteristic histologic changes of synovium
- characteristic histologic changes of nodules.

Most cases are mild and require little or no medical treatment. In others, the disease is characterized by intermittent exacerbations with ultimate progression over many years to typical joint deformities.

Pregnancy is associated with clinical improvement in at least 50% of patients, a phenomenon that may be related to elevated blood levels of free cortisol or to enhanced phagocytosis of immune complexes. The rheumatoid factors (i.e., IgM antibodies against autologous IgG) do not cross the placenta, and there is no fetal or neonatal involvement.

Management of RA during pregnancy should include an appropriate balance of medication, rest and exercise, heat, and physical therapy. The basic reliance on large doses of salicylates, NSAIDs, and analgesics must be modified during pregnancy. Low-dose steroids (e.g., prednisone, 5 mg/d) and low-dose aspirin are recommended. Though gold compounds cross the placenta, no fetal adverse effects or teratogenicity have been reported. Gold therapy can be continued in selected pregnant patients with RA who are unresponsive to glucocorticoids. Other NSAIDs and penicillamine are not recommended because of potential detrimental fetal effects. As in SLE, antimalarials (hydroxychloroquine) appear to be another safe option during pregnancy.

Specialized antenatal surveillance is unnecessary for women with RA. Serial ultrasounds and antenatal surveillance should be reserved for the usual obstetric indications. Joint deformities rarely preclude vaginal delivery but mechanical obstacles may occur in women with hip deformities. Cesarean delivery can usually be reserved for standard obstetric indications. The type of anesthesia (regional vs. general) chosen depends on the presence of skeletal deformities or special problems such as atlantoaxial subluxation.

Other Rheumatic (Collagen Vascular) Diseases

Most disorders of undetermined origin, which are characterized by inflammation of various tissues, have been termed systemic rheumatic or collagen vascular diseases. More recently, many have been classified as autoimmune disorders because of their association with the production of autoantibodies and other immunologic aberrations. This group includes:

- mixed connective tissue disorder
- Sjögren syndrome
- polyarteritis nodosa
- dermatomyositis
- scleroderma.

The risk of both maternal and perinatal death is particularly high in patients with polyarteritis nodosa, mixed connective tissue disorder, and scleroderma complicated by renal disease or cardiopulmonary disease. Scleroderma worsens in at least 10% of women during pregnancy. At least 5% have life-threatening complications, usually related to renal or cardiopulmonary disease.

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a chronic neuromuscular autoimmune disease characterized by fatigue and weakness, usually involving the extraocular, facial, pharyngeal, and respiratory muscles. It is worsened by exertion and relieved by rest and anticholinesterase drugs. Antibodies to human acetylcholine receptors (AChR) are detectable in up to 90% of patients with MG. The anti–AChR antibodies are involved in complement-dependent destruction of the postsynaptic membrane of the myoneural junction, resulting in decreased nerve impulse transmission. Thymoma, thymic hyperplasia, and other autoimmune diseases often accompany MG. The functional abnormalities associated with the disease are similar to those induced by curare. The course during pregnancy is variable, although there is a tendency for

relapse during the puerperium.

The cholinesterase inhibitors and their equivalent doses most commonly used to alleviate symptoms are 0.5 mg of intravenous neostigmine, 1.5 mg of subcutaneous neostigmine, 15 mg of oral neostigmine, 60 mg of oral pyridostigmine, and 5 mg of oral ambenonium. Drugs are adjusted to the dose at which the patient's muscle strength is optimal with a minimum of cholinergic adverse effects. Oral pyridostigmine, or a sustained-release preparation of pyridostigmine, is the most commonly used medication for MG. Overmedication results in unpleasant effects such as abdominal cramps, flatulence, diarrhea, nausea, vomiting, and excessive secretion of saliva and tears. Toxic levels of pyridostigmine lead to a myasthenic crisis-like syndrome involving profound muscle weakness and eventually respiratory failure. Treatment with high-dose glucocorticosteroids has also been used successfully in some patients. Regular rest periods with limited physical activity should be prescribed for the pregnant patient with MG. Infections should be treated aggressively because of their propensity to exacerbate MG.

Careful plans should be made for drug therapy during pregnancy, labor, delivery, and the postpartum period. Some antibiotics such as the aminoglycosides may produce a myasthenic crisis and should be avoided. Other medications may also be harmful in women with MG (Table 18.11). Many patients with MG are sensitive to sedatives, analgesics, tranquilizers, and especially narcotics. Muscle relaxants should be avoided. Local or regional anesthetics are preferable. Magnesium sulfate is contraindicated because the drug diminishes the acetylcholine effect and has been known to induce a myasthenic crisis.

Magnesium salts
Aminoglycosides
Halothane
Propranolol
Tetracycline
Barbiturates
Lithium salts
Trichloroethylene
Colistin
Polymyxin B
Quinine
Lincomycin
Procainamide
Ether
Penicillamine

TABLE 18.11. *Medications that may exacerbate or cause muscle weakness in patients with myasthenia gravis*

Labor typically progresses normally and sometimes more rapidly than usual because smooth muscle is unaffected. Cesarean delivery should be reserved for obstetric reasons. Assisted ventilation should be available in the event of respiratory difficulty. During labor, the patient's oral dose of anticholinesterase should be discontinued and replaced with an intramuscular equivalent.

About 12% to 20% of infants born to women with MG exhibit neonatal MG, which lasts from a few hours to several days. The manifestations are caused by the transplacental transfer of acetylcholine-blocking factor. Interestingly, neonatal MG does not occur in all infants born to mothers with MG. The classic features of neonatal MG differ from those seen in adults. The symptoms usually do not develop until day 1 or 2 of life, probably because of some protection to the infant from the maternal blood levels of anticholinesterase agents. A high index of suspicion is necessary to recognize this phenomenon because an infant who appears healthy at birth may later develop respiratory failure with asphyxia. The involved infant shows generalized muscle weakness and hypotonic limbs and is limp and motionless. The Moro reflex often is weak or absent, and there may be a feeble cry, inability to suck, and associated difficulty in swallowing and breathing. Arthrogryposis (i.e., joint contractures), which may develop as a result of reduced intrauterine movement, has been reported in several infants born to mothers with MG.

SUMMARY POINTS

ERYTHROBLASTOSIS FETALIS

- Rh immunoglobulin should be given to Rh–negative, unsensitized women at 28 weeks gestation, within 72 hours after delivery, and in the event of antenatal procedures and complications associated with fetomaternal hemorrhage.
- Rh–alloimmunized women with anti–D titers 1:16 or greater should be referred for measurements of amniotic fluid bilirubin.
- Serial measurements of amniotic fluid bilirubin are used to identify fetuses at risk for significant fetal anemia.
- Intravascular intrauterine transfusion is most efficacious for the treatment of severely anemic fetuses with hydrops.

PLATELET ALLOIMMUNIZATION

- Platelet alloimmunization results in severe fetal and neonatal thrombocytopenia, which may be ameliorated with maternal administration of intravenous immunoglobulin.

MATERNAL THROMBOCYTOPENIA

- Gestational thrombocytopenia is a benign disorder characterized by mild thrombocytopenia (>70,000/mL), no history of excessive bleeding, no history of thrombocytopenia, resolution of thrombocytopenia 1 to 2 weeks after delivery, and no serious risk to mother or fetus.
- Autoimmune thrombocytopenia is characterized by thrombocytopenia before and after pregnancy, megathrombocytes on peripheral smears, bone marrow aspirate with normal or increased numbers of megakaryocytes, history of excessive bleeding, and absence of splenomegaly.
- Antiplatelet antibodies are not useful in differentiating between gestational thrombocytopenia and autoimmune thrombocytopenia.
- Autoimmune thrombocytopenia is not associated with a significant risk of fetal thrombocytopenia leading to intracranial hemorrhage.

SYSTEMIC LUPUS ERYTHEMATOSUS

- The diagnosis of lupus is based on specific clinical criteria.
- A positive antinuclear antibody (ANA) test is confirmatory in 98% of patients but elevated levels of antibodies to double-stranded DNA are most specific for disease activity.
- Most lupus flares during pregnancy are easily treated with glucocorticoids.
- Prophylaxis with glucocorticoid medication is not indicated to prevent flare during pregnancy.
- Lupus flare during pregnancy is best detected by frequent and thorough clinical assessment.
- Congenital cardiac heart block associated with neonatal lupus is characterized by fetal bradycardia diagnosed in the second trimester in a fetus with a structurally normal heart.

ANTIPHOSPHOLIPID SYNDROME

- The diagnosis of antiphospholipid syndrome (APS) should be based on the presence of thromboembolism or pregnancy loss in combination with medium to high titers of anticardiolipin antibodies or the lupus anticoagulant.
- A regimen of heparin and low-dose aspirin reduces the risk of thromboembolism and pregnancy loss in women with APS.

RHEUMATOID ARTHRITIS

- Pregnancy is associated with clinical improvement in at least 50% of patients with rheumatoid arthritis.

MYASTHENIA GRAVIS

- Myasthenia gravis (MG) is a chronic neuromuscular autoimmune disease characterized by fatigue and weakness, usually involving the extraocular, facial, pharyngeal, and respiratory muscles.
- Women with MG should avoid magnesium sulfate and aminoglycoside preparations, narcotics, and muscle relaxants.
- Neonatal MG occurs in 12% to 20% of infants born to mothers affected with MG.

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Chapter 19

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Obstetric and Perinatal Infections

Human Immunodeficiency Virus
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Microbiology
Epidemiology
Pathophysiology
Management
TOXOPLASMA
Introduction
Microbiology: Transmission
Epidemiology
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Diagnosis in Pregnancy
Treatment and Prevention
CYTOMEGALOVIRUS
Introduction
Microbiology
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Pathophysiology
Diagnosis
Management
HERPES SIMPLEX VIRUS
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SUMMARY POINTS FOR HIV, TOXOPLASMOSIS, CMV, AND HERPES
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SUGGESTED READINGS
HIV
Toxoplasmosis
Cytomegalovirus
HSV
Intraamniotic Infection
Postpartum Endometritis

Human Immunodeficiency Virus

Introduction

In this chapter, we will discuss four important perinatal infections—human immunodeficiency virus (HIV), toxoplasmosis, cytomegalovirus (CMV), and herpes—and two common bacterial infections—intraamniotic infection (IAI) and postpartum endometritis.

It has been more than 20 years since an article appearing in the Morbidity and Mortality Weekly Report drew the nation's attention to a previously unrecognized illness. That report described five gay males who had been diagnosed with *Pneumocystis carinii* pneumonia, an illness theretofore seen only among debilitated hosts. An accompanying editorial noted, “the fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis* pneumonia in this population” and “all the above observations suggest the possibility of a cellular–immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis.” Although that editorial showed remarkable insight, almost no one at that time perceived that report to be the harbinger of an epidemic that would devastate large swaths of the globe, become a leading cause of infant mortality, and change the practice of medicine and obstetrics around the world.

The ensuing years have been marked by dramatic progress that resulted from the harnessed energies of the nation's scientific community. In rapid sequence an etiologic agent was discovered, diagnostic tests were developed, public health interventions were instituted, and highly active pharmaceutical agents were developed. For those fortunate enough to be able to afford these interventions, the transformation of the epidemic could not have been more remarkable. No longer did a diagnosis ensure a short painful life and a certain death and for pregnant women mean a 25% chance of birthing an HIV-infected child. With access to state-of-the-art treatment there began to be concrete reasons for hope. Although the diagnosis still signals the beginning of a difficult, life-long struggle against the virus, there are effective, although toxic, therapies and the prevention of perinatal transmission can be ensured in almost 99% of cases. In this section of the chapter, developments in the field will be summarized in a fashion that should allow their integration into the practice of obstetrics and, thereby, ensure HIV-infected women the best possible prognosis for themselves and for their children. The focus of practice must be on two components of care, ensuring the health of women and minimizing the risks of transmission.

Microbiology

Retroviruses constitute a large and diverse family of enveloped RNA viruses that use as a replication strategy the transcription of virion RNA into linear double-stranded DNA, with subsequent integration into the host genome. The characteristic enzyme used for this process, an RNA-dependent DNA polymerase that reverses the flow of genetic information, is known as reverse transcriptase. The unique lifestyle of the retrovirus involves two forms, a DNA provirus and an RNA-containing infectious virion. Infection is initiated by the binding of a protein on the surface of the virus (gp120 Env protein) to the CD4 molecule found on some T cells, macrophages, and microglial cells. CD4 was first shown to be a viral receptor in a number of studies showing the susceptibility of CD4-bearing cells to infection and the ability to block infection with anti-CD4 monoclonal antibodies in culture.

HIV is composed of core (p18, p24, and p27) and surface (gp120 and gp 41) proteins, genomic RNA, and the reverse transcriptase enzyme surrounded by a lipid bilayer envelope. The virion contains three structural genes *(gag, pol*, and *env)* and a complex set of regulatory genes, including *tat, vif, nef, vpu*, and *ref* that control the rate of virion production. As noted, it preferentially infects cells with the CD4 antigen, particularly helper lymphocytes, but also macrophages, cells of the central

nervous system and, according to some evidence, cells of the placenta. At least two other cell surface molecules help HIV enter cells. These co-receptors for HIV, called CXCR4 and CCR5, are receptors for chemokines. Individuals who are homozygous for a deletion at the *CCR5* gene appear less likely to acquire HIV, while deletion heterozygotes progress less rapidly if infected.

Epidemiology

Approximately 25% of the 800,000 to 900,000 Americans living with HIV disease are women. Not coincidentally, the vast majority of cases of pediatric acquired immunodeficiency syndrome (AIDS) are secondary to vertical transmission of HIV from mother to fetus. Although AIDS rates are lower in women than men (9.3 per 100,000 women versus 32.4 per 100,000 men in 1999), the cumulative percentage of AIDS cases in women almost tripled from 6.7% in 1986 to 18% in 1999. Women of color constitute an increasing majority of AIDS cases in women. In 1999, African American women accounted for 63% of newly reported AIDS cases, and the case rate for Latinas (14.9 per 100,000) was more than 6 times the rate for white women. By 1998, HIV was the third leading cause of death among African American women ages 25 to 44.

The mode of acquisition of HIV in American women has evolved over time. Early in the epidemic, the majority of female AIDS cases were due to injection drug use (IDU). However, by 1995, the proportion of women infected through the heterosexual route surpassed that of IDU. As of 1999, the proportion of women who had sex with a known HIV-infected partner or an individual at high risk had increased to approximately 40%, while only 30% acknowledged using injection drugs. The proportion of women with no known risk increased to slightly greater than 30% in that same survey. Studies suggest that at least 50% of the latter individuals may have acquired HIV through heterosexual means. A report by the Centers for Disease Control and Prevention (CDC) estimates that 81% of those reporting no ascertained risk were infected via heterosexual means. Although noninjected drugs are not a direct vehicle for infection, cohort studies have revealed that much of the heterosexual risk of HIV is associated with use of drugs, such as alcohol and cocaine, which may mediate risk-taking behaviors.

Other important trends characterize the epidemic in women. For example, an increasing proportion of AIDS cases are occurring in women in the South, perhaps reflecting the dramatic increase in other sexually transmitted diseases (STDs) first seen in that region a decade ago. Poverty status might also vary with gender, with women substantially more likely to be covered by Medicaid and less likely to be privately insured. Poverty, in turn, is associated with risk behaviors (e.g., drug use) that are linked to HIV acquisition. These data demonstrate, yet again, that poverty, drug use, and STDs continue to fuel the HIV epidemic among women in the United States.

Pathophysiology

HIV infection leads to a progressive debilitation of the immune system, rendering infected individuals susceptible to opportunistic infections (e.g., *P. carinii* pneumonia and central nervous system toxoplasmosis) and neoplasias (e.g., Kaposi sarcoma) that rarely afflict patients with intact immune systems. An HIV-infected patient with one of several specific opportunistic infections, neoplasia, dementia encephalopathy, or wasting syndrome, is diagnosed as having AIDS. The diagnosis of AIDS also can be made in the absence of laboratory evidence of infection if the patient has no other known cause of immune deficiency and has the definitive diagnosis of one of a number of indicator diseases. In 1993 the CDC changed the case definition to include all individuals with HIV infection whose CD4 cell counts drop below 200 per cubic millimeter, as well as HIV-infected individuals with advanced cervical cancer, pulmonary tuberculosis, and recurrent pneumonia.

At the time of initial infection, an individual may be asymptomatic or may develop an acute mononucleosis-like syndrome that can be accompanied by aseptic meningitis. There is then an immediate viremia of substantive proportions (up to ten billion viral particles turned over per day) and an equally impressive immune responsive with similar levels of T-cell turnover. Antibodies can be detected in almost all individuals 6 to 12 weeks after exposure but, in rare circumstances, this latent period (the so-called *window phase*) can be longer. After seroconversion has occurred, an asymptomatic period of variable length usually follows. The median clinical latency in the absence of effective therapy was estimated at approximately 11 years. Very few infected persons (<5%) develop AIDS within 3 years. Evidence of immune dysfunction may be followed by clinical conditions ranging from fever, weight loss, malaise, lymphadenopathy, and central nervous system dysfunction to infections such as herpes simplex virus or oral candidiasis. These nonspecific conditions are usually progressive and are a prelude to an opportunistic infection that is diagnostic of AIDS. Studies of infected individuals have noted that 5 years after infection was confirmed, up to 35% had progressed to AIDS. A study of subjects with hemophilia demonstrated that the incidence rate of AIDS after seroconversion was 2.67 per 100 person-years and was related directly to age younger individuals developed AIDS at a slower rate). It should be noted that all these statistics antedate the use of new, more powerful antiretroviral agents, which have a significant effect on both clinical outcomes and surrogate markers of disease progression. The level of virus in the plasma can provide an estimate of the probability that an individual will develop AIDS within 5 years.

Once AIDS is diagnosed, the short-term prognosis is improving (e.g., surviving an initial episode of *P. carinii* pneumonia). The effect that the newest antiretroviral agents, including protease inhibitors (PIs), will have on survival cannot yet be clearly gauged, but they do provide reason for cautious optimism. Conversely, the long-term morbidity related to medications that have been linked to lipodystrophy, among other problems, also remains to be determined. Viral load and CD4 cell counts can be used to predict the likelihood that an individual will develop AIDS during a given follow-up period. Appropriately controlled studies reveal no convincing evidence that the natural history of HIV infection is influenced by gender or pregnancy (Fig. 19.1).

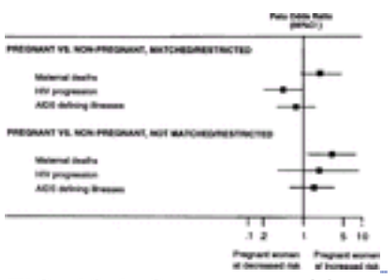

FIG. 19.1. Summary odds ratio of studies which attempted to control for confounding by matching or restriction techniques compared with those which had not used matching or restriction. (From French R, Brocklehurst P. The effect of pregnancy on survival in women infected with HIV: a systemic review of the literature and meta-analysis. Br J Obstet Gynecol 1998;105:827–835, with permission.)

Management

Monitoring The guiding principle in the care of HIV-infected pregnant women continues to be strict adherence to the standards of care that apply to all other HIV-infected individuals. The first step in that care is the monitoring of the woman's immune status with CD4 cell counts and viral load measurements. Monitoring of resistance is becoming a frequent addendum to monitoring regimes (vide infra). Viral loads can be checked every 3 months. Once a decision to initiate therapy is made, viral load monitoring should occur monthly until virus is no longer detectable and then can be cut back to every 2 or 3 months. With appropriate therapy, one can anticipate a drop of 1.5 to 2.0 logs within 1 month of initiation of treatment. The recommended timing of initiation of therapy (vís a vís CD4 cell counts and viral loads) has undergone several revisions over the last few years. Despite the clear benefits of therapy, well-recognized toxicities may make it difficult to maintain strict adherence. Some data suggest that no harm befalls patients who delay therapy until viral loads rise and CD4 cell counts drop further than had previously been recommended. Guidelines are to start therapy in nonpregnant women when the viral load is over 30,000 by HIV RNA (55,000 by polymerase chain reaction [PCR]) or when the CD4 cell count drops below 350 per cubic millimeter. In the nonpregnant state, when those thresholds are passed, highly active antiretroviral therapy (HAART) should be initiated. Initiation during pregnancy is discussed below. Resistance testing has become a staple of care for the HIV-infected woman. Most randomized trials of resistance testing have demonstrated that those assigned to study arms with access to resistance test results had a greater reduction in viral load after the initiation of salvage therapy, although follow-up generally has been short. These tests are recommended for individuals who have just seroconverted or who have failed therapy. *Treatment failure* is defined as the failure to attain an undetectable level of virus or the persistent presence of virus after it had become undetectable. Transient low-level viremia may not be the same as a drug failure, and sustained response to treatment can occur even with occasional low-level viremia. Blood for testing should be obtained before a failing regimen is discontinued lest wild-type virus overgrow before the test is performed. In that circumstance, an individual with no apparent resistance would still fail therapy when reexposed to drugs that favor the growth of the resistant virus over the wild-type strain. In essence, resistance testing is more useful for ruling out, than for ruling in, therapies to be used in a given patient. That is because, as noted, the absence of resistance may merely reflect the reemergence of a wild-type strain after an antiretroviral agent has been withdrawn. In that circumstance, the assays will not detect a low volume of a minority mutant strain. However, if the patient is reexposed to the offending agent, the resistant strain may again attain dominance. It is not possible to perform resistance studies if there are fewer than 1,000 copies of virus detectable. Two types of testing are available, genotypic and phenotypic, each with distinct advantages and disadvantages. Phenotypic testing compares the ability of the virus to replicate in various concentrations of an antiretroviral drug with its replication in the absence of the drug. In general, if the amount of drug required to inhibit viral production by 50% is four-fold or greater for the patient's virus than the control strain, then the patient's strain is considered resistant. Specific cutoffs for resistance for each drug are being developed based on clinical correlation and the serum levels usually attainable for a given drug. Measurement of drug levels per se has not yet been shown to be a useful addendum to standard monitoring. Genotypic testing is directed at detecting mutations in the genes that encode reverse transcriptase and protease formation by the virus. Point mutations in the virus result in the substitution of

amino acids in the proteins produced, namely reverse transcriptase or protease. The significance of these point mutations has to be determined by correlating specific mutations with phenotypic resistance, as measured by viral susceptibility assays and correlation with clinical response to therapy. Genotypic changes leading to resistance are believed to result from the combination of the rapid turnover of HIV (10^7–10^8 rounds of replication per day) and the high error rate of reverse transcriptase when replicating the nearly 10,000 nucleotides present in the HIV genome. Genetic mutants with resistance to antiretroviral agents are then selected by evolutionary pressure when incompletely suppressive drug regimens are used. The rate at which resistance develops will depend on the number of mutations necessary for a significant change in susceptibility to occur. The genetic basis for resistance must be understood before the impact of a specific mutation can be predicted. In addition, mutational interactions may make prediction of phenotype (i.e., susceptibility) difficult when multiple mutations are present. Prediction of cross-resistance to other drugs within a class such as protease inhibitors can be difficult to predict based only on genotype. In clinical practice, most clinicians will rely upon algorithms developed by panels of experts or found in on-line databases. Obstetricians should interpret and act upon these results in consultation with an expert in the field. It has been suggested that HIV-infected pregnant women will benefit routinely from resistance testing, but a few caveats are necessary in that regard. The goal in all cases of HIV infection in pregnancy is to maintain a viral load under 1,000, because that would both allow a vaginal delivery and minimize the mother-to-child transmission rate. However, if a regimen were successful in dropping the load to or below that level, it would be impossible to perform resistance testing. If the regimen is unsuccessful, then resistance testing is warranted, regardless of the patent's pregnancy status. That said, there are considerations that are unique to pregnancy and they relate to the fitness of resistance virus for mother-to-child transmission of HIV. In general, resistance to zidovudine (ZDV, also commonly known as AZT) and other resistance mutations have not been associated with an increased risk of perinatal transmission in most perinatal transmission studies. In one study, detection of ZDV resistance was associated with transmission when adjustment was made for duration of ruptured membranes and total lymphocyte count. Factors associated with resistance at delivery included ZDV use prior to pregnancy, higher log HIV RNA, and fewer $CD4^+$ lymphocytes present. Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and it is not clear that the presence of mutations increases the risk of transmission. In a multisite study of HIV-infected pregnant women (WITS), it was reported that when a transmitting mother had a mixed viral population of wild-type and low-level resistant virus, only the wild-type virus was found in the infant, suggesting that virus with low-level ZDV resistance may be less transmissible.

Pharmaceutical Therapy Although the number of HAART regimens that have been shown to achieve persistently low viral loads continues to increase, they generally fall into one of a few broad categories. The original regimens described in 1996 included dual nucleoside therapy accompanied by a protease inhibitor. There are seven nucleoside reverse transcriptase inhibitors (NRTIs), three nonnucleoside reverse transcriptase inhibitors (NNRTIs), and six PIs approved for therapy, with many others in the pharmaceutical “pipeline,” so theoretically a large number of choices within these categories exists. However, certain medications should not be used in combination. For example, ZDV and D4T have overlapping toxicities, ddI and ddC should not be used in combination, and ddI and d4T have been linked to several fatal cases of mitochondrial toxicity in pregnancy. Because the number of new drugs continues to multiply, as does information about their benefits and toxicities, it has become increasingly difficult for busy clinicians to stay abreast. To assist in that endeavor, the U.S. Department of Health and Human Services has established a Web site (http://www.aidsinfo.nih.gov/) that is regularly updated. The expert panel that authors those update guidelines “strongly recommends” regimens that include either one or more PI(s) (indinavir, nelfinavir, ritonavir + saquinavir, ritonavir + indinavir, ritonavir + lopinavir) or an NNRTI (efavirenz in the nonpregnant patient) in combination with one of several two-NRTI combinations. There is a great deal of clinical outcome data that support the use of a PI in combination with two NRTIs. Some of the PIs, such as ritonavir, are not usually chosen as first-line therapy, because patients often have difficulty tolerating standard dosages and because of the drug's many interactions. Other PIs, such as saquinavir-SGC, create difficulties for many patients because of the large pill burden associated with their use; however, if a woman can maintain the dosage and it is working well, then there is no reason to change drugs. A critical factor to recognize is that poor results often occur with antiretroviral regimens used in a patient who has experienced virologic failure with a previous regimen. That suggests that the first regimen affords the best opportunity for long-term control of viral replication. Because the genetic barrier to resistance is greatest with PIs, many would consider a PI + two NRTIs to be the preferred initial regimen. However, efavirenz (NNRTI) + two NRTIs appears to be at least as effective as a PI + two NRTIs in suppressing plasma viremia and increasing $CD4^+$ T-cell counts, and many would prefer such a regimen initially because it may spare the toxicities of PIs for a considerable time. However, concerns about teratogenicity that have been demonstrated in animal models, as well as a case report of a myelomeningocele after in utero exposure in a human, make this a poor choice for use in early pregnancy. Thus, although the demonstrated ability of efavirenz in combination with two NRTIs to suppress viral replication and increase $CD4^+$ T-cell counts to a similar degree as a PI with two NRTIs supports a preference for efavirenz over the other available NNRTIs, in pregnancy the choice of a different NNRTI may be preferable. Abacavir, a new NRTI + two other NRTIs (i.e., a triple NRTI regimen), has been used with some success, as well. Such a regimen, however, may have short-lived efficacy when the baseline viral load is more than 100,000 copies per milliliter, and has recently been shown to be less effective than efavirenz. Using two NRTIs alone does not achieve the goal of suppressing viremia to below detectable levels as consistently as do the other regimens discussed above and should be used only if more potent treatment is not possible. Use of antiretroviral agents as monotherapy is contraindicated, except when there are no other options, or in pregnancy to reduce perinatal transmission as noted below. When initiating antiretroviral therapy, all drugs should be started simultaneously at full dosage with the following three exceptions: dosage escalation regimens are recommended for ritonavir, nevirapine and, in some cases, ritonavir plus saquinavir.

Considerations Related to HAART Therapy for Pregnant Women Although therapeutic recommendations should not be modified a priori because of pregnancy, a few comments deserve particular mention. First, in regard to the dosage of ZDV, a drug that has been a cornerstone of therapy in pregnancy since 1994, it should be remembered that the antenatal dosing regimen used in the PACTG 076 trial (100 mg administered orally 5 times daily) was selected on the basis of standard ZDV dosage for adults at the time of the study. However, administration of ZDV 3 times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing. Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily. Thus, the standard dosing for ZDV, whether used as a part of a HAART regimen or as single-drug therapy for transmission prevention (discussed below), is 200 mg 3 times daily, or 300 mg twice daily. Although it is possible that these dosing regimens may not have efficacy equivalent to that observed in PACTG 076, a regimen of 2- or 3-times daily is likely to enhance maternal adherence. NRTIs were the first class of drug used for treatment of HIV, and there is a greater experience with their use in pregnancy than with other classes of drug. Most information is available for ZDV, the first agent to be used widely in pregnancy. Most data regarding the safety of ZDV have been reassuring. Almost 1,000 children have been tracked for 4 years with no increase in incidence of neurodevelopmental delay or carcinogenesis. Some concern had been raised, however, as a result of mouse data reported from the National Cancer Institute. That report suggested that mice exposed to high dose rates of ZDV in the third trimester birthed pups that were subsequently found to have high rates of liver, lung, skin, and genitourinary tumors in midlife. Although other investigators have not reported similar findings, the National Cancer Institute data should chasten those who would dismiss all concerns regarding these therapies and reinforce the need for thorough counseling and long-term follow-up. In regard to monitoring of the mother on ZDV, it is necessary to measure the blood count and liver functions only on a monthly basis. The only abnormality that occurs with any frequency is anemia. Other NRTIs have been well tolerated generally and have not been demonstrated to be teratogenic in humans. However, concerns have been raised about potential adverse effects on both mothers and infants related to the avidity of these drugs for mitochondria. By binding to mitochondrial ?-DNA polymerase and interfering with replication, these drugs can induce mitochondrial dysfunction. The greatest inhibition of mitochondrial ?-DNA polymerase is demonstrated by ddC, followed in order by ddI, d4T, 3TC, ZDV, and abacavir. Clinical disorders associated with mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. In regard to potential maternal toxicity, several cases of lactic acidosis, three of which were fatal and two of which were accompanied by pancreatitis, have been reported among pregnant or recently delivered women who had been on ddI and d4T therapy along with a variety of third agents since before conception. Two cases of fatal liver failure in pregnant women on ZDV, lamivudine, and nelfinavir also have been reported. These cases developed in late pregnancy, and in several cases the clinical picture was similar to that seen with acute fatty liver of pregnancy, a condition that has been linked to mitochondrial fatty oxidation disorders in the fetus (homozygotic) and mother (heterozygotic). This has led to speculation that the metabolic changes of late pregnancy may enhance susceptibility to complications of nucleoside agents, especially those with greater inhibition of mitochondrial ?-DNA polymerase. That susceptibility is suggested both by the syndrome of acute fatty liver of pregnancy and animal data that demonstrate reduced mitochondrial fatty acid oxidation in late pregnancy and in animals treated with exogenous estradiol and progesterone to mimic pregnancy levels. However, many cases of death outside of pregnancy have been reported related to these medications as well. In any event, although these serious morbidities appear to be rare, providers caring for HIV-infected women receiving nucleoside analog agents should be cognizant of the risk and monitor accordingly. One approach would be to monitor hepatic enzyme levels during the last trimester and to investigate aggressively all new symptoms. Women with substantial elevations in transaminase levels above baseline or other new abnormalities, in the absence of other explanations such as preeclampsia, should have their nucleoside agents discontinued, either with substitution of agents from another class of antiretroviral drugs or discontinuation of all antiretroviral medications. In view of the reports of maternal deaths and toxicity associated with prolonged use of d4T and ddI in pregnancy, this combination should be used in pregnancy with caution and only if other nucleoside agents cannot be used because of resistance or toxicity. In regard to infants, concern about mitochondrial toxicity was raised initially by a French group that reported eight cases of HIV-uninfected infants (among 1,754 exposed fetuses) with abnormalities potentially related to mitochondrial dysfunction, which developed after exposure to prophylactic nucleoside therapy. Two infants had progressive neurologic symptoms and died several months after completing in utero and neonatal courses of ZDV/3TC. Three other infants had mild to moderate symptoms, and three had asymptomatic laboratory abnormalities. Mitochondrial abnormalities were not proven to be the cause of the abnormalities, and the relationship between these findings and in utero and neonatal nucleoside exposure has not been established. In response to these concerns, investigators from several large cohort studies in the United States reviewed all 353 deaths among more than 20,000 children born to HIV-infected women and found no deaths similar to those in the French cohort, although only 6% of the children had been exposed to the combination of ZDV/3TC. Review of data on living children from these cohorts for diagnoses or conditions suggestive of mitochondrial dysfunction is ongoing. Combination therapy also has been linked to increased rates of prematurity in a few European studies, but these have not been confirmed in larger American series. Reports also have warned of an increased rate of neonatal febrile seizures in infants who had been exposed to antiretroviral therapy. Finally, as noted above, efavirenz should not be recommended because of reported teratogenic effects in monkey models. In regard to prophylaxis for opportunistic infections, if the count drops below 200 cubic millimeters, *P. carinii* pneumonia prophylaxis should be instituted, and below 50 cubic millimeters, *Mycobacterium avium* complex prophylaxis should be given and an ophthalmology consult obtained. The specific details of management of the myriad infections to which these women are prone are beyond the scope of this chapter. If HAART therapy is successful in returning CD4 cell counts to levels above the threshold for prophylaxis of opportunistic infections and those levels are maintained for 6 months, then the prophylaxis can be discontinued.

Preventing Perinatal Transmission It has been almost a decade since the results of PACTG Protocol 076 were released. Those results demonstrated that a regimen of ZDV given during pregnancy, labor, and to the newborn for 6 weeks was able to reduce remarkably the risk of perinatal HIV transmission; an almost 70% reduction in transmission risk was observed, from 25% in the placebo group to 8% in the ZDV group. Subsequently, ACTG 185 demonstrated that similar results could be seen, even among women who had previous exposure to ZDV or who had CD4 cell counts below 200 cubic millimeters. ZDV has now been integrated successfully into clinical practice in the United States and Europe, and its widespread use has been accompanied by dramatic declines in perinatal transmission rates in these countries. The regimen consists of ZDV 200 mg 3 times a day in the antepartum period (beginning after 14 weeks). In the intrapartum period, a loading dose of 2 milligrams per kilogram over the first hour is followed by a maintenance dose of 1 milligram per kilogram per hour thereafter. During the neonatal period the infant receives ZDV syrup

for 6 weeks at a dosage of 2 milligrams per kilogram every 6 hours. There are insufficient data to justify the substitution of any agent for ZDV in most circumstances, save perhaps for times when women have not received therapy prior to labor (vide infra). Even if there is evidence of ZDV resistance, which might make ZDV therapy for the prevention of mother-to-child transmission seem futile, ZDV might still have a role. The demonstration of transmission of escape mutants from mother to child suggests that an individual ZDV-susceptible virus might be transmitted, even if the predominant strain(s) in the mother is (are) not susceptible. If the mother is intolerant of ZDV, it may be reasonable to consider using an alternative agent, which potentially could reduce viral load during the antepartum period, and then adding ZDV for the intrapartum (depending on the type of toxicity experienced by the mother) and neonatal periods. Thus, if the therapeutic regimen being used to treat a woman's HIV disease does not include ZDV, it would seem judicious to incorporate it if she becomes pregnant. The recommendation to use ZDV, as opposed to other antiretroviral agents, for the prevention of mother-to-child transmission of HIV is based on two considerations. First, there are empiric data that strongly support its use in that regard. No other agent has been studied similarly. Second, pharmacokinetic studies demonstrate that high levels of drug are available in the fetal compartment. Similar information is unavailable for most other agents. The importance of placental passage of drug is not certain. If viral load thresholds truly are central to transmission risk, than viral dynamics on the maternal side of the placenta might be as important as placental passage of drug. Several publications (Fig. 19.2) suggest that a correlation exists between maternal viral load and rates of mother-to-child HIV transmission and, further, hint at the existence of a clinically relevant threshold. Although other researchers disagree, most data support the thesis that dropping viral loads as low as possible in pregnancy is a useful strategy. There is clear evidence that, even if the viral load is low, those women on antiretroviral therapy will fare better than women with similar viral loads who are not on therapy, and data suggest that combination therapy is even more effective than ZDV alone in reducing rates of transmission. A French team reported that adding 3TC to ZDV reduced transmission rates to 1.6%. A longitudinal study in the United States found that 20% of women with no antiretroviral therapy transmitted HIV to their infant as compared with 10.4% who received ZDV alone, 3.8% who received combination therapy without a PI, and 1.2% who received a combination that included a PI.

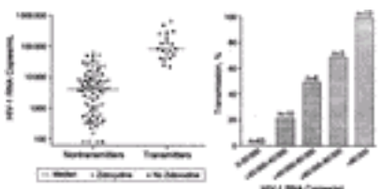

FIG. 19.2. Left: Maternal human immunodeficiency virus–type 1 (HIV-1) RNA levels at delivery in infected nontransmitting and transmitting mothers. Mothers who received zidovudine during gestation or labor and delivery are indicated by the *open circles;* mothers who did not receive zidovudine during gestation, labor, or delivery are indicated by the *darkened circles. Horizontal bars* indicate the median for each of the measured variables. **Right:** Perinatal transmission rate according to HIV-1 RNA levels at delivery. (From Dickover RE, Garratty EM, Herman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission. JAMA 1996;275:599–605, with permission.)

The vast majority of perinatal HIV-1 infection occurs in the developing world. Unfortunately the PACTG 076 ZDV regimen is too costly and logistically complex for many nonindustrialized countries to implement on a widespread scale, and its efficacy in a breast-feeding population (where postpartum transmission remains a real concern) is unknown. An ideal preventive intervention would be cheap, nontoxic to mother and fetus, easy to administer, only need to be given once or for a limited period, and have utility in preventing postpartum transmission. The results of PACTG 076 have spurred the worldwide evaluation of multiple other modalities to reduce transmission. Many of the regimens designed for countries with fewer resources have attempted to achieve reduced numbers of infected children with shortened courses of antepartum and neonatal therapy. These regimens have included a Thai regimen of 4 weeks of antepartum ZDV combined with oral ZDV therapy during labor that reduced transmission to 9% compared with 19% in a placebo arm. Similar findings have been reported from the use of an abbreviated course of ZDV and 3TC in an African trial. An even more dramatic finding emerged from the HIVNET 012 trial which revealed that a single does of nevirapine during labor and again to the neonate could reduce transmission at 6 weeks from the 21% seen in those receiving a short course of ZDV to only 12%. Unfortunately, the benefits of all these regimens are attenuated in populations that breast-feed after the regimens have been completed. Perhaps of greater relevance to American populations are data that demonstrate that even patients whose serologic status is unknown until the peripartum period may benefit from pharmaceutical interventions. In a review of the New York state experience, Wade and colleagues found that the transmission rate from mothers who received no therapy was lowered significantly with ZDV even when therapy was delayed until the first 24 hours postpartum. It was lowered to an even greater extent when therapy was begun during the intrapartum period. Other efforts to prevent transmission have focused on attempts to reduce peripartum and postpartum exposure to the virus. Reduction of intrapartum exposure could include attempts to minimize the duration of ruptured membranes, which has been related to the rate of mother-to-child transmission of HIV (Fig. 19.3). Cesarean delivery is the one strategy that can guarantee that the infant will not be exposed to the risks associated with ruptured membranes during parturition. Evidence has accumulated that cesarean section may be a beneficial addendum to pharmaceutical therapy. Read and her colleagues published a meta-analysis performed on primary data from 15 prospective cohort studies, including more than 7,800 mother-child pairs. In that meta-analysis, the rate of perinatal HIV-1 transmission in women undergoing elective cesarean delivery was 8.2% and 2.0% in those receiving no antiretroviral agents and in those receiving ZDV, respectively. Both rates were significantly lower than those seen among women delivered by either nonelective cesarean or vaginal delivery.

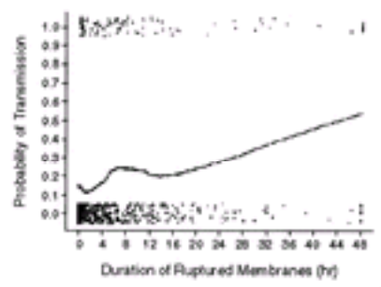

FIG. 19.3. Probability of HIV-1 transmission in relation to the duration of ruptured membranes. The *dots* at the top represent women who transmitted HIV-1 to their infants and those at the bottom, women who did not transmit. (From Landesman S, Kalish L, Burns D, et al. The relationship of obstetrical factors to the mother-to-child transmission of HIV-1. N Engl J Med 1996;334:1617–1623, with permission.)

Subsequently, the results of a European randomized trial of cesarean section were reported (Table 19.1). The results were remarkably consistent with those that had been found by Read. In the European study, HIV-infected women between 34 and 36 weeks of gestation were randomly assigned elective cesarean delivery at 38 weeks or vaginal delivery. Three (1.8%) of 170 babies born to women assigned cesarean delivery were infected compared with 21 (10.5%) of 200 born to women assigned to vaginal delivery ($P < .001$). Seven (3.5%) of 203 infants of women who gave birth by cesarean section were infected compared with 17 (10.2%) of 167 born vaginally ($P = .009$). Unfortunately, the number of participants was too small to allow a separate analysis of the benefit of cesarean section for a patient receiving antiretroviral therapy, and HAART use was not reported from the cohort. There were few postpartum complications, and no serious morbidity was noted in either group. Despite the shortcomings of the trial, it does suggest that among women who were not optimally treated with HAART, cesarean section could have an important effect on reducing rates of mother-to-child transmission of HIV.

TABLE 19.1. *HIV-1 infection status of children according to allocated and actual mode of delivery*

In sum, the above-cited studies indicate that compared with other types of delivery, cesarean delivery performed prior to the onset of labor and prior to rupture of membranes (elective, or scheduled, cesarean) significantly reduces the rate of perinatal HIV-1 transmission by odds ratios of 0.2 to 0.4. On the basis of the data, the American College of Obstetricians and Gynecologists published a committee opinion that concluded that HIV-infected women should be offered scheduled cesarean section in order to reduce the rate of transmission beyond that which could be achieved with ZDV alone. They also pointed out that data are insufficient to demonstrate a benefit for women with viral loads less than 1,000 copies per milliliter of plasma. They suggested that scheduled cesarean sections should be performed at 38 weeks of gestation and that amniocentesis should not be performed in order to avoid contamination of the amniotic cavity with viral antigen from maternal blood. They also suggested that prophylactic antibiotics be employed because of concerns of heightened risks of postoperative infectious morbidity. The data supporting a heightened risk for postoperative morbidity among HIV-infected women are not robust; however, the evidence that all women undergoing an operative delivery face a greater risk of infectious morbidity is overwhelming. The liberal use of antibiotics in the setting of cesarean section and HIV infection would, therefore, seem reasonable. Although not as compelling as the data just cited, there is some evidence that cesarean section could be beneficial even when viral loads are under 1,000 copies. That data come from a meta-analysis of studies that focused exclusively on women who had viral loads lower than 1,000 copies. In those women, antiretroviral therapy still played a major role in reducing transmission, dropping rates from approximately 10% to approximately 1%. Cesarean section apparently dropped the rate from 6% to 1.5%, but there was no control in that analysis for the use of antiretroviral therapy. In sum, there is no strong evidence that cesarean section will provide additional benefit to the HIV-infected woman on therapy who has an undetectable viral load.

TOXOPLASMA

Introduction

Primary maternal toxoplasmosis occurs in approximately 1 of every 900 pregnancies in the United States. This estimate is based on a prospective study of sera from 23,000 pregnant women done in early and late gestation. That study, which was conducted by the National Institutes of Health, also showed that 38% of the women tested had antibodies to *Toxoplasma gondii*, indicating previous infection with the organism. More recent data suggest that the seroprevalence may now be somewhat lower (15% among women of childbearing age). In the earlier data, the presence of antibodies correlated with increasing patient age and was twice as frequent among blacks as among whites. None of the mothers tested had evidence of significant clinical disease. It has been estimated that between 400 and 4,000 babies are born with congenital *T. gondii* infections each year. Some data suggest that congenital infections occur in approximately 1 in 10,000 births.

Microbiology: Transmission

Cats The cat is the definitive host for *T. gondii*, a protozoan parasite. About one half of the cats tested in the United States have antibodies to *T. gondii.* It is thought that cats acquire infection by eating infected wild rodents and birds. A week after infection, the cat begins to shed oocysts in its feces. Shedding of the oocysts persists for about 2 weeks before the cat recovers spontaneously. These animals are susceptible to reinfection and may also shed toxoplasma oocysts when infected with other organisms. Although the cats excrete unsporulated (i.e., noninfectious) oocysts in their feces, within days to weeks these oocysts sporulate and become extremely infectious. The fecal oocysts are an important source of infection to humans through inadvertent ingestion. Because sporulation of the organism occurs after days to weeks in the litter, it may be prevented by having a nonpregnant person change the litter daily. Care must be taken in disposing of cat litter, because the oocysts can remain infectious for long periods in favorable climates.
Meat In Europe, where the use of refrigeration is more limited and meat usually is not frozen, ingestion of infected meat is an important cause of toxoplasmosis. In contrast, in the United States, much of the meat is frozen at some point during storage or transport. Freezing is probably one of the factors responsible for the difference in incidence of toxoplasmosis here and in Europe. Worldwide, about 1% of cattle, 20% of hogs, and 30% of sheep have toxoplasmosis, according to estimates based on isolation of the organism from animal muscle tissue. To avoid contagion from meat, it should be cooked thoroughly at adequate temperatures.

Epidemiology

T. gondii has a worldwide distribution and has been reported from wherever cats are found. It is somewhat more common in tropical and coastal regions and is less common in regions that are either cold, warm and arid, or at high elevation. The infection rate in the United States is significantly lower than that in France. Within the United States, seroprevalence rates are lower in the west central and mountain states, and higher in east Atlantic and east central states.

Pathophysiology

T. gondii exists in three forms: trophozoites or proliferative form (Fig. 19.4), tissue cysts, and the oocytes. The organism undergoes a substantial portion of its life cycle in the cat where, after between 5 and 8 days of infection, there is peak oocyte production. As many as ten million oocysts per day can be shed in feces for periods varying between 7 and 20 days. These oocytes sporulate within 1 to 3 days and can remain infectious for several months in moist soil. At that point they may be carried from point of deposition by other animals (e.g., flies) and deposited in food. It has also been suggested that they can also become airborne from a dried out litter box and lead to human infection. Eating undercooked or raw meat that contains tissue cysts causes approximately one half of infections in most humans. In the human, the trophozoite form of *T. gondii* is seen in the acute phase of the infection, and it is during this phase that host cells are invaded. Thereafter, the organism multiplies every 4 to 6 hours until the cytoplasm becomes so filled with trophozoites that the cells rupture, releasing organisms to invade other cells.

FIG. 19.4. *T. gondii* in trophozoites or proliferative form. (From Jones JL, Lopez A, Wilson M, et al. Congenital toxoplasmosis: a review. Obstet Gynecol Surv 2001;50:296–305, with permission.)

In Utero Transmission Newborns with congenital toxoplasmosis become infected in utero by transplacental passage of the parasite when the mother has acute infection. Chronic infections (onset precedes pregnancy) do not lead to congenital infection except in the rare circumstance of an immunocompromised host (e.g., patient with systemic lupus erythematosus taking steroids, HIV disease). In general, the likelihood of fetal infection increases with each trimester of pregnancy, being approximately 15%, 25%, and 60% in the first, second, and third trimester, respectively. The severity of damage associated with congenital toxoplasmosis also is related to the timing of maternal infection, but in this situation, the risks decrease toward term. Severe fetal disease or fetal death occurs in about 10% of cases when infection occurs during the first trimester and is extremely rare with infection during the third trimester. Mild damage is more frequent in the second and third trimesters (about 5%). Subclinical infections increase from about 2% with first-trimester infections to 50% with third-trimester infections. The results of a case-control study of women with poor pregnancy outcomes and controls suggested that acute infection could be associated with preterm delivery and stillbirth but not with spontaneous abortion. Chronic infections were not associated with any untoward outcomes.

Diagnosis in Pregnancy

Mother Maternal infection with *T. gondii* is usually asymptomatic, although 10% to 20% of infected mothers have lymphadenopathy. Posterior cervical lymphadenopathy is the most frequent finding associated with acute maternal toxoplasmosis. The infection also can result in a mononucleosis-like syndrome with fatigue and lassitude and, rarely, can cause encephalitis. Acute toxoplasmosis should be considered in any pregnant woman who has lymphadenopathy, particularly involving the posterior cervical chain, or mononucleosis-like symptoms. The vast majority, however, of those acutely infected with *T. gondii* are asymptomatic. The clinical picture can be much more severe in immunocompromised adults. In the absence of symptoms, clinicians are forced to rely on serologic tools for the diagnosis of toxoplasmosis in pregnancy. The diagnosis of primary infection with *T. gondii* during pregnancy requires either (a) the demonstration of a seroconversion to this organism, (b) a significant rise in antibody titer obtained from maternal sera taken at two different times, or (c) the detection of toxoplasma-specific immunoglobulin M (IgM) antibody. Adults with primary infection develop immunoglobulin G (IgG) and IgM antibody to toxoplasma rapidly. Toxoplasma-specific IgG antibody develops within 2 weeks after infection, peaks in 6 to 8 weeks, drops down over the subsequent several months, and then persists for life. Toxoplasma-specific IgM develops within 10 days after infection and remains elevated for 6 months to more than 6 years. Some researchers have suggested that the presence of high-avidity IgG antibodies exclude acute infection within the previous 3 months, thereby making it a useful test for first-trimester infection. Because IgM antibody remains elevated for many months, this test may not provide useful information to document recent primary infection in pregnant women. The enzyme-linked immunosorbent assay (ELISA) test for IgM frequently shows the development of high titers of antibody that can persist for many years. Indirect immunofluorescence antibody (IFA) tests for toxoplasma-specific IgM usually show high titers for only about 6 months after infection, following which the titer rapidly drops. The IFA test, then, frequently is more useful than ELISA in differentiating remote from recent primary infection of a pregnant woman. In any case, the presence of IgG and the absence of IgM suggest an infection that is probably at least a year old. Because of difficulties with the reliability of some commercially available tests for IgM, it has been recommended that all positive test results be confirmed in a reference laboratory. Approximately 50% of placentas of congenitally infected infants will show *T. gondii* cysts on histologic slides, and their presence supports the diagnosis of acute infection in the mother during pregnancy. Additional cases can be detected by the presence of parasites in the cord blood. The organism also has been isolated from placental tissue of acutely infected mothers in 2% to 25% of cases. Recovery was more frequent when infection occurred later in pregnancy. Isolation of organisms from tissue specimens, buffy coat heparinized blood, and body fluids can be used, also, for diagnosis. These specimens produce the organism after inoculation into the intraperitoneal cavities of mice or into tissue culture.
Prenatal Diagnosis Antenatal diagnosis of fetal toxoplasmosis used to rely on culture of amniotic fluid (15–20 cc) or fetal blood (1.5–3.0 cc) obtained at the time of diagnostic amniocentesis or cordocentesis, respectively. The specimen was cultured commonly in mice or fibroblast cells. The main difficulties with culture techniques have been that some assays may take up to several weeks to get complete results, and very few laboratories are able to perform the assay. Toxoplasma-specific IgM, when present in fetal blood from cordocentesis, has also been used to diagnose fetal infection prenatally. Unfortunately, fetal-specific IgM antibody frequently does not develop until after 21 to 24 weeks gestation and is positive in only about 50% of infected cases. Additionally, cordocentesis is a procedure that entails some risk. More recently, the PCR has been used to detect *T. gondii* in amniotic fluid and has been shown to be useful in the detection of fetal infections in utero. In one large series, PCR performed better than conventional tests (sensitivity 97.4% versus 89.5%; negative predictive value 99.7% versus 98.7%). PCR of amniotic fluid has, to a large extent, rendered cordocentesis obsolete for the purpose of diagnosing toxoplasma infections.
Child Most congenitally infected newborns are asymptomatic at birth. Literature has shown that detection of toxoplasma-specific immunoglobulin A (IgA) may be a reliable method for the diagnosis of toxoplasmosis in the newborn. A number of these asymptomatic, untreated infants will go on to have delayed and potentially serious manifestations. The 20% with clinically obvious symptoms at birth will exhibit multiple findings. The most frequent clinical findings are chorioretinitis, jaundice, fever, and hepatosplenomegaly. Hydrocephaly or microcephaly and cerebral calcifications can be seen in severe cases. Demonstration of toxoplasma-specific IgM infection may be diagnostic, although in newborns, approximately 20% of infections are not detectable by toxoplasma-specific IgM at birth.

Treatment and Prevention

Treatment of acute toxoplasmosis is primarily supportive. The prognosis, in general, following acute infection is good, except in cases of profound immunosuppression.

The treatment in pregnancy is a bit more complex. In Europe, where the seroprevalence and, hence, the clinical experience is greater, spiramycin is the first-line agent used. However, that agent generally does not cross the placenta, and if fetal infection is detected, women are also treated with a combination of pyrimethamine, folinic acid, and a sulfonamide. Although not definitive, treatment with these regimens may prevent maternal-to-fetal transmission of the infection or improve the outcome among infected fetuses. In one study from France, 163 mothers diagnosed with toxoplasmosis prior to 28 weeks were treated with spiramycin (23 also received pyrithiamine and sulfadiazine). Three fetuses died in utero and 27 were diagnosed with congenital toxoplasmosis. All 27 were free from symptoms and had normal neurologic development at 15 to 71 months. Most studies that control for gestational age at the time of infection suggest that transmission rates are not altered markedly by therapy, but the degree of fetal sequelae may be.

The standard dosage is 25 mg of pyrimethamine by mouth given daily and 1 g of sulfadiazine by mouth 4 times daily for 1 year. Pyrimethamine is a folic acid antagonist and, therefore, may have teratogenic effects when given in the first trimester. Whenever possible, treatment with pyrimethamine in the first trimester should be weighed against potential risk of drug teratogenicity to the infant. Folinic acid, 6 milligrams given intramuscularly or by mouth every other day, should be used to correct the depletion of folic acid induced by pyrimethamine.

Spiramycin can be obtained in the United States through the CDC. It is used more commonly in Europe and, hence, there are no good controlled studies of its efficacy in this country. It has not been found to be teratogenic in humans or animals.

Case-control studies in France, where women routinely receive serial assessments to detect seroconversion, have revealed that risk factors for acquisition of infection include poor hand washing, eating undercooked beef or lamb, and owning a pet cat. Based on these sorts of data, the CDC has recommended that sero-susceptible pregnant women should be counseled to avoid eating raw or undercooked meats that may contain the *T. gondii* cysts. This can be accomplished by using a food thermometer to ensure that the meat is cooked all the way through. Fruits and vegetables should be peeled and washed before eating. Gloves should be used for gardening and during any contact with soil or sand, because cat waste might be found there. Pregnant women should avoid close contact with cat feces, such as changing cat litter. CDC also highlighted the need for obstetricians to educate their pregnant patients about these important preventive steps.

In countries such as France, with extremely high seroprevalence rates, routine serologic screening programs have proven successful in diagnosing recent seroconverters, allowing for prenatal diagnosis of fetal status and either termination of pregnancy or prenatal therapy. There is no consensus for routine screening in the United States. Because of the low prevalence of the disease and the possibility of false-positive results, the American College of Obstetricians and Gynecologists does not recommend routine screening.

Most recently, programs have been undertaken that focus on screening of newborns and the institution of treatment during the neonatal period to minimize the morbidity that would otherwise accrue to congenitally infected children. Many infections in children, that otherwise would be missed on routine clinical examination, can be detected with IgM assays. Treatment of these infected infants has been associated with very low rates of subsequent neurologic or retinal disease.

CYTOMEGALOVIRUS

Introduction

CMV, a member of the herpes virus family, is the largest virus to infect humans. It can code for over 200 proteins, through which it can lead to substantial down-regulation of the immune system and many diseases, such as infectious mononucleosis in young adults. It also causes the most common congenital viral infection, affecting approximately 1% of all live births, about 35,000 infants annually in this country. Congenital CMV infection is acquired by the fetus in utero when the mother develops primary CMV infection while pregnant or with reactivation of a prior maternal infection. Although reactivated disease in the pregnant woman accounts for more than one half of the congenital infections, primary maternal CMV infection is much more likely to result in a severely affected and symptomatic infant. Passive in utero transfer of maternally derived CMV-specific IgG antibody appears to provide some protection to the fetus when CMV is reactivated during pregnancy.

The great majority of infants with congenital CMV are asymptomatic (90%), but some have evidence of disease during the newborn period (10%). About 10% of the symptomatic group have full-blown cytomegalic inclusion disease. An additional 10% of infected infants who are asymptomatic at birth later develop symptoms related to CMV infection. The most common late-onset symptoms in these cases are mental retardation and deafness. These infants usually shed high titers of virus in the urine and saliva for a number of months.

CMV infections can be acquired by the child during the postpartum period through (a) exposure of the infant to infectious maternal body fluids such as cervical secretions, urine, saliva, and breast milk, (b) following blood transfusion or tissue transplantation from an infected donor, or (c) most frequently, through contact with infected individuals, such as in the newborn nursery, day care centers, or from other family members in the household. These cases are called acquired CMV infections, in contrast to congenital infections.

Microbiology

Cytomegaloviruses are members of the herpes virus group. The virus has a diameter of about 180 nanomeres and is encapsulated by an icosahedral capsid containing 162 capsomeres. Within the capsid is double-stranded DNA of about 230 kilobases that is enclosed by a lipid bilayer envelope. The diagnosis of CMV requires laboratory confirmation and cannot be made on clinical grounds alone. Seroconversion, monoclonal antibody, and PCR are among the tools available for diagnosis.

Antibody response (whether maternal or fetal) may play a less important role in transmission and, subsequently, in the development of symptomatic disease than other viral factors, such as the amount of maternal viremia or the timing in pregnancy during which infection and subsequent maternal-to-fetal transmission occurs.

Epidemiology

Seroprevalence of CMV among adult populations shows significant geographic variability. Rates range from 40% to 100% depending on the region surveyed, with most infections being detected solely by serologic screening (i.e., asymptomatic). Countries or regions with low socioeconomic status usually demonstrate very high seroprevalence rates. The risk of seroconversion during pregnancy for a seronegative woman is approximately 2%. However, because congenital infections can follow either primary disease (maternal seroconversion) or reactivation of disease, congenital infections may occur in a much higher percentage of cases. There are two periods in life when infection rates are particularly high-perinatal (related to mother-to-child transmission, breast-feeding, and child-to-child) and reproductive age (putatively related to sexual transmission).

Pregnant women acquire CMV infection either through exposure to infected children (the infected children shed virus in urine, saliva, and nasopharyngeal secretions and are infectious for a prolonged period) or through sexual contact. About 1% to 2% of American women shed CMV from their cervix at any given time, although that number is higher in women with multiple sexual partners.

Pathophysiology

Following primary infection, the virus goes into a latent phase. Intermittent periods of reactivation frequently occur, and virus is again excreted in the nasopharynx, cervix, urine, saliva, and breast milk. Maternal viral shedding increases throughout pregnancy, and neonatal infection becomes increasingly likely as cervical shedding rates increase toward term.

Acquisition of disease by neonates at the time of birth is much more common than congenital infection, but much less devastating. The former types of infection come from CMV carried in the cervix during the late stages of pregnancy and from CMV in breast milk. After primary infection during the prenatal period, the congenital infection rate has been reported to be as high as 55%. Although the great majority of infants with congenital CMV are asymptomatic, infants with symptomatic infection at birth usually have findings associated primarily with the reticuloendothelial and central nervous systems. The severe cases of congenitally acquired symptomatic infection result from primary rather than recurrent infection in the pregnant woman and from infections occurring early in pregnancy. The most common findings in these cases include hepatosplenomegaly, jaundice, a generalized petechial rash, and microcephaly. Less common findings include chorioretinitis with or without optic atrophy, pneumonitis, cerebral calcifications, microphthalmia, microcephaly, seizures, and cerebral and cerebellar atrophy. The mortality of newborns with symptomatic disease is approximately 30%.

Diagnosis

Mother The great majority of primary maternal infections with CMV are asymptomatic and unrecognized. When symptoms do occur, they may go unrecognized because they appear as a mild, infectious, mononucleosis-like illness, with lymphadenopathy, fatigue, and slight fever. Even though CMV is hepatotropic, elevations in liver enzyme levels rarely are seen in primary or recurrent infections. About one third to two thirds of all pregnant women have IgG antibodies to CMV, indicating previous infection. Detection of CMV-specific IgM during the acute phase of infection is useful for making the diagnosis of CMV infection, but only 80% of women with primary infection demonstrate this antibody. In addition, more than a third of mothers with recurrent CMV from latent infection will be positive for CMV-specific IgM. CMV-specific IgM antibodies may persist from 4 to 9 months, and some test methods may give false-positive results because of cross-reactions with other herpes viruses, antinuclear antibody, or rheumatoid factor. A microneutralization assay may be of some utility. In one study, the antibodies did not appear until 15 weeks after infection and persisted thereafter. Thus its absence, shortly after a presumed infection, can help to rule out infection. Viral culture is the gold standard for the diagnosis of CMV infection. Virus usually is detected in the cervix, nasopharynx, and urine of infected individuals. However, culture results are positive with both primary and recurrent infections. PCR has also proven to be quite useful in the detection of CMV. Quantitative PCR testing has proven particularly useful in the management of AIDS and transplant in patients whose high serum levels augur complications, and it offers an early opportunity for the initiation of antiviral therapy.
Prenatal Sonography may be useful for identifying some abnormalities in the fetus that may be related to CMV infection. Nonspecific sonographic findings of fetal hydrops, intrauterine growth retardation, polyhydramnios, fetal ascites, and specific central nervous system anomalies (e.g., ventriculomegaly, periventricular calcifications) suggest an intrauterine infection, possibly CMV, and should be evaluated further with amniocentesis or cord blood sampling. Lynch and others reported the successful prenatal diagnosis of fetal infection by a combination of amniotic fluid culture and measurement of total and CMV-specific IgM and ?-glutamyl transpeptidase in fetal blood samples. In a study of 189 pregnancies with known outcome, Enders and colleagues reported 89.5% sensitivity with the use of amniotic fluid and fetal blood assessments for virus and anti-CMV IgM. They noted that the correct diagnosis of in utero infection with CMV by amniotic fluid analysis could be expected after 21 weeks of gestation and at least 6 weeks after the diagnosis of infection in the mother. Other authors have reported similar sensitivities and have pointed out that those instances of false-negative results often are associated with infants with minimal stigmata of disease. Further studies are needed on the sensitivity and specificity of these methods in identifying infected infants prior to birth. The definitive diagnosis is best made through the detection of viruria during the first week of life. The presence of IgM antibodies in cord serum is suggestive but not sufficiently specific to make a definitive diagnosis.

Management

Mother Susceptible pregnant women have a 2% risk of seroconverting while pregnant. Because this is a relatively low risk of infection and there is a somewhat low rate of possible damage to the fetus, and because no effective therapy is available to infected infants, routine serologic testing of pregnant women generally is not recommended. Probably the single most important method of preventing primary infection during pregnancy is minimizing exposure in high-risk areas, such as nurseries, day care centers, and other places that have a high concentration of young children. Careful hand-washing techniques, as well as proper handling of potentially infectious body fluids, should be instituted to minimize spread of the infection. There are no protocols for the use of antiviral agents (acyclovir and ganciclovir) during pregnancy to decrease the risk of mother-to-child transmission of CMV. It is hoped that a vaccine ultimately will be developed that will prevent CMV. Some authors have suggested that in order to target both mothers most likely to transmit to infants and those most likely to transmit to pregnant women, that young unmarried mothers and all toddlers and preteen children should be considered for vaccination.
Infant Clinically evident infection in newborns and infants is treated symptomatically. In the most severe cases of neonatal infection, antiviral agents such as acyclovir and ganciclovir have been used to suppress the infection, but discontinuation of the medication results in reappearance of the infection. Foscarnet (phosphonoformic acid) has been used in primary symptomatic neonatal disease and has been effective in reducing viral shedding.

HERPES SIMPLEX VIRUS

Introduction

Herpes simplex virus (HSV) causes an extremely common STD with potentially devastating consequences for the perinatally infected neonate. It also is the cause of more calls to the national STD hotline than any other STD. Management of these infections in pregnancy has undergone substantive evolution over the last decades, reducing reliance on operative delivery.

Microbiology

HSV is an encapsulated double-stranded DNA virus that infects susceptible mucosal surfaces. The DNA-containing core is surrounded by an envelope that contains viral proteins that are important for attachment to host cell receptors, cell penetration, and immune escape mechanisms. There is approximately a 50% homology in the DNA sequences of HSV type 1 (HSV-1) and HSV type 2 (HSV-2), the latter being predominantly genital and the former predominantly oral. Either virus can cause serious illness in the neonate. Immunity to one virus may lead to an attenuated illness if an individual becomes infected with the other.

Epidemiology

Whereas only approximately 5% of the reproductive-age population gives a history of clinical herpes infections, serologic surveys suggest that up to 20% of the sexually active population has had genital herpes. That represents a 30% rise in the age-adjusted risk since the late 1970s. The National Health and Nutrition Evaluation Survey revealed that slightly over 25% of women are seropositive for HSV-2 (Fig. 19.5). A large majority of those individuals who are seropositive will shed virus intermittently for many years after the initial infection. The rate of shedding does not vary significantly between those with and those without a history of genital herpes. The reason that most seropositive women are unaware of their status may be related to the presence of antibody to HSV-1 that offers sufficient protection from HSV-2 to mute any symptoms. However, with proper education a large percentage of women can be trained to recognize recurrences. The infection is transmitted from both symptomatic and asymptomatic individuals, with the latter being the cause of the majority of new infections. Transmission seems to occur with greater facility from men to women. However, condoms seem to be more effective in preventing transmission from men to women than from women to men. There is little evidence to suggest that pregnancy, in itself, increases either the frequency or the severity of genital HSV infections. In one study, in an unselected patient population, HSV shedding occurred in only 0.1% to 0.4% of all deliveries. In other studies of pregnant women with histories of HSV, positive culture results have been found in 0.2% to 7.4% of asymptomatic women. It has been estimated that if PCR is used in lieu of cultures, shedding would be detected about 8 times as frequently. The rate of shedding at term is no higher than at other times in pregnancy. Unfortunately, from the therapeutic perspective, most women who shed viruses are not aware that they are shedding or that they are seropositive for HSV.

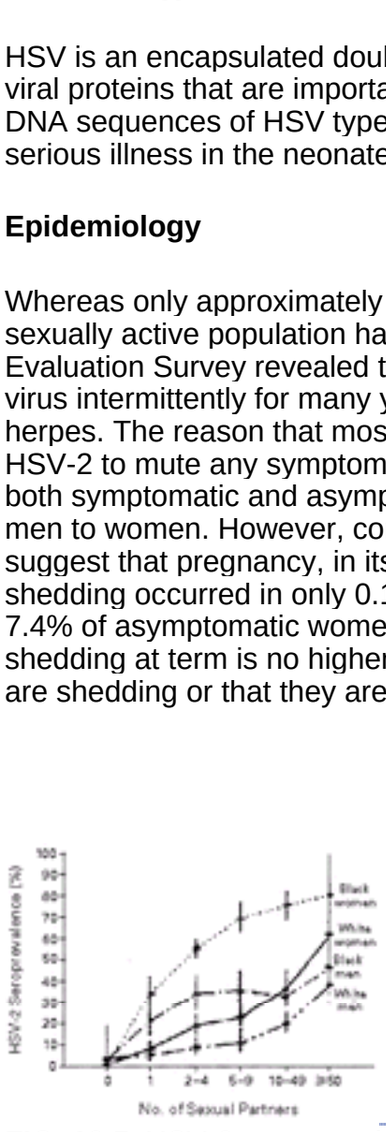

FIG. 19.5. HSV-2 seroprevalence according to the lifetime number of sexual partners, adjusted for age, for black and white men and women in National Health and Nutrition Evaluation Survey (1988–1994). *Bars* indicate 95% confidence intervals. (From Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976–1994. *N Engl J Med* 1997;337:1105–1111, with permission.)

Pathophysiology

HSV has an incubation period of 2 to 10 days, followed by a primary infection that is characterized by focal vesicle formation and a pronounced cellular immune response. The infection enters a latent phase, with the virus ascending peripheral sensory nerves and coming to rest in nerve root ganglia. Recurrent exacerbations occur intermittently, stimulated by poorly understood mechanisms. Infection may be primary, with a 2- to 3-week course; recurrent, with a 5- to 10-day course; or asymptomatic. Primary infection poses the greatest risk to both mother and infant. Clinically it is extremely difficult to distinguish primary from recurrent disease. Fifty percent of infants born vaginally to mothers with a primary infection will themselves have HSV infection, compared with only 4% of those born to mothers with recurrent infection. Primary infection also may be associated with abortion, low birth weight, preterm birth and, rarely, congenital infection, although less commonly than was once thought. As expected, viral shedding occurs for a significantly longer period with primary infection (1–2 weeks) than with recurrent infection (3–6 days).

Antibodies appear approximately 7 days following the onset of primary infection, reaching a peak in 2 to 3 weeks, and generally remain detectable for life. Titers do not rise significantly with recurrent infections. The significant difference in infection rates in neonates born to mothers with primary infections (50%) versus those born to women with recurrent infections (4%) suggests that maternal antibodies provide some protection. With recurrent infection, the infection rate has been estimated to range from zero to 8% when virus is present at the time of vaginal delivery.

Fortunately, disseminated primary HSV infections in pregnant women are rare. When these infections become disseminated during pregnancy, mortality is high for both the mother and fetus, and systemic antiviral therapy is recommended.

Although HSV shedding occurs in approximately 0.1% to 0.4% of deliveries, the frequency of neonatal infection is actually much lower, occurring in approximately 0.01% to 0.4% of deliveries. The reason for this 10-fold difference in infection between mother and newborn is unknown but probably is related to both a protective benefit of maternal antibodies and to the size of the viral inoculum to which the fetus is exposed during birth. The viral inoculum associated with asymptomatic shedding is several logs less than that associated with primary infection. Because of the inability to mount a timely immune response, maternal seroconversion around the time of delivery may be particularly likely to result in an infected neonate.

Neonatal infection may result from either HSV-1 or HSV-2. The majority of cases of neonatal HSV infections, however, are caused by HSV-2, with approximately 76% of isolates from infected neonates being HSV-2. It is estimated that approximately 90% of cases of neonatal HSV infections can be traced to a maternal source of infection and are secondary to either ascending infection with ruptured membranes or to colonization during the actual birth process.

As noted, approximately 50% of mothers delivering vaginally with a primary genital HSV infection will give birth to an infant with HSV infection. Of these infected neonates, 60% will die during the neonatal period. Of equal concern is that approximately 50% of the survivors will have significant sequelae, such as microcephaly, mental retardation, seizures, microphthalmia, retinal dysplasia, chorioretinitis, meningitis, encephalitis, hypertonicity, apnea, and coma. Although less common, the neonate may also acquire infection from exposure during the neonatal period from either or both parents or from other family members, from other infected infants, or from infected health care workers.

Although there have been isolated reports of “congenitally infected” fetuses with malformations, other investigators have found no such associations. Congenital infections have been defined by the presence of skin vesicles or scarring, chorioretinitis, hydranencephaly, microphthalmia, microcephaly, or an abnormal CT scan of the brain within the first week of life.

Diagnosis

The diagnosis of primary infection is relatively easy to make from a clinical standpoint. There generally are multiple painful ulcers on an inflamed surface. The lesions progress to ulcers, and there may be accompanying painful adenopathy and fevers. However, recurrent infections may be more difficult to diagnose solely on clinical grounds, and other ulcerative lesions (e.g., syphilis, chancroid) can occur, also. Virus isolation by tissue culture remains the most accurate method of confirming the diagnosis of HSV infection and should be utilized if there is any lack of certainty on clinical grounds. Cultural sensitivity decreases with the duration of the lesion. Cytologic tests, such as Pap smear and Tzanck preparations, tend to be less accurate. Rapid accurate tests for HSV, such as PCR, have been demonstrated to have utility in research settings and undoubtedly will eventually establish a role in clinical medicine.

Management

In the nonpregnant individual there are many treatments now available that will shorten the course or ameliorate symptoms. Even before antiviral therapy is instituted, there are some therapies that can be offered. Application of topical cool compresses with Burow solution for 15 minutes 4 to 6 times daily may be helpful for patients with extensive erosions on the genitalia. For an initial case of genital herpes, several medications are available.

- Acyclovir ointment can be applied every 3 to 6 hours (6 times daily) for 7 days. Severe cases may be treated with intravenous acyclovir 5 milligrams per kilogram, infused at a constant rate over 1 hour, every 8 hours for 7 days in patients with normal renal function) or oral acyclovir 200 milligrams 5 times daily for 7 to 10 days.
- Valacyclovir tablets (1 g b.i.d. for 10 days).

For the woman with a recurrent lesion there are also several choices. One is acyclovir (200 mg p.o. 5 times a day for 5 days, 400 mg p.o. b.i.d. for 5 days, or 800 mg p.o. b.i.d. daily for 5 days), generally started during the prodrome or within 2 days of onset of lesions. Famciclovir also is useful for treatment of recurrent genital herpes (dose is 125 mg q12h for 5 days in patients with normal renal function) started at the first sign of symptoms. Finally, valacyclovir (dose is 500 mg q12h for 5 days in patients with normal renal function) can be used.

In pregnancy there are additional considerations: First, it should be remembered that HSV is an STD, so those individuals diagnosed during pregnancy should be screened for other STDs. In regard to the prevention of mother-to-child transmission of HSV, management has changed greatly over the last decades. It was once recommended that pregnant women suspected of having a genital HSV infection or who had a history of prior HSV infection or sexual partners with HSV infections be monitored closely, with third-trimester cultures, for recurrent infection or for asymptomatic HSV shedding. Those women who had a positive culture result near to term were scheduled for elective cesarean section in order to avoid contact between the neonate and the virus during delivery.

That protocol had little impact on the overall incidence of neonatal HSV infection for several reasons. Most women who delivered infants with neonatal HSV infections had no history of infection and no lesions at the time of delivery, and thus would not have met the criteria for monitoring in the first place. It was calculated that a weekly screening strategy would cost approximately $1.8 million for each case of neonatal HSV infection averted. It is not clear whether the neonatal morbidity and mortality actually prevented by such a protocol outweighed the maternal mortality that would result from complications of cesarean delivery. Moreover, cesarean delivery, even with intact membranes, will not prevent all cases of neonatal herpes infections secondary to maternal genital HSV infection. There are many reported cases of neonatal HSV infections in infants that were delivered by cesarean with intact membranes.

Recommendations for pregnant women with HSV infections include the following:

- Cultures should be performed to confirm the diagnosis when a woman has active HSV lesions during pregnancy. If there are no visible lesions at the onset of labor, vaginal delivery is acceptable.
- Weekly surveillance cultures of pregnant women with a history of HSV infection, but no visible lesions, are not necessary and vaginal delivery is acceptable.
- Amniocentesis in an attempt to rule out intrauterine infection is not recommended for mothers with HSV infection at any stage of gestation.
- Cesarean section should be performed if lesions are present at the onset of labor.

It has been suggested that oral acyclovir prophylaxis might have a role in the prevention of recurrence and, thereby, could reduce the need for cesarean section. Several studies have pointed to lowered shedding and cesarean section rates when women with outbreaks during pregnancy are started on acyclovir in later stages of pregnancy. Cost savings with that strategy have been suggested, based upon decision analysis. Although acyclovir is a nucleoside that incorporates into DNA, registries have not revealed an untoward rate of adverse outcomes among exposed infants. Preliminary trials with acyclovir in pregnancy have reported that the need for cesarean section was reduced, with no increase in morbidity for exposed neonates.

Intrapartum It is recommended that term patients who have visible lesions, are in labor, and have ruptured membranes should undergo cesarean delivery. There has been a suggestion that the policy of cesarean section in such circumstances for women with recurrent lesions should be rethought. The presence of antibody in such women may make the mother-to-child HSV transmission rate so low as make the risks of routine cesarean section unjustified. However, most clinicians still opt for cesarean section with visible lesions regardless of the mother's history. Although it has been classically taught that cesarean delivery of women with visible lesions should be performed only if membranes have been ruptured for less than 4 to 6 hours, not all neonates born to mothers with HSV infections become infected, even with membranes ruptured for more than 24 hours. In contrast, neonates born by cesarean delivery within 2 hours of rupture of membranes have developed HSV infection. For patients with active HSV infections and premature rupture of membranes remote from term, there are not enough data to recommend a management protocol that would apply in all clinical situations. The risk of extreme immaturity must be weighed against the risk of neonatal HSV infection. There have been several case reports of infants born without sequelae after prolonged periods of conservative management. Although the use of scalp electrodes has been implicated as a rare etiology of neonatal infection, monitoring by fetal scalp electrode is not contraindicated if needed to adequately assess fetal condition in women with history of HSV infection but without lesions or symptoms. It has been suggested that cultures be obtained at delivery in women with a history of HSV infection to aid the pediatrician in assessing the need for therapy in the newborn.

Treatment

There is no known cure for HSV infection. The purine analogue acyclovir has been used to treat both primary HSV infections and to prevent recurrent HSV infections in nonpregnant women.

Prevention

Although it is not necessary to isolate the infant from the infected mother, the infected parturient should be counseled regarding hand washing and good hygiene to prevent infection of the infant. Every effort should be made to avoid direct contract of the newborn with herpetic lesions.

INTRAAMNIOTIC INFECTION

Introduction

Clinicians continue to apply a number of terms to this entity, including chorioamnionitis, amnionitis, intrapartum infection, amniotic fluid infection, and IAI. We use the last designation to distinguish this clinical syndrome from bacterial colonization of amniotic fluid and from histologic inflammation of the cord or placenta. Prospective studies published in the last few years report rates of 4% to 10% among non-privately insured and privately insured patients, respectively.

Pathogenesis

The ascending route is the most common pathway for development of IAI. A hematogenous or transplacental route of infection occurs with *Listeria monocytogenes.* Other virulent organisms, such as group B streptococci, may lead to a similar blood-borne infection. IAI may occur infrequently as a complication of invasive diagnostic procedures, such as amniocentesis or intrauterine transfusion.

In large investigations using logistic regression analysis, risk factors for IAI were identified as follows: low parity, prolonged duration of membrane rupture, prolonged duration of labor, larger number of vaginal examinations, and duration of internal fetal monitoring. In regard to the use of internal fetal monitoring, we feel that this technique should be used if it enables the practitioner to diagnose and treat labor abnormalities more efficiently.

Once IAI develops, the fetus may swallow and aspirate the infected fluid and is prone to develop pneumonia, enteritis, meningitis, and sepsis. Indeed, a clinical diagnosis of IAI is one of the most important risk factors for neonatal sepsis.

Microbiology

IAI is a polymicrobial infection, involving both aerobic and anaerobic bacteria. Table 19.2 shows the most common isolates in the amniotic fluid of over 400 cases of IAI.

Organism[a]	Number (%)
Group B streptococci	59 (14.6)
Escherichia coli	33 (8.2)
Enterococci	22 (5.4)
Gardnerella vaginalis	99 (24.5)
Peptostreptococci	38 (9.4)
Bacteroides bivius	119 (29.4)
Bacteroides fragilis	14 (3.4)
Fusobacterium spp.	22 (5.4)
Mycoplasma hominis	123 (30.4)
Ureaplasma urealyticum	190 (47.0)

[a]For bacteria, all isolates shown were found in concentrations of $\geq 10^5$ cfu/mL. Genital mycoplasmas were cultured qualitatively.

Source: Sperling RS, Newton E, Gibbs RS. Intra-amniotic infection in low-birth-weight infants. *J Infect Dis* 1988;157:113, with permission.

TABLE 19.2. *Amniotic fluid isolates in 404 cases of intraamniotic infection*

Diagnosis

The most common clinical criteria are fever, leukocytosis, and ruptured membranes; fetal and maternal tachycardia are noted in variable percentages of cases. Foul-smelling amniotic fluid and uterine tenderness, although more specific signs, occur in a minority of cases. In cases of clinical IAI, maternal fever was present in 85% to 99%, fetal tachycardia in 37% to 82%, maternal tachycardia in 19% to 37%, uterine tenderness in 13% to 16%, and foul-smelling amniotic fluid in 9% to 22%. The determination of amniotic fluid glucose concentration is a practical test for diagnosing clinical IAI. With an amniotic glucose concentration less than 5 milligrams per deciliter, the likelihood of amniotic fluid culture results being positive is approximately 90%. On the other hand, when the amniotic fluid glucose concentration is greater than 20 milligrams per deciliter, then the likelihood of a positive culture result is approximately 2%. At intermediate values (for example 14 and 15 mg/dL), the likelihood of a positive amniotic culture result is 30% to 50%.

Management

When IAI is diagnosed, there is a need for delivery of the fetus and for antibiotics. With regard to timing of delivery, there has been excellent maternal–neonatal outcome without use of arbitrary time limits. Cesarean delivery has been performed for standard obstetric indications, not for IAI alone. In nearly all cases, delivery occurred within 8 hours after diagnosis of IAI, and the mean time was between 3 and 5 hours. No critical interval from diagnosis of amnionitis to delivery could be identified. Cesarean section rates are higher among patients with IAI, running 2 to 3 times greater than in the general population. The reason for the increase most likely results from two things. First, IAI commonly develops in the patients with dystocia as an underlying problem. Second, the uterus with IAI is less sensitive to oxytocin.

The benefits of intrapartum treatment have been well established. Intrapartum initiation of antibiotic treatment improves maternal outcome, decreases neonatal bacteremia, and does not result in delayed sepsis (Table 19.3).

TABLE 19.3. *Outcome by maternal treatment group in cases of intraamniotic infection: results of a randomized study*

As noted above, the traditional antibiotic approach to treatment has been with combination therapy, primarily broad-spectrum penicillin with an aminoglycoside, plus clindamycin in some cases (such as cesarean delivery or apparent sepsis). Because of the expense and complexity of such therapy, there has been recent interest in single-drug treatment of IAI. In view of the well-described microbes involved, there would be several reasonable choices of single-agent therapy, but there have not been sufficient comparative trials to recommend alternative single-agent therapy. Studies have addressed the issue of duration of antibiotic therapy after delivery in the treatment of IAI. In one study, all patients received ampicillin plus gentamicin intrapartum, and those patients delivering vaginally where randomized to receive cefotetan 2 gram intravenously as a single dose or as multiple doses every 12 hours for 48 hours. Patients randomized to single-dose therapy also left the hospital more quickly (33 versus 57 hours, $P = .001$). Patients who received single-dose therapy also had a higher rate of “failed therapy” (11% versus 3.7%, $P = .27$). Although this difference did not achieve statistical significance, a three-fold increase in failed therapy raises concern about the limitation of single-dose therapy.

In a study of antibiotic therapy after cesarean delivery for IAI, all patients received ampicillin during labor and clindamycin and gentamicin, one dose each, preoperatively. Patients were then randomized to receive no scheduled postoperative antibiotics versus clindamycin and gentamicin until they were afebrile (for a minimum of at least 24 hours). No patients in either group developed an abscess or readmission for endometritis. Although there was no significant difference in endometritis (14.8% in those with no routine antibiotic versus 21.8% in those treated with clindamycin and gentamicin), there was a nonsignificant, but still 2.5-fold, increase in wound infection rate in patients randomized to no routine antibiotics (5% versus 1.8% with those randomized to clindamycin and gentamicin postpartum).

Based upon the limited observations of these two trials, the nagging concerns about failed therapy in the first study, and the wound infection rates in the second study, it would appear premature to conclude that therapy, after either vaginal delivery or cesarean delivery, in the presence of IAI, is unnecessary.

Outcome

Short-term Outcomes From descriptive studies largely from the early 1980s, several strong consistent observations may be made. Maternal outcome was excellent, with bacteremia occurring in only 2% to 6%. Maternal outcome was more complicated in patients having cesarean delivery. No critical diagnosis to delivery interval was demonstrable. Specifically, neither prenatal mortality nor maternal complications correlated with more prolonged intervals from diagnoses of IAI to delivery. Yet all patients delivered within 4 to 12 hours, and nearly all patients received intrapartum antibiotics. Although prenatal mortality was relatively high, little of this was directly attributable to infection, because most of the prenatal mortality was due to accompanying prematurity. Prior to term pregnancy, neonates have a higher frequency of complications if they are delivered of mothers with IAI. The group with IAI had a significantly higher number with respiratory distress syndrome and any diagnosis of infection. Thus, IAI has a significant adverse effect upon the mother and neonate. Short-term outcome is dependent largely on the organisms in the amniotic fluid (with *Escherichia coli* and group B streptococci more likely to result in maternal or neonatal bacteremia), low birth weight (with low-birth-weight infants faring more poorly), and timing of antibiotic therapy (with intrapartum administration improving outcome).
Long-term Outcomes Traditional complications of IAI have been maternal and neonatal sepsis, neonatal pneumonia and meningitis, and neonatal death. Studies indicate that complications of IAI should be expanded to include periventricular leukomalacia, cerebral palsy, respiratory distress syndrome and, perhaps, other neonatal complications. The hypothesized mechanism is that ascending infection leads to placental and congenital infection. This leads to an overly exuberant production of inflammatory cytokines which, in turn, leads to cell damage. Evidence for these expanded neonatal complications after IAI are as follows:

1. Intrauterine exposure to maternal or placental infection is associated epidemiologically with an increased risk of cerebral palsy.
2. Levels of inflammatory cytokines are increased in the amniotic of infants with brain white matter lesions or respiratory distress syndrome.
3. Experimental intrauterine infection has led to brain white matter lesions in rabbits.

Prevention

Within in the last few years, several intervention strategies for preventing clinical IAI have been evaluated. These are summarized in Table 19.4.

1. Identify dystocia promptly and treat hypotonic dysfunctional labor promptly with oxytocin.
2. In patients with premature rupture of the membranes at term, induce labor with either oxytocin or prostaglandin preparations.
3. In patients with preterm premature rupture of membranes and without contractions, give broad spectrum antibiotics such as ampicillin or amoxicillin plus erythromycin for 7 d.
4. Follow Centers for Disease Control and Prevention and American College of Obstetricians and Gynecologists guidelines for prevention of perinatal group B streptococcal infection.

For patients with preterm labor but without rupture of membranes, perinatal Group B Streptococcal Guidelines should be followed, but broad-spectrum antibiotics for the purpose of preventing chorioamnionitis have not been effective.

TABLE 19.4. *Clinical measures to prevent IAI*

POSTPARTUM ENDOMETRITIS

Introduction

Seven decades into the antibiotic era, genital tract infections continue to pose a common and occasionally severe threat to women after childbirth. Although substantial progress has been made in the control of puerperal sepsis, infection still ranks as the fourth most common cause of maternal death.

The most common cause of puerperal fever is uterine infection, occurring in approximately 1% to 3% of women after vaginal delivery and up to 27% after cesarean delivery, even when prophylactic antibiotics are used. The infection is variously called endometritis, endoparametritis, or simply metritis. Criteria for endomyometritis include fever, uterine tenderness, and purulent or foul lochia, peripheral leukocytosis, and exclusion of another infected site. Nonspecific signs and symptoms such as malaise, abdominal pain, chills, and tachycardia may be present. In the vast majority of cases of uterine infection, initial signs and symptoms develop within the first 5 days after delivery.

Pathophysiology

The major risk factors are summarized in Table 19.5. Cesarean section is the most important predisposing clinical factor for pelvic infection. The severity of infection also is increased in abdominal delivery. Those patients with electively scheduled operations (with no labor and no rupture of membranes) have lower infection rates than those with emergency or nonelective procedures. This observation has been made nearly universally in a large number of studies.

Duration of labor
Cesarean delivery, especially nonelective
Nonelective cesarean delivery, without prophylactic antibiotics
Duration of rupture of membranes
Failure to progress in labor
Number of vaginal examinations
Duration of internal fetal monitoring
Low socioeconomic status
Diabetes

TABLE 19.5. *Major risk factors for postpartum infection*

Risk factors of labor, rupture of membranes, vaginal examinations, and internal fetal monitoring are intricately interrelated, and even sophisticated statistical techniques may not be able to discern which of these factors is an independent variable. Whether amniotomy increases postpartum infection has been the subject of many reports. Amniotomy, as part of a plan of active labor management, probably does not increase the risk. Regardless of race, indigent patients have higher puerperal infection rates than do middle-class patients. The cause is unclear, but differences in flora, hygiene, and nutrition have all been postulated as reasons. Diabetes is also a risk factor for endometritis, with diabetic patients having approximately a four-fold increase in risk. Among patients without labor or ruptured membranes, 9.1% (5/55) of diabetics developed endometritis or wound infection versus 1.8% (2/110) of nondiabetics ($P = .042$). Among patients with either labor or rupture of membranes or both, the infection rate for diabetics was 25% (6/24) versus 6.3% (3/48) for nondiabetics ($P = .032$). Endometritis most often is caused by a mixture of aerobic and anaerobic bacteria from the genital tract. Table 19.6 shows the isolates from one carefully done study.

Isolate(s)	No. (%) of isolates
Facultative gram positive	*51 (40)*
Group B streptococci	8 (6)
Enterococci	7 (5)
Staphylococcus epidermidis	9 (7)
Lactobacilli	4 (3)
Diphtheroids	2 (2)
Staphylococcus aureus	1 (1)
Facultative gram negative	*28 (22)*
Gardnerella vaginalis	15 (22)
Escherichia coli	6 (5)
Enterobacterium spp.	2 (2)
Proteus mirabilis	2 (2)
Others	3 (2)
Anaerobes	*49 (38)*
Bacteroides bivius	11 (9)
Other *Bacteroides* spp.	9 (7)
Peptococci-peptostreptococci	22 (17)
Mycoplasmas	
Ureaplasma urealyticum	39 (30)
Mycoplasma hominis	11 (9)
Chlamydia trachomatis	*2 (2)*

Source: Rosene K, Eschenbach DA, Tompkins LS, et al. Polymicrobial early postpartum endometritis with facultative and anaerobic bacteria, genital mycoplasmas and *C. trachomatis*; treatment with piperacillin or cefoxitin. *J Infect Dis* 1986;153:1028, with permission.

TABLE 19.6. *Endometrial isolates (collected by a triple-lumen catheter) from 51 patients with postpartum endometritis*

Diagnosis

The diagnosis of endomyometritis usually is based on symptoms of fever, malaise, abdominal pain, and purulent or foul lochia. Other sources of fever should be excluded. In clinical investigations, various temperature criteria have been used in the definition of endometritis. These include 100°F (37.8°C) and 100.4°F (38°C) on two or more occasions. When there are signs of infection, multiple risk factors for infection, or persistence of low-grade fever in the puerperium, it is reasonable to presume a genital tract infection is present and proceed with the workup and treatment. We believe that appropriate specimens include a complete blood count, blood cultures, and an aerobic uterine culture. Gram staining of the genital specimen may be helpful when hemolytic streptococci, clostridia, or other anaerobes are suspected.

Treatment

With supportive therapy and appropriate antibiotics, the vast majority of patients improve within 1 to 3 days. For patients with endomyometritis after vaginal delivery, the treatment should include good anaerobic coverage, probably using a single agent (such as broad-spectrum penicillin or cephalosporin or a penicillin–ß-lactamase inhibitor combination).

Among patients with endomyometritis after cesarean section, response to antibiotics is poorer. Initial therapy for endometritis after cesarean section should consist of broad-spectrum antibiotics, with activity against anaerobes as well as Gram-positive and Gram-negative aerobes. In many clinical trials, the combination of clindamycin and aminoglycoside has been considered the standard for comparison for treatment in genital tract infections after cesarean section. A large number of new penicillins and cephalosporins have become available to treat postpartum infection. Although no single agent provides activity against the entire bacterial spectrum, most have sufficient aerobic and anaerobic activity to merit use in endometritis. Table 19.7 gives specific regimens.

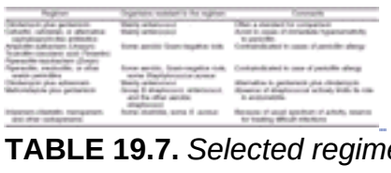

TABLE 19.7. *Selected regimens for initial parenteral therapy of postpartum endometritis*

The new penicillins and cephalosporins usually are tolerated very well and have few side effects. Administration of a single agent requires less time and equipment, but the higher cost of most new agents must also be considered. Metronidazole has excellent anaerobic activity. Because it has little activity against aerobes, its use as single-agent therapy is unwise. Its use in combination with gentamicin still leaves the Gram-positive aerobes (notably group B streptococci and enterococci) uncovered. New antibiotics are being formulated that may replace gentamicin as initial therapy. The monobactams (e.g., aztreonam) have exquisite Gram-negative activity, but they have little activity in the rest of the bacterial spectrum. These agents have the same spectrum as the aminoglycosides and have fewer side effects. Clinical trials of these monobactams in combination with clindamycin have shown excellent results, equivalent to clindamycin plus gentamicin.

For patients who respond promptly to parenteral antibiotics, some questions arise: How long should therapy be continued? Is oral therapy needed as an adjunct? It has been recommended that parenteral therapy should be continued for 24 to 48 hours after the patient becomes afebrile and asymptomatic. Then intravenous antibiotics may be discontinued and the patient discharged without oral antibiotics, unless the patient has had staphylococcal bacteremia. The approach is based upon several descriptive studies plus a randomized trial of oral antibiotic therapy after successful intravenous therapy in women with puerperal endometritis. Patients given placebo had similar subsequent courses to those of patients given oral amoxicillin (after parenteral therapy). Side effects were also similar in both groups (Table 19.8).

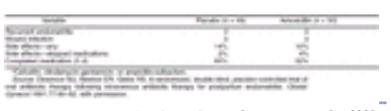

TABLE 19.8. *Oral amoxicillin after intravenous antibiotics for postpartum endometritis*

At the other end of the patient response spectrum, there are patients who do not respond within 48 to 72 hours of appropriate antibiotic therapy. Diagnostic considerations are: (a) an infected “mass” such as abscess or hematoma of the wound or pelvis, extensive pelvic cellulitis, septic pelvic thrombophlebitis, or retained placenta; (b) a resistant organism such as enterococci in patients treated with cephalosporin-like antibiotics or with clindamycin plus gentamicin; (c) a nongenital source of infection such as pyelonephritis, pneumonia, or intravenous catheter phlebitis; (d) a noninfectious fever such as drug fever or factitial fever; or (e) inadequate dosage or inadequate route of otherwise correct antibiotics (Fig. 19.6). Appropriate bedside examination and review of the chart and cultures often reveal the cause. In general, in patients who are stable and not seriously ill, an appropriate change in antibiotics (such as adding penicillin to clindamycin plus gentamicin to add coverage for enterococci) is effective in about 80% of those who had not responded in the initial 48 hours.

FIG. 19.6. Causes of poor response to antibiotics. (From Sweet RL, Gibbs RS. Postpartum infection. In: Sweet RL, Gibbs RS. Infectious diseases of the female genital tract. Philadelphia: Lippincott Williams & Wilkins, 2002, with permission.)

In about 20% of cases, the initial failure to respond is due to resistant organisms, and in another 30%, no cause for the failure is identified. We believe that 48 to 72 hours is an appropriate point to change therapy unless the patient is unstable, when changes are needed more promptly. In the remaining 40% to 50%, the reason for poor response to initial therapy is an infected mass. If the mass or collection is present in the wound after cesarean section, physical examination usually identifies the

source. In other cases, radiographic studies are helpful in identifying pelvic masses or deep-seated wound infection.

Ultrasonography or a CT study may reveal a mass in the pelvis. In patients with persistent pelvic infection after vaginal delivery, an ultrasonographic examination is helpful, because it may reveal a pelvic mass, retained placental tissue, or septic pelvic thrombophlebitis. Sonography is readily available, is inexpensive, and requires no special preparation. When patients are obese or have an open wound, ultrasonography provides a limited examination, and computed tomography is useful (Fig. 19.7 and Fig. 19.8).

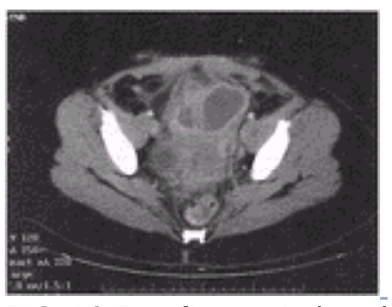

FIG. 19.7. Left parauterine abscess in a patient after cesarean delivery. (From Sweet RL, Gibbs RS. Postpartum infection. In: Sweet RL, Gibbs RS. Infectious diseases of the female genital tract. Philadelphia: Lippincott Williams & Wilkins, 2002, with permission.)

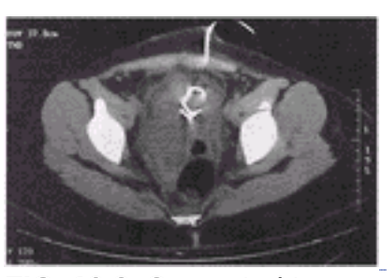

FIG. 19.8. Computed tomography scans showing percutaneous placement of a pigtail catheter in an abscess after cesarean section. (From Sweet RL, Gibbs RS. Postpartum infection. In: Sweet RL, Gibbs RS. Infectious diseases of the female genital tract. Philadelphia: Lippincott Williams & Wilkins, 2002, with permission.)

Prevention

Principles for use of antibiotic prophylaxis to prevent endometritis after cesarean delivery are well established. These are summarized in Table 19.9.

TABLE 19.9. *Recommendations for use of prophylactic antibiotics in cesarean section*

SUMMARY POINTS FOR HIV, TOXOPLASMOSIS, CMV, AND HERPES

- All pregnant women should have HIV testing recommended to them.
- HIV-infected pregnant women should have regular monitoring of their CD4 cell count and viral load.
- All HIV-infected women should receive ZDV per the PACTG 076 protocol.
- Standards of care for HIV infection should be upheld during the prenatal period.
- During the intrapartum period, attempts should be made to minimize the duration of ruptured membranes among women with HIV infection.
- All pregnant women should be counseled regarding ways in which to minimize the risk of acquiring infection with *T. gondii.*
- Pregnant women who acquire *T. gondii* infections should have studies performed to ascertain the status of the fetus.
- If congenital infection with *T. gondii* is diagnosed and the patient continues the pregnancy, antiparasitic therapy should be instituted.
- CMV is the most common congenital infection in the United States.
- Although patients with antibodies may have reactivation resulting in infected newborns, these children are less frequently and less severely infected then those whose mothers have primary infections.
- Primary, first episode, genital HSV infection may increase the risk of untoward perinatal events, including preterm birth, low birth weight, and congenital infection.
- Viral shedding in labor should be determined by clinical assessment and should be managed with an operative delivery.
- Nucleoside analogues may be used to reduce the frequency of HSV viral shedding and, thereby, the need for cesarean section.

SUMMARY POINTS FOR INTRAAMNIOTIC INFECTION AND POSTPARTUM ENDOMETRITIS

- Both clinically evident IAI and postpartum endometritis are polymicrobial, upper genital tract infections, involving anaerobes, aerobes, and genital mycoplasmas most commonly.
- The benefits of intrapartum treatment of IAI with broad-spectrum antibiotic therapy are well established.
- In addition to causing maternal and neonatal sepsis, neonatal pneumonia, meningitis, and neonatal death, intraamniotic infection is now strongly associated with long-term neonatal adverse outcomes including cerebral palsy, respiratory distress syndrome, and other complications.
- Several effective measures have been identified to prevent clinical IAI.
- Response of postpartum endometritis is very good to a variety of antibiotic regimens, which have coverage against likely aerobes and anaerobes.
- Oral therapy generally is not needed after successful parenteral therapy for endometritis.
- Antibiotic prophylaxis strategies are well established for cesarean section.

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Chapter 20

Helen H. Kay

Placenta Previa and Abruption

PLACENTA PREVIA

Incidence
Definition
Pathophysiology
Risk Factors
Diagnosis
Clinical Features
Management
Complications
Outcomes
Prevention

VASA PREVIA

PLACENTAI ABRUPTION

Incidence
Definition
Pathophysiology
Risk Factors
Diagnosis
Clinical Features
Management
Complications
Outcomes
Prevention

SUMMARY POINTS

REFERENCES

All bleeding during pregnancy should be investigated by examination and by imaging studies. There are many etiologies for bleeding in pregnancy but the most clinically significant are placental previa and placental abruption since these conditions can lead to serious fetal compromise. Other causes of bleeding that should be excluded are cervical lesions such as carcinoma or polyps, vaginal lacerations from trauma or carcinoma, other uterine bleeding such as dehiscence of a prior cesarean section scar, and premature cervical dilation, although these usually do not involve large amounts of blood loss. The presence of either placenta previa or abruption places the patient in a high-risk situation that warrants close monitoring. A definitive diagnosis is extremely important since either placenta previa or abruption, in many cases, commits the patient to a period of prolonged bed rest and hospitalization.

PLACENTA PREVIA

Incidence

Placenta previa is encountered in approximately 0.5% to 1% of all pregnancies but its incidence may be higher now than in the past due to the increased diagnosis by widespread use of ultrasound scanning. It is fatal in 0.03% of cases ([1]). Formerly, the diagnosis of milder degrees of placenta previa without hemorrhage may have gone unnoticed by clinical exam. It is more common in multiparous than nulliparous women, occurring in only one in 1,500 nulliparas and as many as 1 in 20 grand multiparas. The incidence in the United States is declining, probably in part due to the declining number of grand multiparous women.

Definition

The definition of placenta previa has been complicated because the original descriptions referred to the location of the placenta in relation to a dilated cervix (i.e., one in labor) determined by digital exam. In this definition of a complete previa, the placenta extends over and beyond the internal os. A partial previa refers to a placenta with its edge partially over the dilated cervix, meaning that if we were to visualize the cervix with a speculum, we would see placental tissue over some part of the dilated cervical area, but not all. The last type of previa, the marginal previa, refers to a placenta where the edge lies very close to and up to the edge of the os but does not cover any of it. In those original descriptions, the distance between the placental edge and the internal os was never defined in terms of centimeters (Fig. 20.1). However, with the advent of transvaginal ultrasound imaging, the cervix can be routinely imaged, even when not dilated, and the internal os is seen as a point, hence the confusion over the terminology. In today's practice, any suspected low-lying placenta seen by transabdominal scan should be further evaluated by a transvaginal scan to determine the distance between the edge of the placenta and the internal os (Fig. 20.2). Those cases where the placental edge completely covers the cervical os will be labeled as a complete previa. Those with the placental edge at the cervical os should be labeled as partial or marginal (partial/marginal) since it is impossible to determine whether those placentas will remain covering the dilated cervix during labor or whether they will remain at the edge of the dilated cervix. The cases in which the placental edge is located within 1 to 2 cm of the internal os are the most confusing. Studies that have evaluated this report that patients with a placenta edge less than 1 cm from the cervical os tend to have cesarean sections because they are most like placenta previa patients (i.e., with bleeding and these are delivered by cesarean section) ([2]). Patients with the edge between 1 to 2 cm of the internal os, however, remain in the gray zone. These patients will benefit most with either a double setup at the time of labor or with close observation in labor and an attempt for a vaginal delivery if there is no bleeding. Patients with a placental edge greater than 2 cm from the cervical os are considered to have normal placentas and not a previa.

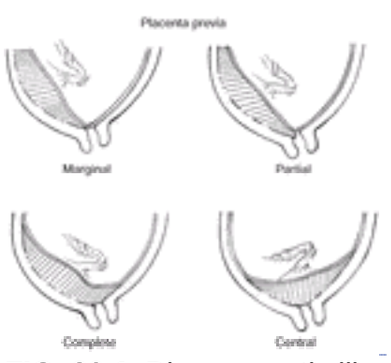

FIG. 20.1. Diagrammatic illustration of the three classic types of previa: Marginal, partial, and complete. These relate to diagnosis by digital or visual examination when the patient is in labor with a partially dilated cervix. The term *central previa* refers to a previa in which the central portion of the placenta lies directly over the cervical os.

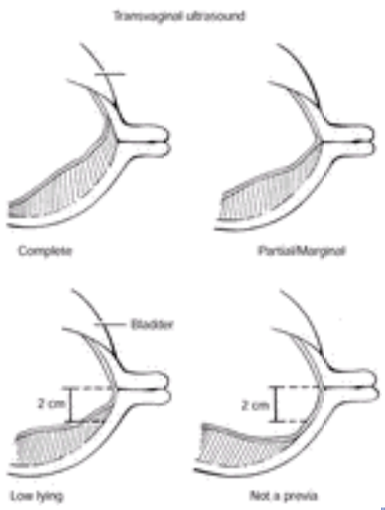

FIG. 20.2. Diagrammatic illustration of the classes of placenta previa diagnosed by transvaginal ultrasound. In the nonlaboring, patient the internal os is seen as a point, and the distance between this and the lower edge of the placenta becomes the more critical reference.

Pathophysiology

Placenta previa is a condition of abnormal implantation (i.e., into the lower uterine segment rather than the corpus or fundal region). The exact pathophysiology is unknown but because it is seen more frequently in patients who tend to be older, multiparous, and had prior cesarean sections or prior uterine curettage, it is thought to result from scarring in the endometrium. This leads to abnormal endometrial tissue, poor vascularization, thinner myometrium, and a less favorable location for implantation. Presumably, the embryo is attracted to healthier tissue which would be the untampered endometrium of the lower uterine segment. Interestingly, it would appear that the anterior uterine segment after cesarean section would be an unfavorable site for implantation but, for uncertain reasons, the uterine trauma from cesarean sections actually increases the risk of previa by as much as six-fold.

Risk Factors

Several risk factors have been found in association with placenta previa (Table 20.1). The most significant is a prior cesarean section (approximately 1 in 200 deliveries; the incidence is higher if a woman has undergone two or more C-sections). Black or minority patients seem to be at higher risk as are women older than 35 years. Other risks include increased gravidity and parity, and cigarette smoking, with a 2.6- to 4.4-fold increase ([3], [4] and [5]). Interestingly, meta-analyses have shown a preponderance of male gender among the fetuses with placenta previa ([6]). The mechanism for this is unknown. Previous abortion has not been consistently shown to be associated with an increase in risk for previa.

Black and minority
Advanced maternal age
High gravidity
High parity
Previous abortion—induced and spontaneous
Prior cesarean section
Cigarette smoking

TABLE 20.1. *Risk factors associated with placenta previa*

Diagnosis

The diagnosis of placenta previa can be made by transabdominal ultrasound. With the advent of the curvilinear probe, the cervical and lower uterine segment is much better imaged and the relationship of the lower placental edge to the internal cervical os can be routinely visualized. However, the most common pitfalls include a full, distended bladder and a lower uterine segment contraction that can lead to misdiagnosis. Of those diagnosed in the second trimester, 90% to 95% resolve by the third trimester due to further development of the lower uterine segment, also referred to as migration of the placenta. However, if the placenta covers the internal os by 20 mm or more, meaning that it crosses the os by 20 mm, there is a 100% sensitivity rate for detection of previa at delivery requiring cesarean section ([2]). Three-dimensional scanning may further increase prenatal detection but remains a new investigational technique for previa at this time. Therefore, it is imperative that follow-up scanning be performed to determine if there is resolution of what appears to be a placenta previa. Marginal and partial placenta previa are significantly less likely to persist into the third trimester (i.e., <5% chance).

Although initially thought to be contraindicated in patients with suspected placenta previa, transvaginal scanning can be safely performed with caution. In many cases, the relationship between the placental edge and the internal os can be difficult to assess and only a close-up view with a transvaginal approach can make a definitive diagnosis (Fig. 20.3). This approach to scanning has been studied carefully and it does not appear to lead to increased vaginal bleeding, in part because it is technically impossible to introduce the probe through the cervix. Another alternative approach is with translabial scanning which has been reported to be 100% sensitive for detection of a previa. However, on occasion, bowel gas can interfere. When a clear diagnosis of placenta previa is made by a transabdominal or translabial scan, there is no need to perform a transvaginal scan. However, when a partial/marginal placenta previa or low-lying placenta is suspected, a transvaginal scan should be performed to confirm the diagnosis and the distance between the internal os and lower placental edge should be determined. Both types of scanning have greatly reduced the false-positive rate by transabdominal scanning alone which is reported to be as high as 25%.

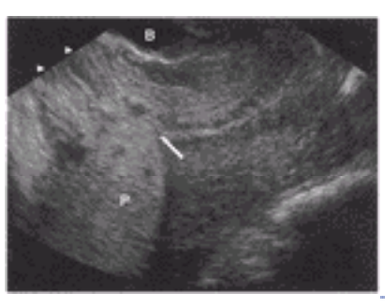

FIG. 20.3. A transvaginal ultrasound image of a complete placenta previa. The *arrow* points to the internal os. *P*, placenta; *B*, bladder.

It is debatable whether transvaginal scanning has made the double setup examination obsolete because the relationship between the placenta and cervix can be identified well by experienced scanners. However, there is probably still a place for this exam, particularly in those patients with a placental edge between 1 to 2 cm from the internal os, and with no bleeding. This type of exam can be used in labor to determine the relationship between the placental edge and the cervix by carefully introducing the examining finger into the cervix with the patient prepped and draped in the operating room so that if placenta is encountered at the internal os, an immediate cesarean section can be performed, particularly in the event of acute hemorrhage. If the cervix is dilated, a finger can be passed through the cervical canal to the internal os and placental tissue can be palpated as gritty, fibrous tissue in contrast to the fetal membranes that are smooth to touch, particularly with amniotic fluid behind them. If placental tissue is palpated to cover the os or is located easily within reach, it is considered to be a previa. In this case, the distance relationship (i.e., whether it is 1 or 2 cm from the os) is insignificant since that is an ultrasound imaging determination. At that point, the patient would be managed by proceeding with a cesarean delivery. However, if the cervix is dilated, the membranes are ruptured to allow the fetal vertex to be better applied to the cervix, tamponading what bleeding may develop and enabling the patient to continue laboring to achieve a vaginal delivery or to augment labor with Pitocin.

Clinical Features

Patients with placenta previa typically remain asymptomatic until they have vaginal bleeding. Many are now detected during second trimester ultrasound screening although they remain asymptomatic. It is becoming increasingly rare to have a patient present late in the third trimester with new diagnosis. There are no means to predict which patients will bleed and when they will bleed. Approximately one-fourth of patients do not bleed prior to 36 weeks ([7]). Usually the first episode of painless

vaginal bleeding occurs without any precipitating event, although intercourse and excessive activity by the patient may be inciting factors. Complete previas are more likely to bleed earlier than partial or marginal previas. The thinning lower uterine segment most likely tears into the intervillous space of the placenta. The blood can bring about uterine irritability and occasionally preterm contractions. The amount of blood in this first bleed tends to be variable, from slight to heavy, although it is usually unlikely to be heavy enough to prompt delivery. However, the amount of subsequent bleeds tends to be increasingly heavier as the cervix and lower uterine segment changes. Blood seen on a patient's feet is usually a good indication of a heavy bleed.

Most patients stop bleeding with bed rest, particularly those in the second trimester. Many patients are placed at bed rest either at home or in the hospital until resolution of bleeding. The bright red blood usually converts to a brownish discharge. In the third trimester, though, the amount of bleeding increases and often, delivery is prompted by one massive bleed after multiple earlier bleeds. The blood is typically of maternal origin and therefore the fetus is usually not in jeopardy. In cases with massive bleeding, the fetal heart rate tracing may show signs of distress, usually with repetitive late decelerations.

Patients with placenta previa are at increased risk for abruptio placentae (rate ratio 13.8), cesarean delivery (rate ratio 3.9), fetal malpresentation (rate ratio 2.8), and postpartum hemorrhage (rate ratio 1.7) ([1]). Although fetal growth restriction was formerly thought to be an outcome of placenta previa, more recent studies do not show an association when comparisons were made between a study group and a well-matched control group and when gestational age at delivery was controlled ([8]). Although it is impossible to predict which patients will bleed and when, one report suggests that patients with elevated maternal serum alpha-fetoprotein (MSAFP) levels greater than 2.0 multiples of the median (MoM) have a 50% chance of requiring hospitalization for bleeding before 30 weeks gestation, to be delivered preterm before 34 weeks, and to be delivered for pregnancy-associated hypertension before 34 weeks ([9]). MSAFP elevations did not predict those with placenta accreta or emergent cesarean hysterectomy. Careful note of the MSAFP levels in the second trimester may help us target those patients who need to be cautioned more specifically about adverse outcomes due to the presence of the previa.

Management

Patients diagnosed in the second trimester should be cautioned about the possibility of bleeding. Intercourse should be avoided unless a follow-up scan reveals further migration of the placenta. Otherwise patients may be allowed their usual activities without excess exertion. A repeat scan approximately every 4 weeks should be performed to determine the persistence or resolution of the previa. If further scans reveal resolution, no further evaluation is necessary. However, if follow-up shows persistent previa into the third trimester, the patient should be further counseled regarding her chances of bleeding. Decreased physical activity would be advisable and travel away from home should be discouraged.

Every patient who bleeds needs to be evaluated. Fetal status should be documented. Depending on the amount of bleeding, intravenous fluids should be started and blood should be cross-matched or, at a minimum, typed and screened. Subsequently, continuous availability of cross-matched blood does not appear to be necessary, as few antepartum patients require emergent transfusion. Rh status should be checked and RhoGam should be administered if patients are Rh-negative and unsensitized. A baseline blood count with hemoglobin and hematocrit should be determined to assess degree of bleeding. These blood counts should be interpreted carefully in the context of normal reserve in these pregnant patients as well as the hemodilution with intravenous hydration. Because pregnant women have such reserve, their vital signs and laboratory values may not directly reflect their vascular compromise until they have had a very large amount of bleeding. Their status may be deceptively stable until they get close to serious decompensation. If signs of hypovolemia are present, such as hypotension and tachycardia, the patient more than likely has had severe hemorrhage—more than might be clinically observed. Since it is rare to develop a coagulopathy with a bleed from a previa, a coagulation profile is not necessary at the onset. A Kleihauer-Betke test for fetal blood is also not necessary since it is rare to find an abnormal test result.

If the fetus is clearly previable, continued monitoring and stabilization of maternal hemodynamics is appropriate. Blood can be transfused as needed to maintain the maternal blood count in a normal range (hematocrit >30) until fetal viability is reached. In patients who decline transfusions, erythropoietin may be a good option. In addition, the use of autologous blood donation in these patients may be a safer therapy in some parts of the world. If bleeding ceases, the patient may be a candidate for continued outpatient bed rest. Outpatient expectant management has been analyzed and the cost–benefit ratio was favorable with no outcome difference between those managed as outpatients versus those managed as inpatients ([10]). Antenatal steroids for fetal lung maturity should be administered between 24 and 34 weeks gestation.

In the third trimester, the threshold for discharging the patient should be higher. A period of prolonged bed rest and observation is warranted and it is not unreasonable to consider hospitalization until delivery. If it appears that immediate delivery is not necessary, patients should be given a course of antenatal steroids, from 24 to 34 weeks with intact membranes. Continuous fetal monitoring should be carried out until the bleeding is stable and then daily fetal assessment is appropriate. Additional episodes of bleeding, despite full bed rest, are not uncommon. Approximately 70% of patients treated expectantly will have a second episode of bleeding and 10% will have a third bleed. Unless acute bleeding mandates preterm delivery, the patient can undergo semi-elective amniocentesis after 36 weeks and delivery if fetal lung maturity can be documented. Approximately 25% to 30% of patients will achieve 36 weeks gestation. If significant bleeding occurs after 34 weeks gestation, a decision to proceed directly to delivery without amniocentesis is justified.

In the event of severe hemorrhage on admission, the medical team should prepare for immediate delivery if the fetus has reached a viable gestation. The anesthesiologist and neonatologist should be notified immediately. Two large-bore intravenous lines should be established and blood should be cross-matched immediately. A Foley catheter should be inserted to monitor urine output. A coagulation panel should also be sent. Continuous fetal monitoring should be performed while preparing for delivery and any decompensation should hasten the delivery process.

In about 20% of the cases with bleeding, the uterus contracts and the additional problem of managing preterm labor needs to be confronted. A transvaginal or translabial ultrasound scan can be performed to assess the cervix if bleeding is not too heavy. If fetal lung maturity is not documented or unlikely, efforts to arrest the labor should be attempted, if only to try to get a course of antenatal steroids on board. However, use of tocolytics is considered controversial and no studies have confirmed their benefit in these patients. The choice of tocolytics should be carefully weighed. Beta-mimetics produce maternal tachycardia and hypotension and are generally contraindicated unless the bleeding appears to be stable. Calcium channel blockers can also cause hypotension. Indomethacin is generally not recommended after 32 weeks because of possible premature closure of the fetal ductus arteriosus. Magnesium sulfate is a popular choice and is the most widely used.

Delivery is by cesarean section for all categories of placenta previa when documented by transvaginal scan with an undilated cervix in the third trimester regardless of whether it is a complete, partial, or marginal previa. However, if the diagnosis cannot be established definitively, such as when vaginal scanning is unavailable, or there is a suspected marginal or partial previa between 1 to 2 cm from the os and without any bleeding, a double setup may be considered when in labor or before labor. If no placenta tissue can be palpated, the membranes should be ruptured and the patient may be allowed to labor. Rupturing the membranes and allowing labor to continue could bring the fetal vertex down, and tamponade any placental bleeding.

In the majority of cases, a low transverse uterine incision can be successfully achieved, particularly with a posterior placenta and with a well-developed lower uterine segment. A transverse incision can still be accomplished in skilled hands even when an anterior placenta is encountered by cutting quickly through the uterus and placenta and delivering the fetus as quickly as possible before there is significant fetal exsanguination. In a good percentage of cases, the placenta previa leads to fetal malpresentation such as transverse lie. In those cases, the best uterine incision would be a vertical, or classical one.

Regional anesthesia may be successfully used for patients with placenta previa. It has been reported that the management of blood pressure for hemorrhage is not a problem and may be the preferred choice due to the lowered amounts of intraoperative blood loss compared to general anesthesia. With heavy bleeding preceding delivery, however, many anesthetists would still opt to use general anesthesia because regional anesthesia in the presence of major hemorrhage may exacerbate hypotension and block the normal sympathetic response to hypovolemia.

Complications

Complications from placenta previa include a longer hospital stay, cesarean delivery (risk ratio [RR] = 3.9), abruptio placenta (RR = 13.8), postpartum hemorrhage (RR = 1.7), fetal malpresentation (RR = 2.8), and maternal death from uterine bleeding (50%) and disseminated intravascular coagulation (DIC) (15.9%) ([1]).

Placenta Accreta One significant complication of placenta previa is placenta accreta, increta, and percreta, particularly with a prior history of a cesarean section. Placenta accreta refers to the placenta being attached to the myometrium but does not invade the muscle; increta is seen with the villi invading the myometrium; and percreta is seen when the villi penetrate through the entire uterine wall and into the bladder or rectum. The presence of placenta previa in a patient with a prior cesarean section is associated with accreta in 10% to 35% of cases. With multiple cesarean sections, the risk may be as high as 60% to 65% ([11]). During antenatal ultrasound scans, the lower uterine segment should be scrutinized for any evidence of a disruption in the demarcation between the placental fibrinoid base known as the Nitabuch layer and the uterine decidua basalis. Color Doppler assessment can be very helpful by demonstrating marked or turbulent blood flow within the placenta and extending into the surrounding tissues, which is also described as lacunar flow. Similar, and perhaps better, scrutiny can be offered by magnetic resonance imaging (MRI) that can demonstrate placental tissue extension through the uterus (Fig. 20.4). MRI diagnosis for placenta percreta may be quite accurate but diagnosis for placenta accreta, a lesser degree of myometrial invasion, is much lower with sensitivity in the 30% to 40% range. The imaging features include a loss of the decreased signal intensity demarcation between myometrium and decidua basalis. However, one report showed a sensitivity of only 38% for the detection of accreta by

MRI. There are some reports of gadolinium-enhanced MRI that can more clearly distinguish a placenta accreta from a percreta. There is not enough data thus far to determine whether MRI is superior to ultrasound for diagnosing placental accreta and percreta.

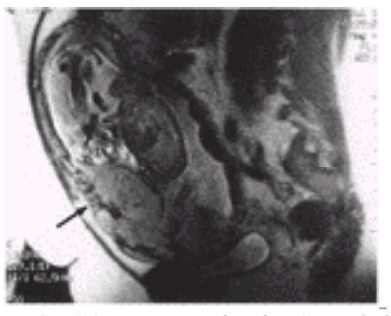

FIG. 20.4. A sagittal T2-weighted magnetic resonance imaged case of placenta percreta. The percreta is low anterior (*arrow*). (Courtesy Dr. Mark Kliewer.)

In the presence of placental accreta, increta, and percreta, the risk of hemorrhage is extremely high. Careful attention should be paid to the lower uterine segment after delivery of the placenta. If bleeding persists despite the usual postpartum uterotonic agents and uterine or hypogastric artery ligation, hysterectomy must be considered. Complications are more likely to arise from delay in making the decision to proceed with hysterectomy. It may be a worthwhile exercise to attempt other methods to control the bleeding before hysterectomy such as oversewing the lower uterine segment, uterine artery ligation, ovarian artery ligation, and uterine packing, but all are associated with mixed results. If definitive hysterectomy is not performed, bilateral arterial embolization of the uterine arteries should be the next option of choice although more experience is needed to determine the success rate of such a procedure for placenta percreta. Precautions to control hemorrhage in general should include intravenous access, blood products, and anesthesiology assistance. If these conditions are suspected by imaging studies prior to delivery, a planned cesarean section after uterine artery catheters are placed for possible embolization may be useful to avoid a hysterectomy. Plans should also be made to deliver in an operating room where there would be access to extra assistance and equipment should a hysterectomy be performed. The interventional radiologists should be notified of the possibility for embolization and the proper equipment should be made available. Other types of management have included methotrexate for placenta accreta tissue left in situ from bladder wall invasion, subendothelial vasopressin to control bleeding, and balloon occlusion in the hypogastric arteries before hysterectomy. Some of these have been reported with mixed results. Ongoing improvements in the management, once hemorrhage is recognized, will decrease overall morbidity to the patient. Other complications in the presence of significant hemorrhage from placenta previa could include complications from hypotension such as acute tubular necrosis and Sheehan syndrome of pituitary infarction. Although maternal mortality is low, less than 1%, and perinatal mortality is less than 5%, there can be significant morbidity for both. Lesser complications include risk for hysterectomy (RR = 33.26), antepartum bleeding (RR = 9.81), intrapartum and postpartum hemorrhages (RR = 1.86), blood transfusion (RR = 10.05), septicemia (RR = 5.55), and thrombophlebitis (RR = 4.85) ([12]). Cases of spontaneous uterine rupture attributable to placenta percreta without prior cesarean delivery have also been reported.

Outcomes

Many reports have suggested a causative effect between placenta previa and low birth weight. The association between placenta previa and fetal growth restriction has been assumed to a large extent. However, more recent studies that have controlled for the gestational age at delivery have found no significant association between previa and growth restriction and the previously seen association is most likely due to preterm birth. Other neonatal outcomes of significance also include an increased risk of congenital anomaly, respiratory distress syndrome, and anemia. The mechanism for the increase in congenital anomalies is not known but the increase in respiratory distress syndrome and anemia can be explained by the increased perinatal bleeding. Mortality, intraventricular hemorrhage, and low Apgar scores are not different, reflecting advances in obstetrics and neonatal treatments.

Recurrence risks for placenta previa are 2% to 3% or six- to eight-fold higher than the normal population. Cigarette smoking further increases these recurrence risks.

Prevention

There are no means to prevent placenta previa. However, some studies have suggested that a cervical cerclage placed between 24 and 30 weeks gestation may decrease the chance of bleeding and blood transfusion while prolonging the pregnancy, increasing the birth weight, and decreasing the hospital stay and costs and admission to the neonatal intensive unit. The mechanism is thought to be due to stabilization of the lower uterine segment. This practice, however, is not established and there have been no large randomized trials to test this intervention ([10]). Other trials found some benefits in a prolongation of pregnancy by 1 week, fewer readmissions for bleeding, fewer hospitalization days, and higher birth weights, although none of these were statistically significant.

VASA PREVIA

A vasa previa occurs in approximately 1 in 1,000 to 1 in 5,000 pregnancies and refers to a condition associated with a very high fetal mortality in the range of 33% to 100%. It is seen when a fetal vessel crosses and covers the internal os (Fig. 20.5). Patients at risk include those with bi-lobed placentas, succenturiate-lobed placentas, low-lying placentas, pregnancies from in vitro fertilization, and multiple pregnancies. These conditions all increase the likelihood that fetal vessels in the membrane will rest over the cervical os. It is technically only possible in two conditions. One is in the presence of a velamentous cord insertion and the other is a placenta with a succenturiate lobe. In both cases, unprotected fetal vessels within the membranes can go undiagnosed and at the time of artificial rupture of the membranes or with advanced labor, these fetal vessels can be ruptured leading to fetal exsanguinations.

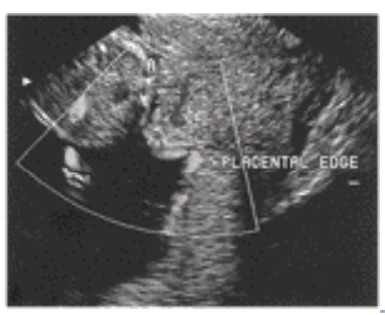

FIG. 20.5. A transvaginal color Doppler ultrasound image of a suspected vasa previa. Markers indicate the distance between the internal os and the cord insertion into the membranes away from the placental edge, a distance less than 1 cm. See color figure 20.5.

When fetal blood is suspected, it may be confirmed quickly by doing a test for fetal hemoglobin. Because fetal hemoglobin is resistant to alkaline pH, several alkaline denaturation tests have been developed such as the Apt, Ogita, and Loendersloot tests. These tests differ only in the duration of the test but all are less than 10 minutes. Therefore, they are all suitable for an acute situation prior to grossly obvious fetal deterioration. Fetal distress can be represented by a sinusoidal pattern on the fetal heart monitor.

It is prudent to identify the location of the cord insertion into the placenta and to look for the presence of a secondary placental lobe at the time of a routine second trimester scan to avoid a disastrous outcome. Color Doppler scanning dramatically simplifies this diagnosis and when combined with either transvaginal or translabial scanning, can distinguish a funic presentation (i.e., cord presenting ahead of the vertex) from a vasa previa. Reports have also suggested that three-dimensional ultrasonography and MRI may help in the diagnosis of vasa previa but further experience with these techniques needs to be demonstrated. Transvaginal scanning with color Doppler is currently the most effective means available.

Early recognition has been reported to be associated with decreased fetal mortality. It can assist in planning delivery and preventing iatrogenic harm such as from artificial rupture of the membranes. Elective cesarean delivery decreases the perinatal mortality. In undiagnosed cases, a heightened sense of suspicion and aggressive intrapartum and neonatal management are the only means to achieve successful neonatal outcomes.

PLACENTAl ABRUPTION

Placental abruption is a pathologic condition in which some part of the placenta prematurely separates from the uterus. It is one of the leading causes of fetal and

neonatal mortality.

Incidence

Many factors lead to placental abruption and its incidence seems to be increasing. The incidence is 0.5% to 1.0%. It is a leading cause of perinatal mortality accounting for 10% to 15% of all perinatal deaths, although this rate may be decreasing with improved neonatal care.

Definition

Three types of placental abruption are:

1. Retroplacental—between the placenta and myometrium; severe is 30% to 40% of the surface area, 50% fetal mortality if greater than 60 mL of blood.
2. Marginal, subchorionic—between the placenta and membranes.
3. Preplacental, subamniotic—between the placenta and the amniotic fluid. These are of no clinical significance.

There are several categories of abruptions, some more dangerous than others (Fig. 20.6). The most significant abruption is a retroplacental abruption that can compromise fetal oxygenation and perfusion. These can derive from a marginal abruption, which refers to those located at the edge of the placenta and is seen as a simple lifting of the placental edge away from the uterus. These can be serious when the abruption extends from the margin to the rest of the placenta. A concealed abruption is a retroplacental abruption in which there is no obvious discernible external bleeding.

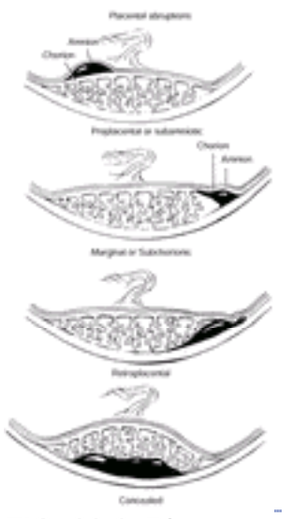

FIG. 20.6. Diagrammatic representation of various degrees of placental abruption: preplacental or subamniotic (between amnion and chorion), marginal or subchorionic (between placenta and membranes), and retroplacental (between placenta and myometrium).

Pathophysiology

The pathophysiology of an abruption depends on the etiology. An abruption is the clinically recognized end result when villi separate from the underlying decidua basalis. In blunt trauma, the cause is clearly a forceful shearing effect. In the majority of other cases, bleeding results from cell death (apoptosis) induced through ischemia and hypoxia. In patients with thrombophilia, the tendency to clotting leads to a thrombotic event in the decidua basalis resulting in ischemia and hypoxia. In patients with chorioamnionitis, lipopolysaccharides and other endotoxins generated from the infectious agents induce the accumulation of cytokines, eicosanoids, and reactive oxygen species such as superoxide. All have cytotoxic potential that promotes ischemia and hypoxia. One of the cytotoxic actions of endotoxin is the induction of nitric oxide synthase (NOS) activity that produces nitric oxide (NO), a potent vasodilator and inhibitor of platelet aggregation. As NO is metabolized, peroxynitrite is generated which is a longer lasting oxidant capable of causing ischemia and hypoxia through actions on vascular endothelial cells. As the beneficial effects of NO are outweighed by the overwhelming inflammation, ischemia and hypoxia result leading to cell death and bleeding. The specific mechanisms involved in this final step are under active investigation ([13]).

Risk Factors

Many risk factors for placental abruptions have been studied extensively ([14]) (Table 20.2). These factors may be categorized. The first is socioeconomic factors with young age, primiparity, single parenthood, and low education being associated with abruption. Also included in this category would be a prior abruption with a recurrence risk ten times higher than those without a prior history. Another category includes physical factors such as blunt abdominal trauma from domestic abuse or a motor vehicle accident. A third category includes uterine defects including myomas and septums. Multiple studies have shown higher incidence of abruptions in patients with a retroplacental myoma, particularly if the myoma volume exceeded 200 cm^3 and was submucosal in location ([15]). The fourth category is the largest and most significant and includes maternal illnesses such as thrombophilias and hypertensive diseases. Finally, a fifth category of iatrogenic causes should be included.

Uterine	
	Myomas
	Uterine septum
	Uterine malformations
Demographic/socioeconomic	
	High parity
	Single parent
	Low education
	Infertility
Medical	
	Unexplained elevated MSAFP and hCG
	Decreased inhibin A
	Antiphospholipid syndrome
	Pregestational diabetes
	Hypertension—chronic and gestational
	Preterm rupture of membranes with chorioamnionitis
Thrombophilias	
	Prothrombin 20210A mutation
	Hyperhomocysteinemia
	Factor V Leiden mutation
	Activated protein C resistance
	Protein C and S deficiency
	MTHFR
	Dysfibrinogenemia
Iatrogenic	
	Sudden decompression of uterus (amniocentesis)
	External cephalic version for breech
	Cigarette smoking
	Cocaine abuse
	Blunt trauma
	Incorrectly applied seat belt
	Cesarean section
	Intrauterine pressure catheter placement
	Heavy physical activity

hCG, human chorionic gonadotropin; MSAFP, maternal serum alpha-fetoprotein; MTHFR, methylenetetrahydrofolate reductase.

TABLE 20.2. *Risk factors associated with placental abruption*

Maternal disease such as hypertension has been associated with increased risks for abruption. In many studies and in a large epidemiologic study of hypertensive women in Nova Scotia, only women with chronic hypertension with superimposed severe preeclampsia were at increased risk for abruption compared to women with chronic hypertension alone, a RR of 3.8 for parous women and 1.6 for nulliparous women. Not surprisingly, the effects of smoking and hypertension appeared to be additive, if not even higher ([16]).

Maternal illness due to premature rupture of the membranes leading to chorioamnionitis has been strongly correlated with the incidence of abruptions from epidemiologic studies, microbiologic, and histopathologic studies of the placentas ([17]). Pathologic evidence to support this includes observations that lipopolysaccharides and bacterial endotoxins are elevated in the amniotic fluid of patients with chorioamnionitis. These agents, in turn, induce the formation of superoxide or free oxygen radicals as evidenced by an increase in the nitrites and nitrates in maternal serum. These are metabolites of NO, an antioxidant that appears to be increased under these infectious conditions. Immunohistochemical studies have demonstrated increased expression of NOS and nitrotyrosine, which are markers for NO metabolism, in placentas from patients with chorioamnionitis and abruptions. Additionally, evidence for apoptotic cell death has been identified in placentas from

both conditions ([13]). This evidence supports a strong link between chorioamnionitis and placental abruption.

Over the past decade, new risk factors have been identified in association with placental abruptions. These factors are encompassed under the umbrella of thrombophilia defects and include anticardiolipin antibodies, presence of the lupus anticoagulant, protein C, S and antithrombin III deficiencies, and the mutations such as factor V Leiden (also know as activated protein C resistance), methylenetetrahydrofolate reductase mutation, and prothrombin *20210A* gene mutation, as well as the more rare congenital dysfibrinogenemia. The autoimmune antibodies, anticardiolipin antibodies, and lupus anticoagulant have been shown for many years to be associated with adverse pregnancy outcomes including placental abruption. Because these are nonspecific antibodies, it is difficult to understand their pathophysiologic role in bleeding. Protein C and protein S deficiency are genetic disorders seen with an increased risk for thrombosis. They have been implicated in preeclampsia and abruption. However, their levels may normally be decreased during pregnancy making it difficult to fully understand their role in the pathophysiology of abruption. More recently, research has focused on specific gene defects that predispose patients to coagulopathy.

Activated protein C resistance (APCR) is the most common genetic factor predisposing to thrombosis and appears to be the most common identifiable cause. This resistance is most often caused by the factor V Leiden mutation and in many cases is used synonymously, although patients can have APCR without the Leiden mutation. In this mutation, there is a nucleotide substitution of adenine for guanine that results in an amino acid substitution of arginine for glutamine. Patients who are heterozygous for this mutation have fewer manifestations of clinical disease than those who are homozygous. Because patients with this mutation have an increased tendency to form clots, they also have a higher risk for abruption due to clotting in the placenta, primarily thought to be in the decidua basalis either early in pregnancy resulting in spontaneous abortions or in the latter half of pregnancy resulting in bleeding and abruption. Furthermore, women with a hypofibrinolytic 4G/4G mutation of the plasminogen activator inhibitor 1 (PAI-1) gene, which is frequently associated with the thrombophilic factor V Leiden mutation, also have a predisposition to thrombosis. A study of women with adverse obstetric complications found that women with placental abruption were more often associated with homozygous and heterozygous factor V Leiden mutation, heterozygous *G20210A* prothrombin gene mutation, homocystinemia, APCR, or anticardiolipin immunoglobulin G (IgG) antibodies. However, other studies have found a weaker link and it is cautioned that these tests should not become standard and routine until larger studies further substantiate their relationship to placental abruption and other pregnancy complications. A concomitant search for therapeutic measures would further justify this type of testing of a beneficial treatment if one can be found ([18]).

One etiologic factor that has been widely studied in association with placental abruption is the condition known as hyperhomocysteinemia. Homocysteine is metabolized from methionine and then remethylated by an enzyme known as methylenetetrahydrofolate reductase (MTHFR) to methionine, with folate and vitamin B_{12} as cofactors. Mutations in the *MTHFR* gene, two known as *C677T* and *A1298C*, prevent this normal remethylation leading to increased levels of homocysteine. These elevated levels of homocysteine can damage vascular endothelium leading to thrombosis formation when they occur in veins or to placental abruption when they cause damage in the spiral arteries supplying flow to the placenta ([19]). Increased levels of homocysteine have been identified in the fasting state in patients with placental abruption and infarction ([20]). Hyperhomocysteinemia was found in 24% of Danish women with a history of placental abruption, intrauterine fetal demise, and fetal growth restriction ([21]). Increasing folate and pyridoxine intake successfully reduced the levels of homocysteine. Pathologic evaluation of the placentas from patients with hyperhomocysteinemia have identified an increase in pathologic features including acute atherosis, infarction, retroplacental hematomas, accelerated villous maturity, and vascular thrombosis ([22]). These abnormalities further support the fact that hyperhomocysteinemia is an etiologic factor in placental abruption. Future randomized trials with folate, vitamin B_6, and vitamin B_{12} supplementation will be informative. For the present, patients with placental abruptions with no obvious etiology should be considered for hyperhomocysteinemia screening.

A final category of risks includes iatrogenic causes. Iatrogenic agents such as nicotine from cigarette smoking and cocaine can both cause vasoconstriction that leads to ischemia and abruption. This alteration in uteroplacental blood flow most likely causes placental lesions (i.e., infarction, oxidative stress, apoptosis, and necrosis) that can bring about disruptions in the placental–uterine interface leading to the abruption. Cigarette smoking was associated with an adjusted odds ratio for abruption ranging from 1.7 in all patients to 3.5 for African Americans, or an approximate two-fold relative risk ([23]). It has also been reported that smoking a pack of cigarettes per day increases the risk by approximately 40% ([24]). In another analysis, approximately 15% to 25% of abruptions can be attributed to smoking ([23]).

Other etiologic factors that are less well studied or less frequent include the iatrogenic risks from cesarean section, extramembranous placement of intrauterine pressure catheters, external version, amniocentesis, incorrect placement of the seat belt, and possibly maternal physical activity. No large case-control study has been performed to settle these associations satisfactorily.

Circumvallate Placenta One final risk for placental abruption is the abnormal placentation known as a circumvallate placenta. It is an abnormality in placental development leading to a thickened placenta with an overall decreased surface area over the uterine wall. In this condition, the membranes of the chorion laéve do not insert at the edge of the placenta but some distance closer toward the center. This leaves a rim of fibrin and blood in various stages of clotting at the membrane and placental junction. The unprotected villi beyond the rim tend to bleed. In addition to hemorrhage, this abnormal placentation can lead to placental abruption, fetal growth restriction, preterm labor, and preterm rupture of the membranes. Typically, a second trimester ultrasound identifies such a placenta by its unusual shape with a raised placental margin that does not lay flat against the uterine wall. However, clinically observed bleeding is usually not seen until the end of the second trimester and beginning of the third trimester. Therefore, when suspicions are raised, the patient will need to be warned of the potential for bleeding and other complications and will need to be followed closely. In summary, many risk factors have now been identified in association with placental abruption. Many are preventable, thus justifying programs that can assess an individual's risk in order to attempt modification of behaviors preconceptually or during pregnancy.

Diagnosis

The diagnosis of a suspected abruption can be made clinically. The symptoms include vaginal bleeding, uterine pain, a tetanic contraction of the uterus, and fetal heart rate abnormalities including a sinusoidal pattern in severe abruption. Bleeding occurs in approximately 80% of cases but the remaining symptoms may be present in less than 20% of cases. A definitive diagnosis can only be made retrospectively after delivery and inspection of the placenta because even ultrasound diagnosis is at best 50% sensitive because hemorrhage can be difficult to visualize. MRI can detect blood through detection of methemoglobin but it is not a practical modality for an acute problem as with an abruption.

Ultrasound diagnosis is usually performed transabdominally but may be supplemented with transvaginal scanning if the bleeding placental edge is low (Fig. 20.7). Careful examination of the retroplacental area is required. False-positive identification of the normal retroplacental complex, the normal vascular complex of uterine vessels, decidua and myometrium, as an abruption has been reported. This complex appears hypoechoic on ultrasound. Acute bleeding may take on a variety of appearances from hypoechoic to isoechoic to hyperechoic and diagnosis of an abruption may be confused by this complex. The hyperechoic retroplacental complex, which is usually no more than 2 cm in thickness, demonstrates very high amounts of blood flow by color Doppler imaging that excludes its likelihood of being a clot that should demonstrate no active flow. Other hypoechoic areas such as a myoma or a uterine contraction can be mistaken for an abruption but again color Doppler can assist in the distinction because contractions demonstrate a large amount of blood flow within them and myomas demonstrate blood flow around most of their periphery and less within them. A repeat scan of a fresh bleed is often helpful since the ultrasound appearance of a clot will change with time, becoming more echogenic at 48 hours and then hypoechogenic within 1 to 2 weeks. Aside from this retroplacental complex, an abruption is also difficult to distinguish from the placenta itself. Acute hemorrhage tends to be difficult to distinguish from the placenta but with time, the clot becomes hypoechoic compared to the placenta.

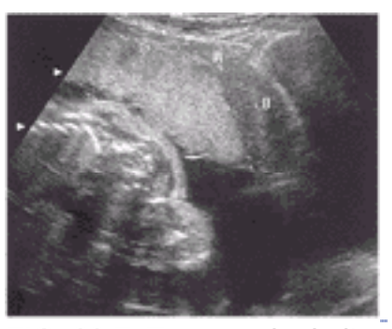

FIG. 20.7. Transvaginal ultrasound image of a retroplacental abruption. The *markers* indicate the size of the clot, 3.5 × 1.0 cm.

Pulsed-wave Doppler is not a useful tool for abruption diagnosis because the results have been inconsistent. Some studies evaluating the use of umbilical artery Doppler velocimetry have shown no abnormalities despite the presence of large retroplacental clots while others have shown elevated resistive indices and waveforms in both the umbilical and uterine arteries in patients with third trimester hemorrhage. These inconsistent findings probably reflect the heterogeneity of patients who presented with an abruption in the published studies. It also reflects the fact that none of the studies to date have had sufficiently high numbers of patients with isolated abruptions. The majority of these studies have evaluated these markers in a heterogeneous group of patients with a wide number of pregnancy complications in addition to abruptions. Uterine artery Doppler studies between 22 to 24 weeks gestation are better for predicting subsequent preeclampsia and fetal growth restriction.

Therefore, undertaking the use of either of these tests to predict subsequent abruption would not be a valued undertaking at this time. However, use of these tests to detect patients at higher risk for pregnancy outcome complications would be a meaningful exercise.

Other means to diagnose or detect placental abruptions include serum biochemical tests. Two markers that have been studied are MSAFP and maternal serum human chorionic gonadotropin (hCG). Presumably, these proteins leak across the placenta when there is an abnormality in its physiologic and anatomic integrity. These markers are elevated in low-risk women with fetal or neonatal death, pregnancy-induced hypertension, placenta previa, preterm delivery, growth restriction, and perinatal complications but who did not have an a priori risk for a neural tube defect or a chromosomal abnormality. The risk of an unexplained elevated MSAFP has been associated with as high as a ten-fold increase of placental abruptions. Among women with third trimester preterm labor, elevated levels of MSAFP at an MoM of 2.0 was observed when an abruption was present with a sensitivity of 67% without bleeding and 100% with bleeding. The negative predictive value can be as high as 94% and 100%, respectively ([25]).

The latest serum marker to be studied in this context is inhibin A, a placental protein that is currently part of a quadruple–serum-marker screen for detection of Down syndrome in which it tends to be increased. Although preliminary, some studies suggest that inhibin A is decreased in patients with systemic lupus erythematosus who also had placental abruptions.

One other marker worth discussion is a test for fetal hemoglobin in maternal blood such as the Kleihauer-Betke test which is a stain for fetal hemoglobin. This test is routinely ordered for Rh-negative patients with a positive blood-screening test to determine how much RhoGam to administer to protect against sensitization. Studies, however, have shown that it is not a useful test to detect suspected placental abruption. This may be explained by the fact that most abruptions consist of maternal blood and most originate in the retroplacental space where there is no overlap of the fetal and maternal blood compartments as would be encountered with an intraplacental bleed where the fetal blood within villous vessels is in close proximity to maternal blood within the intervillous spaces.

Clinical Features

A patient with an abruption will typically present with painless or painful vaginal bleeding. Approximately 20% will have no external bleeding. Typical symptoms include uterine tenderness and irritability. Uterine tone may be increased and may be difficult to distinguish from uterine contractions. Patients with abruptions can have quite significant coagulopathy that develops over a very short time.

Management

The majority of abruptions are marginal abruptions and patients tend to be quite stable. Large retroplacental abruptions are usually quite symptomatic and more easily diagnosed. They also require more acute and aggressive management to prevent disastrous adverse consequences. The chance of a marginal abruption extending to a large retroplacental hematoma is unknown. The decision to hospitalize a patient with any bleeding or with a diagnosed abruption in the latter half of the second trimester or in the third trimester after fetal viability is established is an easy one. On admission, the patient should have blood drawn for a complete blood count and a type and cross or type and screen depending on the amount of bleeding. With large bleeds, 4 units of packed red blood cells should be made available. A coagulation panel consisting of a prothrombin time (PT), partial thromboplastin time (PTT), fibrin degradation product, and fibrinogen level should be drawn if there is a large amount of bleeding. When the fibrinogen level is less than 150 mg per dL, blood in a red top tube may not clot within 6 minutes or forms and lyses within 30 minutes. With mild bleeding, fetal monitoring and observation is appropriate. If significantly previable, intermittent transfusions may be necessary to maintain the hematocrit above 30.

When there is a large amount of bleeding, fetal well-being should be documented by continuous fetal monitoring, a Foley catheter should be inserted to monitor urine output, frequent maternal vital signs should be performed, and a neonatologist and anesthesiologist should be notified of a potential emergent cesarean delivery. An ultrasound should be obtained to ascertain the amount and location of bleeding. Antenatal steroid treatment should be considered if membranes are intact and the fetus is between 24 and 34 weeks gestation. For any patient with bleeding, consideration for treatment with 1 mg folic acid and vitamin B_{12} and B_6 should be undertaken for the possible link between abruptions and hyperhomocysteinemia.

With mild bleeding, the patient will likely resolve her symptoms and should be able to be discharged once an acceptable time interval without any further bleeding has been established, usually 2 to 5 days. However, the decision on when to discharge patients who have had a large bleed is a more difficult one and there are no strict guidelines. Clearly, no decision on discharge should even be considered if the patient is symptomatic either with pain or contractions. Much of the decision will also rest on the patient's home support, whether she will be able to comply with bed rest, and it would not be unreasonable to keep a patient in the hospital until delivery if she is noncompliant or if the home environment will not allow her to undertake bed rest. Whether the patient is an inpatient or an outpatient, some fetal monitoring program should be established.

The issue of tocolytic use in a patient with a known or suspected abruption who has uterine contractions is a debatable one. Although it was formerly taught that no tocolytics should be used in patients with undiagnosed bleeding, it has now become acceptable to consider a short course of tocolytic therapy for patients with bleeding and contractions provided that the patient is stable, the abruption appears to be limited, fetal well-being is established, gestational age is preterm, and there is a controlled environment ([26]). Tocolytics can also be justified if they can prevent labor until a full course of antenatal steroids can be administered and 48 hours posttreatment can be achieved. Because ß-mimetics can mask or blunt the patient's cardiovascular responses to volume depletion, terbutaline and ritodrine should be avoided. Calcium channel blockers may further reduce the blood pressure and nifedipine should be used with caution. The most accepted agent at the present time is magnesium sulfate. As with patients with preterm labor, these agents should be used in the acute setting and efforts should be made to discontinue them when there is a persistent period of quiescence.

Delivery can be by either vaginal delivery or cesarean section depending on the degree of bleeding, the presence or absence of active labor, and the presence or absence of fetal distress. Operative deliveries have been used liberally, in excess of 50% of cases.

When abruption leads to fetal demise, there is a very high rate of DIC. The best marker of severity is the fibrinogen level. Blood products should be administered as needed to correct the coagulopathy and then plans for delivery should be made. Induction of labor and successful vaginal delivery has been reported. Cesarean section may seriously jeopardize the mother's health in the face of a coagulopathy and should be reserved for those cases where there is fetal distress or when it appears that labor and delivery will not be successfully achieved within a reasonable amount of time, between 12 to 18 hours.

Complications

One complication of placental abruption is uteroplacental apoplexy, also known as a Couvelaire uterus. It occurs rarely but is seen with severe placental abruption in which blood extravasates from the clot into the myometrium. The appearance is that of a blue-tinted uterus. This is a very obvious visual diagnosis but biopsies have confirmed the presence of heme throughout the myometrium. This heme can lead to a very hypotonic uterus and on occasion a hysterectomy is needed in order to control the bleeding. Uterine artery embolization is likely not to be effective, although it has not been reported in the literature.

Another complication is disseminated intravascular coagulopathy marked by a fibrinogen level less than 300 mg per dL, a prolonged PT and PTT. If this occurs, large-bore intravenous lines should be placed and crystalloid and blood products should be given as quickly as possible in the form of packed red cells, fresh frozen plasma, cryoprecipitate, and platelets. A Foley catheter should be placed to monitor urine output and a central venous pressure catheter should be considered if urine output drops below 30 mL per minute.

Outcomes

Several significant adverse outcomes have been seen in association with placental abruptions. In a large epidemiologic study of placental abruption in the United States from 1995 and 1996 that incorporated over 7 millions births, the perinatal mortality rate was reported to be 119 per 1,000 births with abruption compared with 8.2 per 1,000 in all other births ([27]). Although there was significant mortality attributed to prematurity and growth restriction, the high perinatal death rate persisted. Term babies of normal size had a 25-fold higher mortality with an abruption than those without abruption. The pathophysiology regulating this outcome remains to be determined. In another similar epidemiologic study, abruption was also found to be associated with a very high risk for stillbirth (8.9-fold), preterm birth (39.6%), and growth restriction (14.3%). These investigators also evaluated outcomes related to the degree of abruption and found that all abruptions had a significant risk for stillbirth (RR of 31.5 for 75% abruption vs. RR of 5.5% for 25% abruption) ([28]).

Patients with an abruption should be counseled that there is a recurrence risk with an adjusted odds ratio of 6.4 and possibly as high as 25%. Efforts should be made to identify risk factors and to modify them. Fetal surveillance in subsequent pregnancies should be monitored starting at least two weeks before the gestational age at which the previous abruption was diagnosed in order to reduce the recurrence risk. Surveillance could consist of serial ultrasound scans for fetal growth restriction and

placental bleeds in combination with fetal biophysical profiles depending on when the gestational age surveillance is initiated.

Other outcome measures such as intraventricular hemorrhage, cystic periventricular leukomalacia, and cerebral palsy have been evaluated. All are seen in higher frequency among infants delivered because of an abruption. However, many of these infants were also growth- restricted, making it difficult to discern whether these adverse outcomes were attributed to the early gestational age, the abruption, or the growth restriction. Many of these studies were also plagued by small numbers of infants studied.

Prevention

There is no established protocol for the prevention of primary or recurrent abruption. Based on the risk factors that have been identified to date, a protocol could be established to educate patients on the signs and symptoms of an abruption, on how to avoid and report domestic abuse, on how to properly use their seat belts, and on the health-related effects of cigarette smoking. A nutritional educational program can focus on how to increase the patient's folic acid and iron intake. A social service contact can be established for those at risk because of a poor home situation and those engaged in hard physical activity. Ultrasound scanning should be used to scrutinize the integrity of the uterine wall in patients with a prior cesarean section and to identify other uterine or placental abnormalities, such as the presence of a myoma or septum and the placental location in relation to it. Finally, patients with medical illnesses such as hypertension should be seen frequently to optimize their medical well-being.

SUMMARY POINTS

- The workup of a patient who presents with third trimester bleeding should be methodical and thorough in order to optimize the neonatal outcome. The two major etiologies, placenta previa and placental abruption, are better diagnosed today by state-of-the art imaging. Best outcomes can be obtained by following a systematic approach. The risk factors for each should be identified in order to prevent similar future events (Fig. 20.8).

FIG. 20.8. Flow diagram summarizing recommended clinical management for bleeding in the third trimester. Individualization is warranted and the entire clinical picture must be factored into the management plan.

- There are two ways to classify a placenta previa: (a) By visual inspection or digital exam—marginal, partial, or complete; and (b) by transvaginal ultrasound—less than 1 cm, between 1 and 2 cm, or greater than 2 cm from the undilated internal cervical os.
- New imaging modalities including color Doppler ultrasound and MRI can improve on making the diagnosis of placenta previa, accreta, and abruption. This has minimized the need for a double setup exam in the case of a previa.
- Arterial embolization is becoming a standard means to decrease the need for a hysterectomy due to postdelivery bleeding from a previa.
- There are many risk factors for placental abruptions and the clinician should know them. When possible, the risks (i.e., cigarette smoking) should be modified to decrease the chance for abruption.
- Placenta previa and placental abruption can both lead to serious bleeding. However, placental abruption is more likely to lead to significant maternal coagulopathy.
- Expectant management is an acceptable plan for placenta previa and abruptions when the gestational age is preterm, there is no fetal distress, and the patient is stable.
- Amniocentesis should be routinely used in patients with placenta previa and abruption to document fetal lung maturity and plan delivery as soon as possible in these potentially unstable situations.

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Chapter 21

Dwight P. Cruikshank

Breech, Other Malpresentations, and Umbilical Cord Complications

BREECH PRESENTATION
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BREECH PRESENTATION

Breech presentation, the most common obstetric malpresentation, complicates approximately 4% of deliveries.

Definitions

Breech presentation is a polar alignment of the fetus in which the fetal buttocks present at the maternal pelvic inlet. Three types are recognized: frank, incomplete, and complete.

In frank breech presentation, the fetal hips are flexed and the knees extended, so that the thighs are apposed to the abdomen and the lower legs to the chest (Fig. 21.1). The buttocks are the most dependent part of the fetus. Frank breech presentation accounts for 60% to 65% of breech presentations; it is more common at term.

FIG. 21.1. Fetal attitude in frank, incomplete, and complete breech presentations.

In the incomplete breech presentation, the fetus has one or both hips incompletely flexed so that some part of the fetal lower extremity, rather than the buttocks, is the most dependent part (hence the terms *single footling* or *double footling*). This presentation accounts for 25% to 35% of breech presentations and is more common among premature fetuses.

Complete breech presentation is the least common type, accounting for about 5% of breech presentations. In this situation, the fetal hips and knees are both flexed so that the thighs are apposed to the abdomen and the legs lie on the thighs. A significant proportion of these fetuses convert to incomplete breech presentations if allowed to labor.

The position of the breech fetus is described with the fetal sacrum as the reference point; thus, it is right sacrum anterior, left sacrum posterior, left sacrum transverse, and so forth.

A spontaneous breech delivery is one in which the entire infant delivers vaginally without manual aid. In the unusual circumstance of a vaginal delivery of a singleton breech the recommended form is the assisted breech delivery, also known as partial breech extraction. In this delivery the fetus is allowed to deliver by the forces of uterine contractions and maternal bearing-down efforts until the fetal umbilicus has passed over the mother's perineum. After this, delivery of the legs, trunk, and arms are assisted manually; the head may be delivered manually or with forceps. A complete breech extraction, in which manual assistance is applied by traction in the groins or on the lower extremities before delivery of the buttocks, is contraindicated in singleton breech presentations.

Incidence

The incidence of breech presentation is closely associated with birth weight. Breech presentation accounts for 4% of births overall but occurs in 15% of deliveries of low–birth-weight (<2,500 g) infants. Furthermore, the smaller the infant, the higher the incidence of breech presentation, which rises to 30% among infants weighing 1,000 g to 1,499 g and to 40% among those weighing less than 1,000 g.

Viewed from another perspective, the association between breech presentation and low birth weight is even more striking. Only 70% of infants who present as breeches weigh more than 2,500 g; 30% weigh less than 2,500 g (compared with 5% to 6% of infants who are in vertex presentation), and 12% are of very low birth weight, weighing less than 1,500 g.

Cause

Factors that predispose to breech presentation are listed in Table 21.1. The importance of fetal anomalies cannot be overemphasized (Table 21.2). Malformations of the central nervous system complicate 1.5% to 2.0% of breech births: the incidence of hydrocephalus is ten-fold greater, and that of anencephaly two-fold to five-fold greater, than it is among infants presenting as vertex. Up to 1% of infants in breech presentation have a significant chromosomal abnormality: One in 200 has Down syndrome, and the incidence of other autosomal trisomies is increased as well. Of those infants presenting as breeches the incidence of major congenital anomalies is 17% among premature infants, 9% among term infants, and 50% among term infants who die in the perinatal period. It is prudent to keep these numbers in mind when deciding on a method of delivery for a fetus in breech presentation.

Fetal anomalies
Head anomalies
Anencephaly
Hydrocephalus
Chromosomal anomalies
Autosomal trisomies
Multiple anomaly syndromes
Uterine anomalies
Septate
Bicornuate
Unicornuate
Uterine overdistension
Polyhydramnios
Multiple gestation
High parity with lax abdominal and uterine musculature
Pelvic obstruction
Placenta previa
Myomata
Other pelvic tumors

TABLE 21.1. *Factors predisposing to breech presentation*

Type of malformation	Incidence (%)
Central nervous system	2.0
Hydrocephalus	0.6
Anencephaly	0.4
Trisomy 21	0.5
Cardiovascular	0.5
Gastrointestinal	0.5
Genitourinary	0.1
Overall among term infants	9.0
Overall among term infants who die	50.0

TABLE 21.2. *Congenital malformations among term Infants in breech presentation*

For many years an association between cerebral palsy and breech presentation (although not vaginal breech delivery) has been assumed. As it becomes apparent that most fetal insults leading to cerebral palsy occur before term, it appears that cerebral palsy is another cause of breech presentation. In fact, among term infants, the risk of cerebral palsy is not related to presentation after correcting for fetal growth restriction.

In more than 50% of cases, no causative factor for breech presentation can be identified.

Diagnosis

On abdominal examination, the first Leopold maneuver demonstrates the fetal head in the fundus. The third maneuver reveals the softer breech over the pelvic inlet. It is useful to remember that the head narrows down to the neck before attaching to the body, whereas there is no such tapering between the buttocks and body. Auscultation of fetal heart tones usually reveals them to be most easily detected in the upper quadrants of the uterus when the fetus is in breech presentation.

The diagnosis is often made by vaginal examination. In frank or complete breech presentation, the anal orifice may be felt, with the bony prominences of the ischial tuberosities directly lateral to it. Face presentation may be difficult to distinguish from frank breech presentation, with the fetal mouth being mistaken for the anus. It is helpful to remember that the mouth is surrounded by bone, whereas the anus is not. In incomplete breech presentations palpation of the feet on vaginal examination is diagnostic. During labor, any presentation that is not clearly vertex by vaginal examination should be confirmed by ultrasound.

Perinatal Mortality

Perinatal mortality is higher in breech presentation than in vertex, being four-fold greater among term infants and two- to three-fold greater among premature infants. Much of this excess mortality is not preventable; 64% of deaths among term infants in breech presentation are due to malformations or infection. Among premature infants, malformations, infection, maternal disease, and intrauterine death before labor account for 56% of perinatal mortality, and complications of prematurity unrelated to the method of delivery account for another 11%. Thus only about one-third of perinatal deaths among breech infants are due to potentially preventable factors. These factors basically fall into two categories: Trauma and asphyxia.

Trauma to the head is a significant risk in both term and premature infants who present in the breech position, regardless of the route of delivery. Unlike the situation in vertex presentation, in which the fetal head is in the maternal pelvis for hours or days during which molding can occur, the aftercoming head of the breech fetus must come through the pelvis as is—there is no time for molding. Thus, minor variations in maternal pelvic architecture, which would be insignificant in vertex presentation, may become major risks. This problem is compounded for the infant at less than 32 weeks of gestation in whom the head is the largest part. In these circumstances the fetal body may deliver through an incompletely dilated cervix, which then entraps the head. Performance of a cesarean does not ensure a traumatic delivery of the aftercoming head. An inadequate incision or suboptimal uterine relaxation may result in head entrapment leading to significant injury to the infant and mother.

Damage to fetal muscles, soft tissue, and viscera may occur with delivery if the fetus is grasped in places other than its bony pelvis. Likewise, delivery may be associated with nerve injury if the arms are not delivered properly, especially if there are nuchal arms. Finally, trauma to the cervical spinal cord may occur with delivery of a breech fetus with hyperextension of the neck.

Asphyxia may be caused by prolapse of the umbilical cord. The incidence of cord prolapse in term fetuses in frank breech presentation is 0.4%. In complete breech presentation, the incidence is 5% to 6%, and with incomplete breech presentation the incidence may be as high as 10%. Cord prolapse in incomplete breech presentation, although an indication for prompt cesarean delivery, is often not the devastating event that it is in vertex or frank breech presentation. Because the cord is prolapsed between the fetal legs, it often is not markedly compressed during subsequent contractions.

Not all of the excess asphyxia among fetuses in breech presentation is caused by overt cord prolapse. Abnormalities of the fetal heart rate pattern during labor are four to eight times more common in fetuses in breech presentation than fetuses in vertex. An unknown percentage of this is undoubtedly due to occult cord prolapse and other forms of cord compression.

Antepartum Management

Breech presentation diagnosed before 32 weeks gestation should be managed expectantly. The fetuses of approximately two-thirds of multiparas and one-third of primigravidas who are diagnosed as being in breech presentation before 32 weeks of gestation will convert to vertex presentation spontaneously before labor. Breech presentation that persists into the late third trimester should be evaluated by an ultrasound examination for congenital anomalies.

When a breech presentation persists beyond 32 weeks of gestation, some obstetricians have recommended attempts at converting the presentation to vertex by external cephalic version (ECV). Ranney reported his experience with 860 patients managed by external version. Attempts were made to turn the fetus to vertex whenever breech presentation was found in the third trimester, and some patients had repeated versions performed. Ranney was able to lower the incidence of breech presentation at term to 0.6%, about one-sixth the expected number, and encountered no fetal trauma or death and no increase in the incidence of placental abruptions.

The results of Kasule and co-workers are less optimistic. All patients with fetuses in breech presentation after 30 weeks of gestation were prospectively randomized to either an external version group (310 patients) or a control group (330 patients). The subjects in the external version group had the procedure performed between 33 and 36 weeks of gestation. If the first attempt failed, or if the fetus reverted to breech presentation, the procedure was repeated up to three times in subsequent weekly visits. No attempts at external version were made after 36 weeks of gestation. Although their immediate success rate was 80%, 46% of fetuses spontaneously reverted

to breech presentation. There were three perinatal deaths attributed to the procedure: two from abruptio placentae and one from premature labor and delivery. Most important, the incidence of breech presentation at delivery was 52% in the external version group and 51% in the control group, with 49% of fetuses in the control group converting to vertex presentation spontaneously before delivery. The authors surmised that many, if not all, of their successful external versions may have been in patients whose fetuses would have converted spontaneously had nothing been done. This hypothesis, coupled with the three perinatal deaths, led them to conclude that “there is no place for external cephalic version before 36 weeks gestation.”

The *Cochrane Database of Systematic Reviews* found three randomized trials of external version prior to 37 weeks of gestation. These studies showed no effect of ECV before term on the rate of breech presentation at delivery (risk ratio [RR] = 1.02; 95% confidence interval [CI] = 0.89–1.17), cesarean section (RR = 1.10; 95% CI = 0.78–1.54), low Apgar scores (RR = 0.81; 95% CI = 0.44–1.49), or perinatal mortality (RR = 1.19; 95% CI = 0.46–3.05). It was concluded that “in view of the lack of evidence of effectiveness, and reports from observational studies of unacceptably high complication rates from ECV before term, there is at present no place for ECV before term in modern obstetrics.”

If external version at term is to be attempted, it should be done in the labor and delivery suite, using monitoring of the fetal position and heart rate by ultrasound. In the past, the consensus was that no anesthesia should be used, pain being considered a reason to discontinue the attempt. As vaginal breech birth has become less of an option, however, a different approach has been proposed. This involves waiting until the pregnancy has progressed at least to 37 completed weeks of gestation, at which time epidural anesthesia is instituted. External version is attempted, and if successful, the patient has an immediate induction of labor; if unsuccessful, the patient is delivered by cesarean. In either case the epidural used for the external version attempt is used for the delivery as well. This approach seems to have merit, provided one is careful not to be overly aggressive with attempts at external version in an anesthetized patient.

Lau and associates reported a prospective case-control study of external version at term. They reported an overall success rate of 57% in nulligravidas and 84% in multiparas. They also found a rate of reversion to breech presentation of 4%. Complications included a 3.3% incidence of transient fetal bradycardia, and a 0.4% rate (one case) of what the authors called placental abruption. This particular patient had a 3-minute episode of fetal bradycardia and some vaginal spotting, although nothing suggesting abruption was found at the time of emergency cesarean. These same investigators have reported another series of 243 women who underwent attempts at external version. Regression analysis identified three independent predictors of failed version: engaged presenting part, difficulty palpating the fetal head, and nulliparity. The chance of success was 0% if all three variables were present, less than 20% if any two were present, 30% to 60% if only one was present, and 94% if none were present. Interestingly, placental location, position of the fetal spine, attitude of the fetal legs, and maternal obesity were not significant variables for predicting successful version, when the other variables were controlled.

Regarding ECV at term, the *Cochrane Database of Systematic Reviews* concludes that “the chance of breech birth and cesarean section may be substantially reduced by attempting ECV at term. The numbers are too small to give an accurate assessment of the risks of ECV. There is sound reason to use ECV at term, with appropriate cautions.”

It should be noted that successful external version does not necessarily reduce the cesarean rate to that found in other vertex presentations. Lau and colleagues reported a 32% cesarean rate in nulliparous patients after successful external version to vertex presentation; the rate in multiparous patients was 11%.

Active labor and ruptured membranes are contraindications to the procedure. Relative contraindications include an engaged presenting part and an estimated fetal weight of 4,000 g or more. Whether a previous cesarean contraindicates attempts at external version is uncertain, but in modern practice, delivery of breech fetus in a woman with a previous cesarean by elective repeat cesarean seems reasonable.

Management of Delivery

Term Breech Presentation Cheng and Hannah (1993) published a critical review of the literature on singleton term breech pregnancies, reviewing all articles in the English language literature between 1966 and 1992. They found that there were only 24 studies that presented results according to the intended mode of delivery, and which presented outcome data in sufficient detail to be analyzed. Of these 24 reports, only two were randomized trials; * eight were prospective cohort studies and 14 were randomized cohort studies. Twenty-two of these studies, including both prospective trials, did not demonstrate a statistically significant difference in corrected perinatal mortality between those patients for whom a vaginal delivery was planned and those for whom a cesarean was planned. Two series did show significantly worse outcome among those for whom vaginal delivery was planned. When the authors combined all of the data, they produced a “typical odds ratio” for perinatal mortality of 3.86 (95% CI = 2.22–6.69) in the planned vaginal delivery group. Their data on low 5-minute Apgar scores, birth trauma, and short- and long-term neonatal morbidity were similar to the data on perinatal mortality, in that the majority of individual studies did not find a difference between those for whom vaginal birth was planned and those for whom cesarean was planned. When the studies were combined, however, the planned vaginal delivery group fared worse in all categories (Table 21.3). The authors of this review carefully pointed out all of the flaws in the papers they reviewed, and concluded that most of these studies were too poorly done to allow definitive conclusions. They conclude their paper by stating “the only way to obtain more definitive information regarding the effectiveness of a policy of elective cesarean versus that of a trial of labor in women with breech presentation at term is to mount an appropriately sized, randomized controlled trial. In the absence of such a trial, a policy of elective cesarean delivery appears to be a reasonable option for the woman with breech presentation at term.”

	Planned cesarean	Planned vaginal delivery
Apgar <7 at 5 min	1.0	3.86 (2.22–6.69)
Birth trauma	1.0	3.96 (2.76–5.67)
Short-term morbidity	1.0	2.54 (1.74–3.71)
Long-term morbidity	1.0	2.88 (1.04–7.97)

CI, confidence interval.
Source: Cheng M, Hannah M. Breech delivery at term: a critical review of the literature. *Obstet Gynecol* 1993;82:605.

TABLE 21.3. *Neonatal morbidity, planned vaginal delivery vs. cesarean. Typical odds ratio and 95% CI*

In order to answer the question of the optimal route of delivery of the term breech, Hannah and associates organized the Term Breech Trial, a randomized trial of planned cesarean delivery versus planned vaginal birth for term singleton frank and complete breech infants. This trial was carried out between January 1997 and April 2000 in 121 hospitals in 26 countries. Sixteen were industrialized nations with low perinatal mortality rates, and ten were underdeveloped countries with high perinatal mortality rates. The results of this trial were published in 2000, and will be presented here in considerable detail because of the uniqueness and importance of the study. Patients were eligible for the trial if they were at 37 or more weeks of gestation with a singleton frank or complete breech. Women were excluded for clinical or radiographic evidence of pelvic inadequacy (91% of subjects in both groups had only clinical evaluation of the pelvis), if the fetus was estimated to weigh more than 4,000 g either clinically or by ultrasonography (60% of subjects had sonography, 40% had clinical evaluations of fetal weight), if hyperextension of the fetal neck was felt to be present by clinical exam (31% of subjects) or ultrasonography (69% of subjects), if there was a contraindication to labor or vaginal delivery, or if there were fetal malformations incompatible with life or predisposing to mechanical problems with vaginal delivery. The labor protocol permitted induction and augmentation of labor for usual indications, and called for either continuous electronic fetal monitoring or intermittent auscultation every 15 minutes in the first stage of labor and every 5 minutes in the second. Adequate labor progress was defined as a rate of cervical dilation of =0.5 cm per hour in the active phase, descent of the breech to the pelvic floor within 2 hours of the second stage, and imminent delivery within 1 hour of active pushing. The method of vaginal delivery was spontaneous or assisted; total breech extraction was not permitted. Most importantly, all vaginal deliveries were to be attended by a clinician experienced with vaginal breech delivery (self-defined with confirmation by the individual's department head). The primary outcomes measured were perinatal/neonatal morality and serious neonatal morbidity. The secondary outcomes measured were maternal mortality and serious maternal morbidity (Table 21.4). Power analysis prior to the study calculated a required randomization of 2,800 subjects. An interim analysis of the first 1,600 births revealed a clear advantage for planned cesarean, and therefore recruitment was stopped at 2,088 women (488 additional women had been enrolled while the interim analysis of the first 1,600 was in progress). In the final analysis, the rate of perinatal mortality and morbidity was 1.6% in the planned cesarean group and 5.0% in the planned vaginal delivery group (RR = 0.33; 95% CI = 0.19–0.56; $P < .0001$). Considering perinatal mortality alone, the respective rates for cesarean and vaginal delivery were 0.3% and 1.3% (RR = 0.23; 95% CI = 0.07–0.81; $P < .01$). Similar data for neonatal morbidity alone were 1.4% and 3.8% (RR = 0.36; 95% CI = 0.19–0.65; $P < .0003$). For every subcategory of neonatal morbidity, infants in the planned cesarean group fared significantly better than those in the planned vaginal delivery group. Most interestingly, the improvement in neonatal outcome with planned cesarean was better in the countries with already low perinatal mortality rates. The authors determined that in industrialized nations, one case of neonatal mortality or serious morbidity could be avoided for every seven additional cesareans, whereas in underdeveloped countries, as many as 39 additional cesareans might be needed to avoid one dead or compromised baby. For the entire population studied, the number of additional cesareans needed to avoid one dead or seriously injured baby was 14. The authors' finding of a significant advantage for planned cesarean birth was maintained even after excluding labors which were prolonged, induced, or augmented and after correcting for whether or not epidural anesthesia was used. Finally, and of equal importance, the authors found no differences between the groups in terms of maternal mortality or serious morbidity; there were no differences in maternal morbidity whether the various morbid conditions were totaled or considered separately.

Serious Neonatal Morbidity	
Birth trauma	
subdural, intracerebral or intraventricular hemorrhage	
spinal cord injury	
skull fracture	
peripheral nerve injury	
Seizures at <24 h of age	
Apgar score <4 at 5 min	
Cord blood base deficit ≥15	
Hypotonia for ≥2 h	
Stupor or coma	
Intubation and ventilation for ≥24 h	
Tube feeding for ≥4 d	
Neonatal intensive care unit admission >4 d	
Serious Maternal Morbidity	
Postpartum hemorrhage >1500 mL	
Need for blood transfusion	
D&C for bleeding or retained placenta	
Hysterectomy	
Cervical laceration extending into lower uterine segment	
Vertical uterine incision	
Vulvar/perineal hematoma	
Deep venous thrombosis/pulmonary embolism	
Pneumonia	
Wound infection/breakdown	
Bladder, ureter, or bowel injury	
Genital tract fistula	
Bowel obstruction	
Febrile morbidity (standard definition)	

Source: Hannah ME, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomized multicentre trial. *Lancet* 2000;356:1375–1383.

TABLE 21.4. *Primary and secondary outcomes in the Term Breech Trial*

The *Cochrane Database of Systematic Reviews* includes a systematic review of the three randomized, controlled trials of planned cesarean versus planned vaginal delivery for breech presentation (Collea and colleagues, 1980; Gimovsky and colleagues, 1983; Hannah and colleagues, 2000) and concludes “policy of planned cesarean section for term breech presentation is associated with a large decrease in perinatal/neonatal mortality, and neonatal morbidity, and a modest increase in maternal morbidity (RR = 1.29; 95% CI = 1.03–1.61). Overall the results clearly favor a policy of planned cesarean section.” Based on this information the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice issued Committee Opinion #265 in December 2001, concluding, “patients with a persistent breech presentation at term in a singleton gestation should undergo a planned cesarean delivery.” It is important to point out that they further stated “a planned cesarean delivery does not apply to patients presenting in advanced labor with a fetus in breech presentation in which delivery is likely to be imminent, or to patients whose second twin is in a nonvertex presentation” (see Chapter 14). There are many points on which one can criticize the Term Breech Trial. It is not a perfect study, but it is a good study. It brings real evidence to bear on the question of breech delivery, and given today's medicolegal and social climate, it may be the best evidence we are ever going to have. Two other points are pertinent. First, almost no obstetrician completing residency in the past 10 years has the training or experience to be skillful at vaginal breech delivery, and the cadre of obstetricians capable of imparting these skills is retiring or giving up obstetrics. Second, the argument that vaginal delivery is significantly safer than cesarean for the mother is becoming more and more difficult to prove. A growing number of studies, including the Term Breech Trial, have shown that maternal morbidity and mortality is as good or better with planned cesarean delivery as with vaginal birth. On the other hand, emergency cesarean or cesarean after a trial of labor is clearly more morbid than either elective cesarean or vaginal delivery. In nearly all recent series, including those in the Cochrane Database, 40% to 45% of women given a trial of labor for breech presentation eventually were delivered by cesarean, which greatly increases the overall risk of morbidity and mortality in the total group for whom vaginal breech delivery is planned. Two fairly large retrospective studies of term breech delivery from Sweden confirm the findings of the Term Breech Trial. Herbst and Thorngren-Jerneck published a series of 1,050 term singleton breeches delivered at a single institution between 1988 and 2000. A planned vaginal delivery group of 699 women was compared to a planned cesarean group of 327. Acidemia at birth, low 5-minute Apgar scores, neonatal intensive care unit admissions, and the rate of neonatal neurologic morbidity were all significantly greater among infants in the planned vaginal delivery group. Roman and associates studied 15,818 term singleton breeches delivered in Sweden between 1987 and 1993. A summary of their neonatal data is shown in Table 21.5 and demonstrates a clear advantage for cesarean delivery. Of significant importance, the authors found the same rates of maternal morbidity for elective cesarean (1.7%) and vaginal delivery (1.8%). The maternal morbidity rate for emergency cesarean was 2.8%.

TABLE 21.5. *Neonatal outcome, cesarean vs. vaginal breech delivery (OR and 95% CI)*

Given the data from these studies I believe it is time to consider the matter settled. Unless and until another large, randomized, controlled trial reveals different findings from what is known from these studies, the route of delivery for the term singleton breech should be cesarean.

Premature Breech Presentation Almost no randomized prospective data are published regarding delivery of the premature infant in breech presentation. Penn and co-workers attempted a multicenter, randomized, controlled trial in 26 hospitals in England, in an effort to determine the optimal mode of delivery for breech infants at gestational ages between 26 and 32 weeks. After 17 months of attempting to enroll patients the study was abandoned because only 13 women from 6 hospitals had been recruited. The authors stated, “The low accrual rate was due to clinicians' reluctance to randomize eligible women.” Eller and VanDorsten polled the Maternal-Fetal Medicine Units network and found 7 of 11 centers willing to do a randomized controlled trial comparing cesarean to vaginal birth for breech infants between 24 to 28 weeks of gestation; because of small numbers they calculated this study would require at least 10 years. No center in the network was even willing to study breech birth in pregnancies greater than 28 weeks of gestation. Therefore, management decisions regarding the premature breech must be made based on retrospective data, which suffer from serious shortcomings. These data, however, all indicate that cesarean delivery is preferable for the premature breech.

The Effect of Parity To separate primigravidas whose fetuses are in breech presentation as a group needing cesarean delivery is fallacious for two reasons: First, there are no data to suggest that primigravidas are at more risk than parous women for fetal injury, cord prolapse, difficult vaginal delivery, or perinatal death. Second, this philosophy implies that a parous woman in labor with a fetus in breech presentation is not at very high risk. The parous woman is at no less risk than the multiparous woman because a subsequent fetus may be larger than previous infants delivered, and because the pelvis may be adequate for vertex presentation but not for the unmolded head of a breech fetus.

Extension of the Fetal Neck Ballas and Toaff demonstrated that when the fetal neck is hyperextended to an angle of greater than 90 degrees (Fig. 21.2), vaginal delivery is associated with a 70% incidence of fetal spinal cord transections. This complication is avoided by cesarean delivery if generous abdominal and uterine incisions are employed, and the head is delivered slowly while attempts are made to flex the neck.

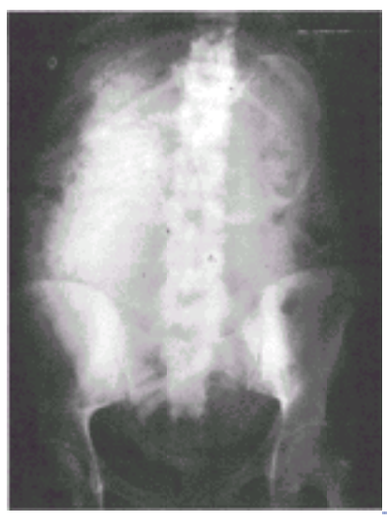

FIG. 21.2. Hyperextension of the fetal neck.

Management of Vaginal Delivery Occasionally a patient will arrive at the hospital in the process of delivering a breech infant. In such circumstances, a vaginal delivery is probably less traumatic to both infant and mother than a rushed cesarean under suboptimal emergency conditions. The Cochrane Review anticipates this problem without providing a solution, stating “one problem with a policy of routine cesarean section for breech presentation at term is that in time the skills of breech delivery will be lost, placing women who deliver before cesarean section can be carried out at increased risk.” To prepare as much as possible for such circumstances, given the paucity of actual experience with vaginal breech delivery, all obstetricians should frequently review the principles of vaginal breech delivery. Vaginal delivery of a fetus in breech presentation requires the attendance of at least an obstetrician and an anesthesiologist. It is preferable to have a pediatrician in attendance as well. The fetal monitor should be taken to the delivery room, and monitoring should be continued until one is committed to a vaginal delivery. Such a commitment occurs when the fetal umbilicus passes over the mother's perineum, at which time the fetal head is in the maternal pelvis. Traction on the fetus before that point constitutes a total breech extraction and should be avoided. Once the fetal umbilicus passes over the maternal perineum, a loop of cord 4 to 6 inches in length should be brought down to prevent subsequent excessive traction on the cord. The legs may then be delivered by flexing the knees and sweeping the legs out from in front of the fetus. A towel is placed around the fetal pelvis, which is then grasped, and downward traction is applied until the fetal scapulae pass under the maternal symphysis. Then the fetal body is rotated so that the shoulders are in an anteroposterior position, and the anterior arm is flexed and swept out under the symphysis. The fetus is then rotated 180 degrees in the direction that will keep the fetal back toward the maternal symphysis, and the other arm is swept out in a similar manner. It is important during delivery of a breech that the fetus not be allowed to assume a position with the fetal face or abdomen toward the maternal symphysis. If the breech infant is delivering so rapidly that cesarean birth is not feasible, the aftercoming head usually delivers spontaneously. Should this not occur, delivery of the fetal head with Piper forceps will be necessary. An assistant must support the fetal body during application of these forceps (Fig. 21.3). The temptation to elevate the fetal body to provide better visualization must be resisted, because this maneuver hyperextends the neck. Rather, the fetal body should be supported parallel to the floor, and the operator should

drop to the knee for application of the forceps. The application is pelvic rather than cephalic, with the forceps being applied to the lateral aspects of the maternal pelvis, not wandered around from the posterior using landmarks on the fetal head, as one would do in vertex presentation. Controlled delivery of the fetal head is then accomplished, with suctioning of the fetal airway as soon as the mouth passes over the perineum.

FIG. 21.3. Breech delivery with Piper forceps to the aftercoming head. Note that the infant's body is being supported parallel to the floor.

A generous episiotomy is necessary for any vaginal breech birth. For the term-sized infant, a mediolateral episiotomy is appropriate.
Management of Cesarean Delivery Abdominal delivery does not guarantee a traumatic birth of the fetus in breech presentation. Just as in vaginal delivery, it is important to grasp the fetal bony pelvis rather than soft tissue during extraction. The most serious complication is head entrapment by the uterus contracting down around the neck after delivery of the body. Some physicians have advocated a vertical uterine incision so that it may be extended should this occur. This may be the best choice for the premature fetus accompanied by a poorly developed lower uterine segment. Because such an incision compromises future childbearing, the obstetrician should perform a low transverse cervical incision for the term fetus or the premature fetus when labor has resulted in a well-developed lower segment. Such an incision can be extended in a J-shaped (rather than a T-shaped) manner, if necessary. A technique that may obviate the need for this in the face of head entrapment is general anesthesia with an agent that rapidly relaxes the uterus. The anesthesiologist should be alerted that this might become necessary even if the cesarean is begun under regional anesthesia.

FACE PRESENTATION

In face presentation, the fetal neck is hyperextended so that the occiput touches the back. The presenting part is that part of the fetal face between the orbital ridges and the chin (Fig. 21.4). The incidence is approximately one in 550 births.

FIG. 21.4. Face presentation.

Cause

Proposed causative factors include anencephaly, high parity, contracted pelvis, large infant, small infant, and nuchal cord. It is interesting to note that, in the majority of studies, one of the larger categories is that in which no causative factor can be identified; this varies from 2% to 97%, with an average frequency of 38%.

Anencephalic fetuses frequently present by the face if the fetal presentation is cephalic. However, because the course and mechanism of labor, management of delivery, and perinatal outcome are entirely different in this situation, these cases should be excluded from consideration of face presentation. The association between face presentation and anencephaly is important to remember, however, because when face presentation is suspected clinically, ultrasound studies are indicated to rule out this anomaly.

Most series demonstrate an association between high parity and face presentation; whether this relation is causal is not clear. The average reported incidence of contracted pelves in series of face presentations is 15%. In reality, the incidence is probably much lower, because in most series only those patients with arrested labor were studied radiographically. Contracted pelvis or cephalopelvic disproportion is probably diagnosed clinically with excessive frequency in face presentation, because the extended head feels larger on abdominal palpation and because the head is often floating at the onset of labor. However, if large series of radiographically diagnosed pelvic contraction are examined, it is rare to find a case of face presentation, none being reported in three series of radiographically diagnosed pelvic contraction totaling more than 700 patients. The weight of evidence seems to indicate that pelvic contraction is not of causative significance in face presentation.

Some authors associate face presentation with large infants, on the assumption that cephalopelvic disproportion may result from excessive fetal size in spite of a normal pelvis. The argument that large infants cause cephalopelvic disproportion, and thus face presentation, is weakened by the high proportion of vaginal deliveries in most series of face presentations. Furthermore, the average incidence of large infants (variously defined) in series of face presentations is 12%, not significantly different from that in the general obstetric population.

Many series have demonstrated an increased proportion of low-birth-weight infants among face presentations and ascribed causative significance to prematurity, although other studies have found no excess of low–birth-weight infants. Part of the discrepancy results from the inclusion of anencephalic fetuses in many series—fetuses that usually are small for gestational age. The average incidence of low birth weight is 11% in those series of face presentation in which it is possible to exclude anencephalics; this is not significantly different from the incidence of low birth weight in the general population. Thus it is difficult to conclude that low birth weight or prematurity are causative factors in face presentation.

Nuchal cord occurs in approximately 25% of cephalic deliveries. The average incidence of nuchal cord in face presentation is 10%. Nuchal cord is not a cause of face presentation.

Of all the proposed causative factors in face presentation, there is no unanimity of opinion regarding their significance, and as reported by Cruikshank and Cruikshank, none can withstand careful scrutiny. There does seem to be an association between face presentation and high parity, but 34% of face presentations occur in primigravidas. All of the postulated causes presume that face presentation develops after the onset of labor. Cases of face presentation that occur before labor are called primary and are thought to be due to increased tone in the extensor muscles of the fetal neck. The usual attitude of the fetal neck is flexion caused by greater tone in the flexor muscles, but occasionally infants are seen in whom the extensors predominate. In addition to face presentation, hyperextension of the neck occurs in transverse lie (i.e., “flying fetus”) and in breech presentation; in fact, up to 5% of breech fetuses have hyperextended necks.

To ascertain the true incidence of primary face presentation, it is necessary to examine large series of x-ray films obtained before labor. In three such series, seven primary face presentations were found among 1,762 patients, an incidence of one face presentation in 251 cases, which is more than twice the reported incidence of face presentation at delivery. These data, coupled with the uncertainties surrounding the proposed causative factors, make it most likely that all face presentations are primary and intrinsic to the fetus and that there are no significant causative factors. The preponderance of multiparas in series of face presentation is compatible with this theory. Increased extensor muscle tone cannot cause extension of the neck if the head is fixed in the pelvis; thus, face presentation is less likely to occur during the last 1 to 2 weeks of pregnancy in a primigravida with an engaged presenting part than in a multipara in whom the head often is not engaged until after the onset of labor.

Diagnosis

The diagnosis usually is made by vaginal examination during labor followed by ultrasound studies. Face presentation is rarely diagnosed prior to the onset of labor, with 35% of cases being diagnosed in the first stage, 27% in the second stage, and 35% at the time of delivery. At the time of diagnosis, 60% of face presentations are mentum (chin) anterior (MA), 15% are mentum transverse (MT), and 25% are mentum posterior (MP).

Mechanism and Course of Labor

In face presentation, the presenting diameter is the tracheloparietal (trachelobregmatic), which is 0.7 cm longer than the presenting diameter in vertex presentation (the suboccipitobregmatic). Internal rotation in face presentation occurs between the ischial spines and the ischial tuberosities, lower than in vertex presentation. After internal rotation to MA has placed the fetal chin under the maternal symphysis, delivery occurs by flexion of the fetal neck. It is important to remember that in face presentation, the distance from the leading edge to the largest presenting diameter is greater than that in vertex presentation. Thus, engagement of the presenting part probably has not occurred until the face is at a +2 station.

Safe vaginal delivery of a term-sized, persistent MP is impossible for two reasons: the short fetal neck cannot span the full length of the maternal sacrum so the fetal head and shoulders must enter the maternal pelvis at the same time, and even if this should occur, the persistent MP would have to deliver under the symphysis by extension, but the neck is already maximally extended. Many MPs will spontaneously rotate and convert to MA; the average reported rate being 35%. This may be an artificially low value because, as pointed out earlier, rotation does not occur until the head is well down in the pelvis. Surgical intervention before that point would make the incidence of spontaneous rotation seem lower. In fact, some series report spontaneous rotation rates of 50% to 65%. When the face is MT at the time of diagnosis during labor, spontaneous rotation to MA usually occurs.

Most patients with face presentations have durations of the first stage of labor similar to those of patients with vertex presentations, although there may be some prolongation in MP presentations. Likewise, the length of the second stage is similar to, or only slightly longer than, that in vertex presentation.

Management

The average reported incidence of spontaneous or elective low forceps delivery in face presentation is 72% (range, 40% to 90%). The average rate of cesarean delivery is 15%, and in only two series was it greater than 29%. In older series, up to 12% of face presentations were delivered by various operative vaginal procedures, including midforceps rotation, version and extraction, and manual conversion of face to vertex (Thorn maneuver). These procedures are associated with high perinatal mortality and maternal morbidity, and there is no place for them in the modern management of face presentation.

Face presentation alone is not a contraindication to oxytocin stimulation of labor, and it can be done for the same reasons and with the same precautions as in vertex presentation. Likewise, outlet forceps delivery in MA presentation can be accomplished using the same criteria one would use in vertex presentation, but midforceps delivery in face presentation should be abandoned. Because of the altered diameters of the presenting part, if the face is not bulging the perineum, any forceps delivery is probably a midforceps operation and should not be attempted.

The old adage “if a face is progressing, leave it alone” is still valid. This applies to MT and MP presentations as well as to MA, because of the likelihood that these presentations will convert to MA. Rotation may not occur, however, until the presenting part is on the pelvic floor. In any face presentation, as in vertex presentation, if progress in dilation and descent ceases despite adequate contractions, delivery should be accomplished by cesarean. Conversely, as long as dilation and descent continue, management should be expectant.

The only series using fetal monitoring extensively in the management of face presentation reported variable decelerations in 59% of 29 infants, severe variables in 29%, and late decelerations in 24%. Only 14% of patients in the study (4 of 29) had no fetal heart rate abnormality. It seems plausible that the increased incidence of fetal heart rate abnormalities is due in part to abnormal pressure on the extended head, neck, or eyes, similar to the mechanism of heart rate abnormalities described in occiput posterior presentations. Therefore, face presentation is an indication for electronic fetal monitoring.

BROW PRESENTATION

In brow presentation, the fetal neck is midway between flexion and hyperextension, and the presenting part is that portion of the head between the orbital ridges and the anterior fontanelle. Brow presentation is less common than face; the reported incidence is approximately one in 1,400 births.

Cause

As in face presentation, numerous factors have been proposed as causative in brow presentation. Most series report a few cases of brow presentation associated with placenta previa, polyhydramnios, uterine anomalies, and fetal malformations, but these are no longer seriously proposed as causes of brow presentation. Likewise, the reported incidence of nuchal cord in brow presentation is lower than that in the general obstetric population, and nuchal cord seems to be related to brow presentation only by coincidence. The average incidence of low birth weight among brow presentations is 13%; this does not seem to be etiologically significant. Most data suggest however that cephalopelvic disproportion is more commonly associated with brow presentation than with face presentation.

Many authors believe that brow presentation, like face presentation, is nearly always primary (i.e., caused solely by factors intrinsic to the fetus). Others believe that brow is an unstable or transitional presentation, representing a head in the process of converting from vertex to face presentation or vice versa. If this is true, and if, as proposed, all face presentations are primary, then all brow presentations must likewise be primary. If so, how can the apparent association between brow presentation and cephalopelvic disproportion be explained? Two factors seem relevant:

1. “Relative” cephalopelvic disproportion is more likely to occur in brow presentation because the presenting diameters of the fetal head are greater than in face or vertex presentation (see “ Mechanism and Course of Labor” below).
2. Persistent brow presentation probably selects for patients with smaller pelves, because in patients with larger pelves, the brow may convert to face or to vertex before being recognized.

Diagnosis

The diagnosis is nearly always made by vaginal examination or sonographic studies, or both. Most cases are diagnosed in labor, with approximately one-half diagnosed during the second stage. If labor is progressing, the diagnosis is often missed until late in the second stage of labor.

Mechanism and Course of Labor

When the fetal head engages as a brow presentation, there are three possible mechanisms of labor, depending on whether the brow converts to a face, converts to a vertex, or persists as a brow. Spontaneous conversion to face or vertex occurs in approximately 50% of cases, with 30% converting to face and 20% to vertex. However, in those series in which the brow presentation was diagnosed early in labor, spontaneous conversion rates of 67% to 75% are reported. In fact, many occiput posterior presentations probably enter the pelvis as brows but are never diagnosed as such.

Regardless of the eventual outcome, the brow usually engages transversely at the pelvic brim. The engaging diameter is the mentoparietal, which is about 1.5 cm longer than the engaging diameter in vertex presentation and 0.8 cm longer than that in face presentation.

Most would agree that there is no mechanism of labor for a term-sized, persistent brow under most circumstances, and therefore vaginal delivery is impossible. Vaginal delivery however can occur if the fetus is quite small or the pelvis very large.

Most series report a definite prolongation of labor with brow presentation, but the duration of labor in those patients who eventually convert to face or vertex is no different from the duration of labor with vertex presentation. It would seem that those cases destined to convert to face or vertex and deliver spontaneously have normal to slightly prolonged labor, whereas those destined to persist as brows often have very prolonged labors unless timely intervention is undertaken.

Management

The best recommendation for management of brow presentations is the same as that for face presentations. If dilation and descent are progressing normally, expectant management is best. If progress ceases, delivery should be by cesarean. The association of cephalopelvic disproportion with brow presentation may contraindicate the use of oxytocin to stimulate labor. Forceps deliveries are acceptable if the brow converts to MA face or vertex. Persistent brow presentations, once progress in labor has ceased, require delivery by cesarean, and all forceps operations are contraindicated.

In assessing whether progress in labor has stopped, it is important to remember that if the fetus becomes arrested at the pelvic brim, tremendous caput succedaneum

may form over the brow, giving a false impression of descent of the head.

SHOULDER PRESENTATION (TRANSVERSE LIE)

When the long axis of the fetus lies perpendicular to that of the mother, the condition is termed a *shoulder presentation* or *transverse lie*. This malpresentation complicates one in 300 births.

Definitions

In transverse lie, the fetal head lies in one maternal iliac fossa and the buttocks in the other. A better term for this would be *transverse presentation*, but this term is avoided because it is often confused with transverse position of vertex presentation. Because the fetal shoulder usually lies over the pelvic inlet, the formal term is shoulder presentation, which should be considered synonymous with transverse lie. The fetal position is described with the fetal acromion used as a reference point and is termed *left or right acromion*, according to which side of the mother the fetal shoulder is directed. Because the fetal back may be directed anteriorly, posteriorly, superiorly, or inferiorly, the additional qualifying terms *dorsum superior, dorsum anterior*, and so on are used as well. Thus, a fetus with its head on the mother's left and its back toward the mother's head would be described as left acromion dorsum superior.

If one fetal pole lies in a maternal iliac fossa and the other pole lies in the opposite upper quadrant of the uterus, the lie is said to be oblique or unstable.

Cause

The most common causative factors are high parity with lax abdominal wall and uterine musculature, and conditions in which the fetus is small in relation to the volume of the uterus (i.e., prematurity and polyhydramnios). Shoulder presentation may also be caused by anything that prevents descent of a fetal pole into the maternal pelvis, such as pelvic contraction, placenta previa, lower uterine segment myoma, or an ovarian tumor in the cul-de-sac. These conditions should be kept in mind for any patient who presents with a transverse lie, but especially in the patient of low parity who has this malpresentation at or near term.

Diagnosis

The diagnosis usually can be made by physical examination of the maternal abdomen, with the fetal head and buttocks palpable in the iliac fossae and no fetal pole at the pelvic inlet. A very high or unreachable presenting part on vaginal examination suggests transverse lie. All such findings should be confirmed by ultrasound.

Mechanism of Labor

The tiny fetus in transverse lie may deliver by the mechanism of conduplicato corpore, in which the fetal body doubles up on itself and the fetal head and buttocks enter the maternal pelvis simultaneously. This is often associated with rupture of fetal abdominal viscera.

If the fetal weight is greater than about 800 g, there is no mechanism of labor. Uterine contractions will wedge the fetal shoulder into the maternal pelvis, and eventually the membranes will rupture and the fetal arm will prolapse into the vagina. Such a condition is termed a *neglected transverse lie.* If labor is permitted to continue, there will be progressive thinning of the lower uterine segment, a Bandl retraction ring will form, the uterus will rupture, and eventually both the fetus and the mother will die.

Management

Shoulder presentations diagnosed before term should be managed expectantly, because most will convert to polar presentations before labor. If the patient is not at term but the cervix is significantly dilated (> 3 cm), hospitalization and bed rest should be considered as the incidence of cord prolapse in such a patient is 10% to 15% should rupture of membranes occur.

If the patient is at term (37 or more completed weeks gestation), external version may be attempted with the same techniques and precautions as described for breech presentation. Induction of labor may be undertaken immediately if the version is successful and the cervix favorable. External version may also be attempted in early labor; provided the membranes are intact and no fetal part has entered the pelvis. Before any version attempt, ultrasound should be used to rule out placenta previa and pelvic masses.

If the patient is in active labor or has ruptured membranes, and the fetus is of a gestational age to be considered viable, delivery must be by cesarean. Because of exceedingly high morbidity and mortality for both mother and fetus, there is no role for internal version and extraction in the management of transverse lie in singleton gestation. Because the lower uterine segment may be poorly developed, vertical uterine incisions are often necessary. If, however, the fetus can be manipulated to a polar presentation after opening the abdomen but before entering the uterus, a low transverse incision may be performed. This usually is possible only if the membranes are still intact.

The patient with a neglected transverse lie is an obstetric emergency. Usually she is septic, and often the fetus is dead. If the uterus is still intact, it is exceedingly thin. Some patients will be completely dilated on arrival at the hospital, but the temptation to try vaginal maneuvers such as internal version must be resisted as this will often result in uterine rupture and may lead to maternal death. Such patients should have basic laboratory studies, coagulation indices, and blood cultures obtained. Rapid intravenous hydration and antibiotic therapy should be instituted, type-specific blood should be available, and the patient should be taken promptly to the operating room for cesarean delivery. Cesarean hysterectomy is often the best procedure for such patients, especially if the uterus has ruptured or is grossly infected. In the past, various vaginal fetal destructive procedures were described for treating the neglected transverse lie with a dead fetus. Given that obstetricians today have almost no training in such procedures, they should be abandoned in favor of cesarean delivery, even in the face of a dead fetus.

COMPOUND PRESENTATION

A compound presentation occurs whenever some part of a fetal extremity is prolapsed alongside the presenting part. By far the most common type is vertex/hand or vertex/arm, in which some part of the upper extremity is alongside the head. Much less common types are breech/arm and vertex/foot. The reported incidences range between one in 400 and one in 1200 births.

Cause

Situations in which the presenting part fills the pelvis poorly predispose to compound presentation. The most obvious of these is prematurity, which is associated with most compound presentations. In fact, the incidence of this complication among infants who weigh more than 1,500 g is only one in 1,600 births.

Diagnosis

The diagnosis almost invariably is made by vaginal examination and generally is made late in labor. At least 50% of these malpresentations are diagnosed in the second stage of labor. Whenever a fetal hand or arm is palpated on vaginal examination, the examiner must be certain that the fetal head is in the pelvis as well, before concluding that the presentation is compound. If the head is not easily palpated in the pelvis in such circumstances, most likely the diagnosis is shoulder presentation with a prolapsed arm, a much more serious and urgent obstetric condition.

Management

Management of vertex/arm and vertex/hand presentations should be expectant. One of three outcomes will occur:

- the prolapsed part will withdraw back up into the uterus as labor progresses
- the baby will deliver with the arm or hand alongside the head
- progress in labor will cease, in which case cesarean delivery is indicated.

The reported incidence of cord prolapse in compound presentation is 10% to 20%, but many of these are related to attempts to replace the prolapsed arm into the uterus, which often necessitates upward displacement of the fetal head. For this reason, attempts at replacement of the prolapsed part in compound presentation

should be avoided.

Because of the increased incidence of cord prolapse, electronic fetal monitoring should be used in these situations. Vertex/arm and vertex/hand presentations are not indications for cesarean delivery in and of themselves. Indications for cesarean delivery in such circumstances include failure to progress in labor, cord prolapse, and fetal distress.

Cases of breech/arm presentation should be managed as any other breech presentation would be managed. Cases of vertex/foot presentation are rare, but those few reported cases have a perinatal mortality two to three times that of other compound presentations, and are best managed by cesarean delivery. In essence, these are variants of shoulder presentation.

There is no role for internal version and extraction in the modern management of compound presentation, although this was commonly done in the past.

UMBILICAL CORD COMPLICATIONS

The mean length of the umbilical cord at term is 55 to 60 cm, and the normal range (5th to 95th percentile) is 35 to 80 cm. The longest umbilical cord reported measured 129 cm. The length of the cord is related to fetal activity in the first two trimesters; there is little change in the length of the cord after 28 weeks of gestation. At term, mean cord length is slightly (1.6 cm) but significantly longer in male fetuses compared with females, and is 4.5 cm greater in vertex infants compared with breech. There is no correlation between cord length and either fetal or placental weight.

Cord Prolapse

The reported incidence of prolapse of the umbilical cord varies between 0.2% and 0.6% of births. Cord prolapse almost never occurs with cords shorter than 35 cm; the incidence is 0.4% with normal-length cords (35–80 cm) and 4% to 6% with cords longer than 80 cm. Besides excessive cord length, other causative factors include malpresentation in approximately 50% of cases, low birth weight (<2,500 g) in 30% to 50% of cases, grand multiparity (more than five pregnancies) in 10% of cases, multiple gestation in 10% and obstetric manipulation, including artificial rupture of membranes, in 10% to 15%. Table 21.6 shows the association between cord prolapse and malpresentation, especially with nonfrank breech, compound, and shoulder presentations. Nearly 50% of cord prolapses occur during the second stage of labor.

Presentation	Incidence (%)
Vertex	0.14
Breech	2.5–3.0
Frank	0.4
Complete	5.0
Incomplete	10.0
Shoulder (transverse lie)	5.0–10.0
Compound	10.0–20.0
Face-brow	Rare

TABLE 21.6. *Incidence of cord prolapse*

The diagnosis of cord prolapse should be suspected in any patient who develops fetal heart rate abnormalities after rupture of the membranes, either spontaneous or artificial. The heart rate abnormalities usually observed are sustained bradycardia and, less frequently, profound variable decelerations (Fig. 21.5). All such patients should be promptly examined or reexamined and the diagnosis confirmed by palpation of the cord alongside the presenting part or in the cervix or vagina.

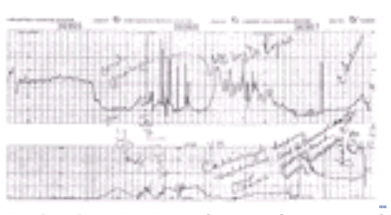

FIG. 21.5. Fetal monitor tracing associated with umbilical cord prolapse.

When cord prolapse is diagnosed, every effort should be made to prevent compression of the cord by the presenting part. The patient should be placed in steep Trendelenburg or the knee–chest position, and the presenting part should be manually elevated as far out of the pelvis as possible and held there until delivery is accomplished. Once the diagnosis is made, further palpation of the cord must be avoided, because this causes spasm of the umbilical arteries and may further compromise the fetus. Confirmation of fetal cardiac activity should be by ultrasound rather than by cord palpation. In fact, ultrasound is the only certain way to confirm fetal viability. There are at least two reported cases in which nonpulsatile cords were palpated and no fetal heart tones were heard with Doppler or stethoscope but ultrasound revealed fetal heart rates of 50 to 80 beats per minute. In both cases, prompt delivery resulted in surviving infants.

Cesarean delivery is the treatment of choice in almost all cases if there is fetal cardiac activity. Even at complete dilation, the perinatal outcome is better with cesarean delivery than with such maneuvers as breech extraction or high forceps. If the fetus is dead with no fetal cardiac activity present by ultrasound, and the fetal lie is polar, the mother usually is better served by allowing continued labor and vaginal delivery.

In most series of cord prolapse, perinatal mortality is approximately 15%. Among term infants and among all infants delivered by cesarean within 10 minutes of cord prolapse, mortality is less than 5%. Murphy and Mackenzie reported a retrospective study of 132 consecutive cases of cord prolapse in a single hospital. The overall perinatal mortality was 9% (12 of 132 infants). However, all but one death was due to either extreme prematurity or congenital malformations; the perinatal mortality rate attributable to asphyxia was 0.8% (one case). Of the 120 survivors they reported, only one infant had a major neurologic handicap.

True Knots

The reported incidence of true knots in the cord is 0.3% to 2.1% of births, the mean being about 1.0%. As is true of all cord accidents, true knots are more common if the cord is abnormally long. Ten percent of true knots occur in cords greater than 80 cm in length, and 3% of cords longer than 80 cm have true knots. However, many true knots must form early in pregnancy, for the incidence in aborted fetuses is 0.9%. True knots can be diagnosed only after delivery in the vast majority of cases, because unless the knot is pulled tight, there is no reduction of flow or increase in perfusion pressure, and thus no abnormality of the fetal heart rate or Doppler velocimetry. The patient with a tight knot will demonstrate a typical cord pattern of variable decelerations (Fig. 21.6) and will, of necessity, be managed like any other patient with fetal heart rate abnormalities.

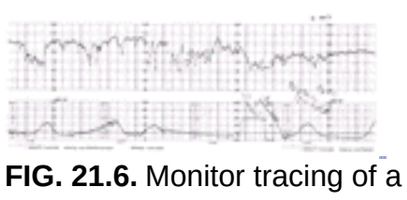

FIG. 21.6. Monitor tracing of a fetus with a tight true knot in the umbilical cord.

The Collaborative Study of Cerebral Palsy found no difference in 5-minute Apgar scores or neurologic abnormalities at 1 year of age between controls and infants born with true knots in the cord. There is an association however between true knots and antepartum stillbirths. About 4% to 5% of stillborns have true knots in the cord, compared with 1% of live-born infants.

Nuchal Cord

The incidence of loops of umbilical cord around the fetal neck is 25% of live-born infants, with 21% having one loop around the neck and 4% having two or more. In fact, 0.1% of fetuses have four or more loops of nuchal cord; the maximum reported number is nine. The incidence is 14% with short cords (<35 cm), 23% with normal length cords, and 53% with cords longer than 80 cm. There is no evidence that nuchal cords cause fetal death or significant degrees of fetal distress. The Collaborative Study of Cerebral Palsy found no increase in the incidence of depressed 5-minute Apgar scores, perinatal mortality, or abnormal neonatal development among infants with nuchal cords. It did demonstrate reduced 1-minute Apgar scores in these infants, however. Although nuchal cords are at times diagnosed by ultrasound, the excellent outcome of these infants demonstrates that no alteration in management is indicated unless the fetus develops bona fide distress during labor.

Body Coils of Cord

The incidence of coils of umbilical cord around various parts of the fetal body other than the neck is 0.5% to 2.0%, and is more frequent with long cords. As with nuchal cords, body coils are not associated with any increase in low Apgar scores, perinatal mortality, or neonatal morbidity.

SUMMARY POINTS

- The singleton breech fetus at term should be delivered by cesarean. This is a level A recommendation based on type I evidence.
- The preterm singleton breech at 28 weeks of gestation and beyond should be delivered by cesarean. This is a level A recommendation based on type II-2 evidence. There is no real evidence about the optimal mode of delivery of the singleton breech at 24 to 27 weeks of gestation.
- In the absence of contraindications, external cephalic version (ECV) should be attempted at term in singleton breech fetuses. At present there is no role for ECV before term.
- Fetal anomalies and chromosome abnormalities are important causes of breech presentation. Likewise, fetuses that have sustained neurologic insults leading to cerebral palsy often present as breeches.
- Nearly all cases of face presentation and compound presentation should be managed expectantly and vaginal delivery anticipated. Persistent mentum posterior (MP) face, persistent brow, and essentially all cases of shoulder presentation should be delivered by cesarean.

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Footnote

*The papers of Collea and colleagues (1980) and Gimovsky and colleagues (1983) deserve special mention as “classic papers.” They are the only two published randomized trials of term breech delivery in all obstetric history prior to the year 2000.

Chapter 22

Donald J. Dudley

Complications of Labor

KEYS TO THE MANAGEMENT OF NORMAL LABOR
EPIDEMIOLOGY OF DYSTOCIA
ETIOLOGY OF DYSTOCIA
Primary Dysfunctional Labor
Cephalopelvic Disproportion
Abnormal Position of the Fetal Head
Asynclitism
Fetal Abnormalities
SPECIFIC LABOR ABNORMALITIES
Prolonged Latent Phase
Arrest of Dilation
Arrest of Descent
Protracted Active Phase
Prolonged Second Stage
EPIDURAL ANALGESIA AND LABOR PROGRESS
OPTIONS FOR THE MANAGEMENT OF DYSTOCIA
Mapping the Progress of Labor
Amniotomy
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Cesarean Delivery
ACTIVE MANAGEMENT OF LABOR
Basic Concepts of AMOL
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SUMMARY POINTS

SUGGESTED READINGS
Keys to the Management of Labor
Epidemiology of Dystocia
Etiology of Dystocia
Epidural Analgesia and Labor Progress
Options for the Management of Dystocia
Active Management of Labor

From 1970 to 1990, the cesarean delivery rate in the United States increased from 5% to 25%. The four primary indications for cesarean delivery include dystocia, elective repeat cesarean delivery, fetal distress, and abnormal fetal presentation. *Dystocia*, translated, means “difficult birth” and includes all abnormalities that may occur in women during labor. Although the incidence of cesarean delivery in the United States has recently equilibrated at between 20% and 25%, it is generally accepted that this number of abdominal deliveries remains excessively high. Perhaps one reason for the continued high rate of cesarean delivery is a poor understanding of the labor process and the lack of an organized approach to the management of labor. This fundamental lack of understanding often leads to unnecessary induction of labor, which has an a priori risk of cesarean delivery of at least 25%, or to inadequate augmentation of abnormal labor. With fewer inductions of labor and better augmentation of labor, one can expect a decline in the cesarean delivery rate.

Efforts at reducing the cesarean delivery rate have more recently focused on the categories of dystocia and repeat cesarean section. Obviously, the best method to decrease the incidence of repeat cesarean deliveries is not to do one initially. Hence, new efforts are being directed at the diagnosis and management of labor abnormalities in term pregnancies. The purpose of this chapter is to review these labor abnormalities and management options.

KEYS TO THE MANAGEMENT OF NORMAL LABOR

A thorough examination of the management of labor and delivery is available in a comprehensive text edited by Creasy, and the normal labor process is reviewed in Chapter 2 of this text. There are several key points in the management of labor (Table 22.1). The first is that normal labor progresses in a predictable fashion after the diagnosis of labor is made. However, diagnosing labor is more difficult than one might believe. If the diagnosis of labor is made in error, all subsequent actions are incorrect, as one is essentially performing an induction of labor and different management is required. Labor in its simplest terms is defined as cervical change effected by regular, painful uterine contractions. In nulliparous women in their first labor, cervical change is usually manifest by cervical effacement, or thinning, followed by cervical dilation (Fig. 22.1). Conversely, in multiparous women, the initial stage of labor is often characterized by cervical dilation followed by effacement.

Labor progress is predictable
Diagnosis of labor is critical
Labor in nulliparas is different from labor in multiparas
Labor progress should be graphically followed
Cardinal movements of labor should occur
Prompt intervention is needed if labor does not progress appropriately
Medical therapy with oxytocin is effective
Clinical judgment must be made regarding the role of cesarean delivery

TABLE 22.1. *Keys to the management of labor*

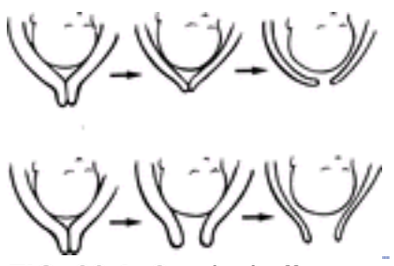

FIG. 22.1. Cervical effacement and dilation: nulliparas versus multiparas. The upper portion of the figure depicts the cervical changes in early labor of the nulliparous woman. Note that cervical effacement precedes significant dilation. The lower portion depicts the cervical changes of the multiparous woman in early labor. Significant cervical dilation may precede achievement of complete cervical effacement.

The normal labor curve as defined by Friedman is shown in Figure 22.2. This curve was developed by Emanuel Friedman based on the observation of several thousand laboring women. The first stage of labor is divided into the acceleration phase, active phase, and deceleration phase. The acceleration phase occurs when the active phase of labor starts. The cervix is usually effaced and dilated less than 4 cm. In the active phase, one can anticipate a minimum of 1 cm of dilation per hour (Table 22.2). The deceleration phase likely is an aberration of the mathematic analysis of Friedman's original data, and as such is likely not a physiologic event. In the second stage of labor, from complete dilation until delivery, one can again anticipate the laboring woman gaining a minimum of 1 cm of station of the fetal head in relation to the maternal pelvis per hour. Cervical examinations should be performed periodically to confirm that progress is being made. Experienced obstetricians often will perform examinations every 2 to 3 hours, depending on the presentation of the patient. After each examination, the progress of labor should be documented

graphically on some form of a labor curve, and a plan formulated with regard to future examinations and potential interventions.

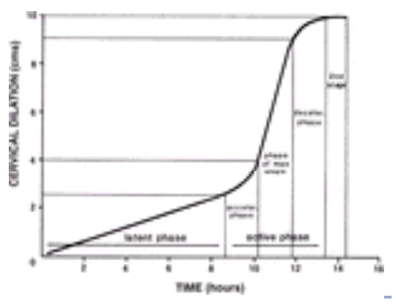

FIG. 22.2. The Friedman labor curve. This figure depicts the normal labor curve developed by Emanuel Friedman. Note the different phases of the first stage of labor, including the latent phase, acceleration phase, active phase, and deceleration phase. (Adapted from Friedman EA. *Labor: clinical evaluation and management*, second ed. New York: Appleton, 1978.)

TABLE 22.2. *Expected length of different phases of labor* [a]

Nulliparous women and multiparous women experience fundamental differences in labor. Figure 22.3 is an example of a labor curve showing the difference in labor patterns expected between nulliparas and multiparas. Labor is the force of uterine contractions overcoming the resistance of the female reproductive tract, including the lower uterine segment, cervix, vagina, and perineum. In nulliparous women, more uterine force is required to overcome resistance in the reproductive tract and the uterus tends to be less effective in maintaining effective uterine contractions. In multiparous women less uterine force is required and the tissues of the reproductive outlet, having been stretched by the previous delivery, have less resistance. As a result, the myometrium of the multipara usually maintains effective contractile activity. Thus, nulliparous women are more likely to develop labor abnormalities that require intervention. Multiparous women usually labor quickly and meet all expected milestones without the need for significant intervention.

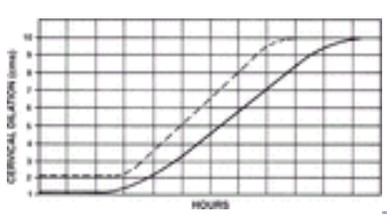

FIG. 22.3. Labor curve of nulliparas versus multiparas. Note that different labor slopes are expected between nulliparous (*solid line*) and multiparous women (*dotted line*).

In addition to graphically depicting labor progress, the practitioner should pay close attention to the *cardinal movements of labor* (Table 22.3). This term refers to the changes that occur in the flexion and position of the fetal head throughout labor. The cardinal movements of labor usually occur in the following sequence: engagement of the fetal head, descent of the fetal head, flexion of the fetal head, internal rotation (assumption of an occiput anterior position), extension (as the fetal head progresses through the birth canal and crowns at the perineum), external rotation (or restitution to the transverse position), and then shoulder rotation after the head has delivered. Abnormalities in the cardinal movements of labor may be reflected by abnormal fetal head position and other specific abnormalities discussed subsequently.

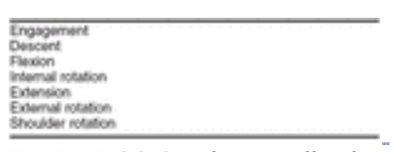

TABLE 22.3. *The cardinal movements of labor*

If labor is progressing appropriately a noninterventional approach is indicated, providing for maternal comfort and encouragement. However, if these landmarks are not achieved by the woman in labor, then timely intervention is recommended. Thus, the next important key in the management of labor is prompt intervention when labor progress is inadequate. Ineffective uterine contractions lead to increased tissue acid content in the myometrium, which further contributes to poor contractility. The longer labor continues in a dysfunctional pattern, the less likely the underlying problem can be corrected with medical therapy. Prompt medical therapy for desultory labor is another important key to success in the management of labor.

A schematic employing these key components of labor management is shown in Figure 22.4. Normal labor is characterized by coordinated uterine contractions, cervical dilation, gain in station of the fetal head, and normal progress in the cardinal movements of labor. With careful attention to achieving these milestones of normal labor, a successful vaginal delivery is likely. However, should the parturient not achieve these milestones, prompt intervention is more likely to increase the chances for vaginal delivery. Although an aggressive approach with regard to diagnosing labor abnormalities may enhance maternal and fetal outcome, the last important key to the successful management of labor is to use clinical judgment on when to abandon medical therapy in favor of surgical management. If the judgment is made that continuing medical therapy may compromise either mother or fetus, then prompt surgical delivery (cesarean or operative vaginal delivery) should be considered.

FIG. 22.4. Keys to the management of labor. This schematic depicts how the keys to the management of labor can be used to help ensure good maternal and fetal

outcomes.

EPIDEMIOLOGY OF DYSTOCIA

The precise incidence of dystocia is difficult to determine and varies with different populations and different labor and delivery units based on local practice patterns. According to the National Center for Health Statistics, 28% of women who delivered in the United States in 2000 were diagnosed with labor abnormalities, with a primary cesarean delivery rate of 16.1%. Dystocia is more common in nulliparous women than in multiparous women and is more common in the first stage of labor than in the second stage of labor. Labor abnormalities occur in approximately 25% to 30% of nulliparous women and 10% to 15% of multiparous women. Dystocia occurs in the second stage of labor in about 5% to 10% of nulliparous women and is relatively rare in multiparas (<2%).

Abnormal labor is a common indication for cesarean delivery. In the United States in 2000, 22.9% of pregnancies were delivered by cesarean (National Center of Health Statistics), down from the highest incidence of 25% in 1988, but slightly higher than the 20.6% rate in 1996. In 1990, the overall rate was 23.7%, with 7.1% for the indication of “failure to progress” or dystocia and 8.5% for a repeat procedure. Other indications included abnormal presentation (2.6%), fetal distress (2.3%), and other problems (3.2%). Improved management of labor with a decrease in the number of cesarean deliveries for dystocia (and then having less need for repeat procedures) should be the goal of every labor and delivery unit in the United States. While there have been many proposed targets for the overall rate of cesarean delivery, none of these figures are based on scientific evidence.

The American College of Obstetricians and Gynecologists (ACOG) published a monograph focusing on cesarean delivery in the United States. This work was developed by a special ACOG task force to address cesarean delivery rates and published in 2000. The primary conclusions of this report were that efforts to reduce the cesarean delivery rate in the United States should focus on two benchmarks. First, there should be a focus on nulliparous women at term (37 weeks or greater) with singleton fetuses in cephalic presentation. In 1996, the cesarean delivery rate for this group was 17.9%, and the ACOG task force concluded that efforts to achieve a reduction to the 25th percentile, or 15.5%, in this group of women were reasonable and could be accomplished. Second, the task force recommended that efforts be made to reduce the percentage of women attempting vaginal birth after cesarean (VBAC). Of multiparas at 37 weeks gestation or greater with singleton fetuses and vertex presentations with prior low transverse cesarean incisions, 30.3% attempted VBAC in 1996. The task force recommended that a primary goal at the 75th percentile for this year, or 37%, would be reasonable. However, in 2000 the rate of attempted VBAC declined to 20.6%. Clearly, efforts to address the cesarean delivery rate in the United States have been a daunting challenge.

ETIOLOGY OF DYSTOCIA

Traditionally, the causes of abnormal labor have been attributed to the “powers” (uterine contractility), the “passage” (maternal pelvimetry), or the “passenger” (position and size of the fetus). In more scientific terms, these represent a primary dysfunctional labor, cephalopelvic or fetopelvic disproportion, abnormal fetal head position, and asynclitism. This section evaluates each of these potential causes of dystocia. The generic term “failure to progress” is often used as a diagnosis to justify cesarean delivery. This term is more appropriately used as a sign of an underlying problem and does not represent a diagnosis. Hence, the term “failure to progress” is not sufficient to describe the labor problem and should not be used.

Primary Dysfunctional Labor

Primary dysfunctional labor refers to inadequate uterine contractility to maintain appropriate progress in labor. In general, an adequate uterine contraction pattern is one in which there are four concerted synchronous contractions every 10 minutes (Fig. 22.5). However, some women contract less frequently and continue to progress adequately in labor such that no intervention or treatment is required. Unlike the cardiac conduction system, the uterus has no defined nervous system for the conduction of electric signals to stimulate muscle contractions. The readiness of the uterus for labor is heralded by the occurrence and widespread distribution of gap junctions throughout the myometrium. Gap junctions allow for the rapid transmission of calcium fluxes through the uterine musculature and, hence, the occurrence of global uterine contractions. The uterus commonly has focal contractions throughout pregnancy (Braxton Hicks contractions) which are not of sufficient strength or duration to effect cervical change and therefore do not constitute labor.

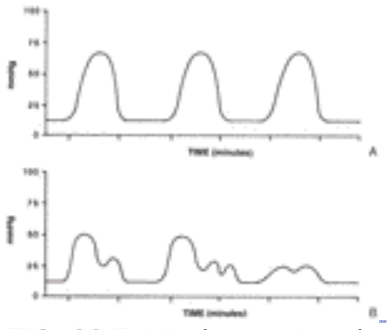

FIG. 22.5. Uterine contraction patterns. Uterine contractions can be depicted using tocodynometry (external monitoring) or direct uterine pressures (using intrauterine pressure catheters). **A:** Contraction pattern of a normal labor. Significant pressure is obtained with contractions every 2 to 3 minutes. **B:** Uterine contraction patterns typical of primary dysfunctional labor. Contractions achieve varying degrees of pressure and are often combined (coupling).

Smooth muscle cells of the uterus are not randomly distributed but are arranged in a specific fashion such that maximal force can be generated to effect vaginal delivery. In women with uterine embryologic abnormalities such as a didelphic uterus or bicornuate uterus, labor is not often successful in achieving vaginal delivery, as global, concerted uterine contractions cannot occur because of the abnormal arrangement of uterine smooth muscle cells. Similar problems may be noted in women exposed to diethylstilbestrol (DES) in utero with uterine anomalies characteristic of this teratogen (e.g., T-shaped uterus).

In the structurally normal uterus, contractions begin to occur less randomly days to weeks before the initiation of labor. Moreover, there is a distinct diurnal variation of uterine contractility such that, in most women, uterine contractions occur more frequently and labor most often commences at night. These rhythmic variations may be the result of hormonal patterns in which specific and predictable changes in different hormones (e.g., corticotropin-releasing hormone, progesterone, estradiol) allow for more frequent and stronger uterine contractions until the final signal for labor. While the precise nature of this signal in women is not known, cortisol appears to play a key role in the initiation of parturition.

As the normal uterus approaches term and labor commences, different foci for the initiation of a uterine contraction may be present (Fig. 22.6). This phenomenon often leads to the clinical scenario in which some contractions are quite hard and lengthy whereas other contractions are mild and of short duration. Women will have mild contractions interspersed with firmer, more painful contractions because of the lack of a dominant “pacemaker” in the uterine musculature. Eventually, as labor progresses, one of these foci of uterine contractility predominates over other foci, resulting in more concerted and painful uterine contractions. As this occurs, true labor commences with effacement and dilation, and this change is reflected in the uterine tocodynometry patterns (see Fig. 22.5). In a primary dysfunctional labor, uterine activity shifts from the concerted global contractions to more focal and less efficient contractions by allowing the reemergence of other pacemaker foci (see Fig. 22.6). Medical therapy with oxytocin is effective at correcting the underlying pathophysiology and restoring the pattern of global and concerted uterine contractions.

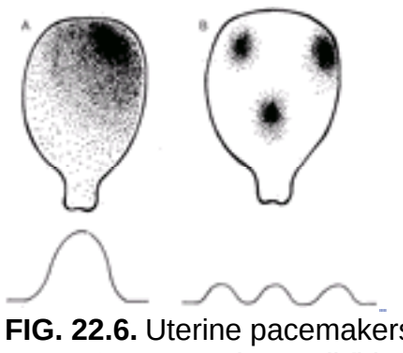

FIG. 22.6. Uterine pacemakers and contractions. **A:** Normal uterine contraction pattern associated with a single dominant pacemaker focus. **B:** A uterus with three separate pacemakers, all firing sequentially. Note that the uterine pressure achieved in this situation is less than that shown with a single dominant pacemaker.

Although usually quite effective, oxytocin therapy may be of little benefit if the woman has intrauterine infection complicating labor. If the parturient has clinical signs of intrauterine infection, then labor progress is often desultory and not remedied with oxytocin augmentation. Clinical signs of intrauterine infection include maternal fever (>38°C), fetal tachycardia (baseline fetal heart rate of >160 beats/min), elevated maternal white cell count, uterine tenderness when the uterus is relaxed, and foul-smelling vaginal discharge. With the diagnosis of intrauterine infection, broad-spectrum antimicrobial agents should be administered and uterine activity stimulated with oxytocin if labor is not progressing adequately.

Cephalopelvic Disproportion

True cephalopelvic disproportion (CPD), or fetopelvic disproportion, is a rare occurrence in the labor and delivery suite. Some authorities believe that CPD occurs in one in 250 pregnancies. CPD occurs when the fetal birth weight or the fetal head is of sufficient size or orientation to preclude entry into the maternal pelvic inlet. This diagnosis if often made in retrospect after the birth weight is known and the positioning of the fetal head has been determined at the time of cesarean delivery. However, in the United States, the term CPD is used to describe almost any unsuccessful attempt at vaginal delivery. Further, the diagnosis of CPD is often used when labor progress is not sufficient and medical therapy is not successful or even not attempted. These cases often reflect inadequate use of oxytocin and are not problems with large fetal size or a small maternal pelvis. CPD is an important diagnosis because it has prognostic information for subsequent pregnancies when VBAC is considered. In women with a prior diagnosis of CPD, success rates of VBAC vary from 50% to 70%. Additionally, they should be managed differently during the VBAC with prompt repeat cesarean if labor does not progress appropriately.

Another important contribution to the fetopelvic relationship is the size of the fetus. Pregnancies with macrosomic fetuses (>4,000 g birth weight) have a greater risk of cesarean delivery for dystocia as a result of true CPD. In a study by Turner and colleagues, fetal macrosomia was associated with longer first and second stages of labor, greater need for oxytocin therapy, and a greater risk for cesarean delivery for CPD refractory to oxytocin. In their patient population, they had an overall incidence of cesarean delivery of 5.2%, but if birth weight was 4,000 to 4,500 g, the incidence of cesarean delivery was 13.8%. Also, forceps delivery was employed in 31.8% of infants with a birth weight of 4,000 to 4,500 g, whereas forceps were used in 13.6% of deliveries overall.

Unfortunately, there are no good predictors of fetal weight to guide management. Sonographic estimates of fetal weight at term are notoriously spurious and can miscalculate birth weight by 500 g or more. The obstetrician employing Leopold maneuvers to estimate fetal weight by palpation of the maternal abdomen can only estimate small, average, or large fetal size. Hence, it is not advisable to induce labor or perform a cesarean delivery for presumed macrosomia unless the obstetrician judges a dangerous situation exists for vaginal delivery (e.g., high risk of shoulder dystocia). Numerous studies of induction of labor for presumed macrosomia consistently show an increase in the cesarean delivery rate with no decrease in neonatal morbidity and poor prediction of macrosomia.

When the diagnosis of a labor abnormality is made, clinical pelvimetry should be performed to assess the dimensions of the maternal pelvis (Fig. 22.7). Only in the rare cases in which the maternal pelvis is markedly small or if there is clear CPD should cesarean delivery be performed without the prior use of oxytocin. For example, labor through a platypelloid pelvis with a normal term-sized fetus is rarely successful because of the markedly shortened anterior–posterior diameter that characterizes this pelvic architecture. After assessment of the pelvic type, approximations of the fetal size should be undertaken. Medical therapy with oxytocin should be instituted unless the fetus appears to be markedly macrosomic (>4,500 g).

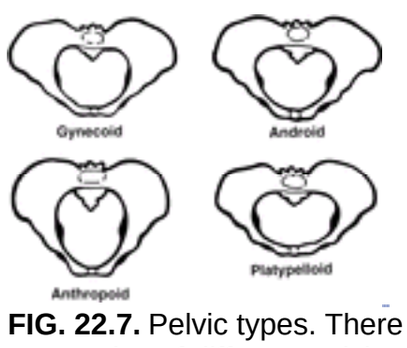

FIG. 22.7. Pelvic types. There are four primary pelvic types: gynecoid, android, anthropoid, and platypelloid. Some women may have a mixed pelvic type with features suggestive of different pelvic types and will not fit conveniently into one of these four categories.

Abnormal Position of the Fetal Head

Abnormal positions of the fetal head include occipital posterior (OP), deep transverse arrest, and deflexion abnormalities such as face and brow presentations and reflect fundamental abnormalities in the cardinal movements of labor. Different positions of the fetal head are depicted in Figure 22.8. An OP position is unfavorable for successful vaginal delivery, particularly if the parturient has an android pelvic structure, as the long diameter of the fetal head negotiates the maternal pelvis at a relatively high station leading to poor descent. Additionally, the fetal heart tracing may have some unusual decelerations that are difficult to interpret, leading to more advanced testing of the fetal acid–base status (e.g., fetal scalp pH determinations). The OP position is a relatively rare cause of dystocia, accounting for about 1 in 250 cesarean deliveries, but it can be corrected with oxytocin therapy. Operative vaginal delivery, either through a Scanzoni maneuver or through a straight OP application with traction, is another option for delivery. A Scanzoni maneuver involves rotating the OP fetus to an occipital anterior (OA) position with forceps and then completing the delivery with forceps from the OA position. A Scanzoni maneuver is associated with a higher incidence of maternal trauma (third- and fourth-degree lacerations of the perineum and sulcus tears of the vagina) and fetal trauma (spinal cord transection). Hence, such deliveries should be performed only by obstetricians skilled in these techniques. Moreover, delivery of the OP fetus with forceps should probably be attempted only if the fetal head has attained at least at +1 to +2 station. At higher stations, cesarean delivery may be the safest alternative. The prudent obstetrician will realize that assigning station in a labor characterized by an OP position is more difficult than in an OA position and often leads to the impression of a lower station than is actually present. Care should be taken to accurately assess the biparietal diameter in relation to the maternal ischial spines.

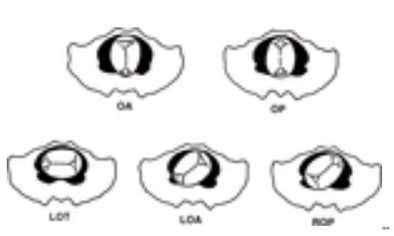

FIG. 22.8. Position of the fetal head. The sutures of the fetal head should be palpated, and the fetal head position should be recorded to ensure that the normal cardinal movements of labor are being followed. The fetal occiput with the maternal position constitute the reference points. Hence, *OA* refers to the occiput anterior position; *OP*, occiput posterior; *LOT*, left occiput transverse; *LOA*, left occiput anterior; *ROP*, right occiput posterior. Any fetal position can occur and should be noted on the labor curve.

A deep transverse arrest occurs in the second stage of labor where the fetus maintains an occipital transverse (OT) position at a low pelvic station. Deep transverse arrests are often associated with abnormal maternal pelvic architecture and may not be easily delivered via forceps. Keilland forceps were designed to address the problem of the deep transverse arrest. Vacuum delivery should probably be avoided in this circumstance, as excessive traction of the fetus with a deep transverse arrest can result in birth trauma. Cesarean delivery is the prudent option if the fetal station is not sufficiently low for operative vaginal delivery or if excessive traction is required to effect delivery. Operative vaginal delivery for a deep transverse arrest should be performed only by obstetricians skilled in the use of forceps for this problem.

Deflexion abnormalities also cause dystocia. The classic forms of deflexion abnormalities include brow and face presentations. Typically, a brow presentation is characterized by the long axis of the fetal head negotiating the short axis of the midpelvis, precluding vaginal delivery. A fetus in the brow presentation may spontaneously convert to a vertex or face presentation. Whereas fetuses with a brow presentation that do not convert rarely deliver vaginally (except in women with generously sized midpelvic dimensions with a small fetus), face presentations will often deliver vaginally if the mentum, or chin, is positioned anteriorly (mentum anterior). Although these extreme flexion abnormalities are usually easily diagnosed and are relatively rare, other mild flexion abnormalities may not be so readily evident. Flexion abnormalities may be suspected in a prolonged or protracted labor unresponsive to oxytocin. Unfortunately, there are no safe and accepted means to

correct flexion abnormalities of the fetal head.

Often, abnormal fetal position may occur as the result of the maternal pelvic type (see Fig. 22.7). For example, android pelvic types often lead to deep transverse arrest or OP position because of the progressive narrowing of the pelvis. Women with an anthropoid pelvis tend to have fetal positions persistently OA or OP, thus interfering with the normal cardinal movements of labor. Finally, women with a true platypelloid pelvis have transverse arrests, assuming the fetal head negotiates the shortened pelvic inlet. Because many women have mixed pelvic types, careful clinical pelvimetry may provide valuable information in the management of dystocia.

Asynclitism

When asynclitism of the fetal head occurs, the sagittal suture of the head is either deviated posteriorly or anteriorly in relation to the maternal outlet (Fig. 22.9). As with other situations involving abnormal positioning of the fetal head, a larger diameter of the fetal head is expected to negotiate the bony pelvis of the mother. In these situations, the second stage of labor is often prolonged and arrest of descent is common, leading to an increased need for operative vaginal delivery. An important aspect of performing operative vaginal delivery involves correction of the asynclitism of the fetal head. This correction can often be accomplished with forceps that have a sliding lock or through vacuum extraction of the fetus, where the precise attitude and positioning of the fetus is of less importance.

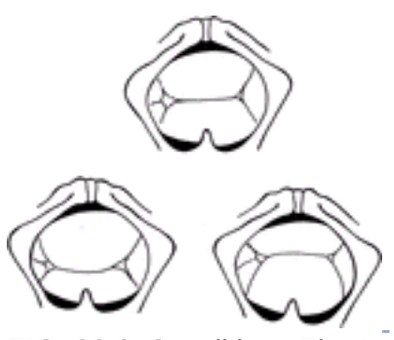

FIG. 22.9. Synclitism. The term *synclitism* refers to the relative orientation of the fetal sagittal suture with the maternal bony pelvis. **Top:** Normal synclitism of a fetus in left occiput transverse position, with the sagittal suture equidistant between the anterior and posterior segments of the maternal pelvis. **Lower Left:** Posterior asynclitism, where the sagittal suture is closer to the posterior bony pelvis, and more of the right parietal bone is palpated. **Lower Right:** Anterior asynclitism in which the sagittal suture is more anteriorly located, and the left parietal bone is more readily evident.

Fetal Abnormalities

Specific fetal abnormalities may contribute to the etiology of dystocia. Fetuses with neuromuscular disease, and particularly those that have suffered an in utero demise, may have flexion abnormalities. Also, fetal conditions such as hydrocephalus, hydrops fetalis, and tumors of the head or sacrum can lead to mechanical obstruction of the birth canal and hence cause dystocia, which is usually not remedied except by cesarean delivery.

SPECIFIC LABOR ABNORMALITIES

Only if the progress of labor is closely monitored can labor abnormalities be diagnosed. Moreover, the timely diagnosis of these labor abnormalities, with prompt medical therapy, should improve the chances of achieving a vaginal delivery. These labor abnormalities can be classified as either arrest disorders (Fig. 22.10) or protraction disorders (Fig. 22.11). Table 22.2 provides parameters for abnormal labor.

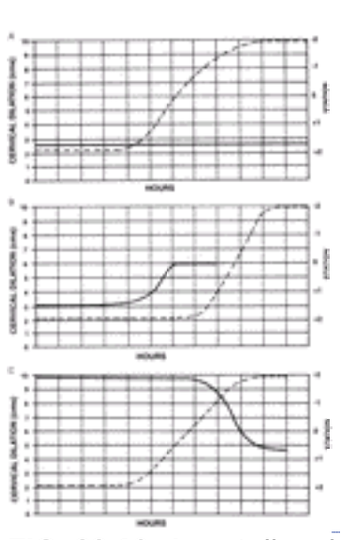

FIG. 22.10. Arrest disorders. These figures depict examples of different arrest disorders. **A:** Prolonged latent phase. Although one might say that a prolonged latent phase is not strictly an arrest disorder, it reflects an abnormality in the normal progress of labor in which the change into the active phase is arrested. **B:** Arrest of dilation, in which the cervix achieves 6 cm of dilation but then does not change for 2 hours. **C:** Example of an arrest of descent. The fetal head moves from a -2 station to a 0 to -1 station but then makes no further progress.

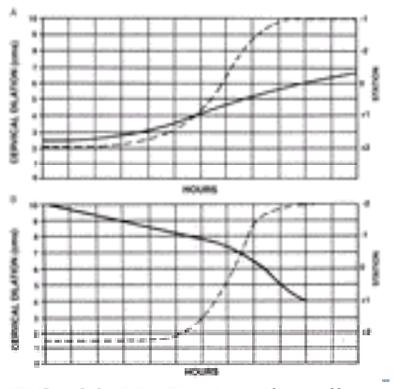

FIG. 22.11. Protraction disorders. These examples of protraction disorders are exaggerated to depict each abnormality. In each case, these abnormalities should be detected early, and appropriate therapy instituted. **A:** Protracted active phase. Note that the average slope is much less than 1.5 cm per hour. **B:** Prolonged and neglected second stage. Intervention should occur sooner than indicated on this partogram.

Prolonged Latent Phase

A prolonged latent phase (see Fig. 22.10A) occurs when regular painful uterine contractions are present for an extended period of time without entering the active phase of labor. Although a prolonged latent phase is not generally classified as an arrest disorder, some authorities believe that the latent phase is an example of a primary dysfunctional labor. In nulliparous women, the definition of a prolonged latent phase is a period of uterine activity without cervical change for more than 20 hours; in multiparas this time period is 14 hours. The cervix may be dilated up to 4 cm and completely effaced. The precise etiology is not clear but likely reflects ineffective uterine contractions without a dominant myometrial pacemaker. The management of a prolonged latent phase is controversial, and in general there are two possible approaches. Some obstetricians believe that a prolonged latent phase reflects an underlying labor abnormality that should be managed aggressively with

amniotomy and oxytocin. The other approach is to provide supportive measures including intravenous hydration and narcotic pain relief. Studies comparing these approaches have not shown either to be a clearly superior choice, so either treatment plan is acceptable as long as the patient understands the plan and risks. The more aggressive approach in some cases may be an induction of labor with the attendant higher risk of cesarean delivery, whereas the more conservative approach runs the risk of prolonging a potentially dysfunctional labor. Either option is acceptable. Deciding which course to take requires obstetric judgment and a motivated, informed patient.

Arrest of Dilation

An arrest of dilation occurs when there is no cervical change after 2 hours in the active phase of labor despite uterine activity (see Fig. 22.10B). In most cases, arrest of dilation occurs as a result of ineffective uterine contractions. Uterine contractions may become dysfunctional and lose their synchronous, rhythmic nature. Figure 22.5 shows an example of the loss of a dominant myometrial pacemaker with the expression of two pacemakers firing independently and without coordinated uterine contractions. In any case, prompt medical therapy with oxytocin usually corrects the underlying problem. In those rare cases where CPD is evident on evaluation of the patient, prompt cesarean delivery is indicated.

Arrest of Descent

After complete dilation is achieved, the primary goal of the second stage of labor is to gain station of the fetal head through the maternal pelvis with eventual delivery. If the patient does not gain station of 1 cm after an hour of adequate pushing efforts, an arrest of descent is diagnosed (see Fig. 22.10C). The cause of this arrest disorder may be one or a combination of several underlying abnormalities, including inadequate uterine contractions, CPD, abnormal fetal position, and asynclitism. If an arrest of descent is diagnosed, the obstetrician has several options, including the use of oxytocin, operative vaginal delivery, or cesarean delivery. The choices for therapy should be guided by the fetal status, station of the fetal head, maternal status, and operator experience.

Protracted Active Phase

When cervical change continues with adequate uterine contractions in the active phase of labor, but over a longer time period than anticipated, then a prolonged active phase is the diagnosis (see Fig. 22.11A). In nulliparous patients, cervical change is less than 1.2 cm per hour, whereas in multiparous patients cervical change is occurring at less than 1.5 cm per hour. A prolonged active phase may be the result of inadequate uterine contractility, but often both the timing and strength of uterine contractions appear to be normal and cervix dilation occurs slowly despite oxytocin therapy. The underlying problem may be true CPD or an undiagnosed flexion abnormality. Oxytocin therapy often is not successful in accelerating labor, and an arrest of dilation or descent may be inevitable regardless of the therapies employed. Should a protracted active phase lead to an arrest of labor despite oxytocin therapy, cesarean delivery is the best therapeutic course.

Prolonged Second Stage

An exaggerated example of a prolonged second stage is shown in Fig. 22.11B. A prolonged second stage is diagnosed when the fetal head descends less than 1 cm per hour. A second stage lasting longer than 2 hours has traditionally been considered abnormal and is an indication for operative vaginal delivery or cesarean delivery. However, more contemporary management allows for more flexibility in the management of the second stage of labor. If the fetus is tolerating the stresses of the second stage well and some gain in station is being made, then there is no indication for terminating the second stage solely on the basis of time in the second stage. Because epidural analgesia may increase the length of the second stage, there is no reason for intervention on the obstetrician's part if the fetal heart rate tracing is acceptable and the mother is comfortable. However, maternal exhaustion will often occur and result in the need for operative intervention. As with the other labor abnormalities, an attentive obstetrician with a plan of management for any contingency should improve both maternal and fetal outcome in abnormal second stages of labor.

In summary, several specific labor abnormalities may occur and can easily be diagnosed. With a rational plan of management, the need for cesarean delivery can be avoided and salutary maternal and fetal outcomes accomplished. The term “failure to progress” thus is not sufficient for a diagnosis. For example, a woman may have “arrest of dilation” followed by treatment with oxytocin. Should this be unsuccessful, then she may require cesarean delivery for “arrest of dilation refractory to oxytocin therapy.” Addressing labor abnormalities in more specific terms enables more rational treatment strategies to be used in the current and future pregnancies, regardless of the outcome.

EPIDURAL ANALGESIA AND LABOR PROGRESS

The impact of epidural analgesia on the occurrence of dystocia and the cesarean delivery rate has been controversial. Epidural analgesia is an excellent form of pain relief for the laboring woman, and in some labor and delivery units, the majority of laboring women opt for this therapy (see Chapter 3). Epidural analgesia is a vital part of the obstetrician's and anesthesiologist's armament to provide pain relief during labor, and both the ACOG and the American Society of Anesthesiologists endorse the use of epidural analgesia for pain management in labor.

However, epidural analgesia may have contributed significantly to the cesarean delivery epidemic of the past two decades. A meta-analysis by Morton and colleagues in 1994 of epidural use in the laboring woman cites an increased risk of 10% for cesarean delivery. Studies have supported this finding. Traynor and associates in 2000 reported that epidural analgesia was associated with a four-fold increased risk for cesarean delivery (12.2% in women with epidural vs. 3.3% in women without epidural), and that the risk for cesarean delivery increased progressively with higher station, less dilation, and less effacement at the time of catheter placement. Similarly, in 2000, Sizer and Nirmal found that epidural analgesia was associated with an increased incidence of OP presentation, leading to a three-fold increase in the risk for cesarean delivery (13.7% for OA presentation, 41.7% for OP presentation) and for operative vaginal delivery (24.4% for OA presentation, 43.7% for OP presentation).

Conversely, other studies contradict these reports and note that epidural use was not associated with an increase in the incidence of OP presentations. Clark and colleagues published a prospective randomized trial in 1998 comparing epidural analgesia with intravenous opioids for pain relief. The cesarean delivery rates were no different in the two groups (13.6% in the opioid group, 9.6% in the epidural group). Imprey and co-workers, in a retrospective review of 1,000 nulliparas, found that an increase in the epidural use from 10% to 57% over the course of 7 years did not result in an increase in the cesarean delivery rate of 3.8% to 5%. Zhang and colleagues, in a summary of studies regarding the use of epidural analgesia and labor outcome, concluded that clinical trials of epidural use of low-dose bupivacaine did not increase the risk of cesarean delivery. Notably, however, observational studies do indicate an increase risk for cesarean and instrumental deliveries, suggesting that selection bias may skew these results. These data depict the exceptional difficulty of studying this clinical issue, given the complexity of the labor process and the multitude of factors that may impact on labor outcomes.

The key to the rational use of epidural analgesia is the approximation of fetal station and cervical dilation. In a 1999 study, Holt and colleagues reported that the strongest risk factor for needing cesarean delivery with epidural analgesia was station at the time of epidural placement. The higher the station at the time of epidural, particularly if -1 or higher, the greater the risk for cesarean delivery. Based on these studies, it seems prudent to recommend that epidural placement be delayed until fetal station has reached the midpelvis. Importantly, women in labor should not be denied epidural analgesia when clinically reasonable and safe.

OPTIONS FOR THE MANAGEMENT OF DYSTOCIA

Once dystocia is diagnosed and a specific abnormality identified, the obstetrician has a number of therapeutic options that can lead to vaginal delivery rather than immediate cesarean delivery. Oxytocin should be administered first unless there is a clear contraindication to this medication, as this is an effective and safe therapy in experienced hands and can correct most labor abnormalities. A schematic depicting an example of one method to manage abnormal labor is shown in Figure 22.12.

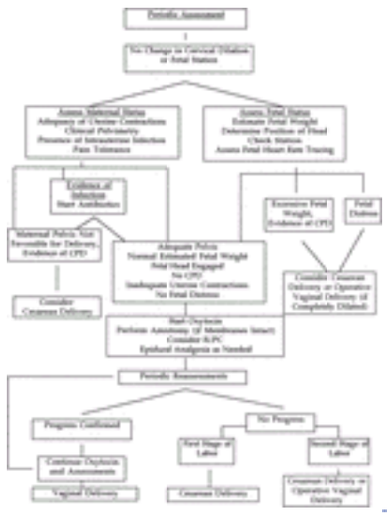

FIG. 22.12. Therapeutic options in the management of dystocia. This schematic provides one algorithm for the management of dystocia. The primary goal is to effect vaginal delivery with good maternal and neonatal outcomes.

Mapping the Progress of Labor

A key adjunct to the management of labor is the use of some form of a labor curve. Several different labor curves have been developed, and no one is better than any other. Several reports have shown that the graphic analysis of labor progress improves maternal and fetal outcomes while lowering cesarean delivery rates, including sites in underdeveloped countries. Many labor and delivery units use the concept of “alert” and “action” lines (Fig. 22.13). In this type of partogram (or labor curve), crossing an alert line merely means that labor progress is slowing, while crossing the action line indicates that a specific action must be taken. Mapping labor progress allows for the timely diagnosis of dysfunctional labor and the prompt institution of medical therapy. Therefore, most contemporary labor and delivery suites have incorporated the use of labor curves into the routine management of laboring women.

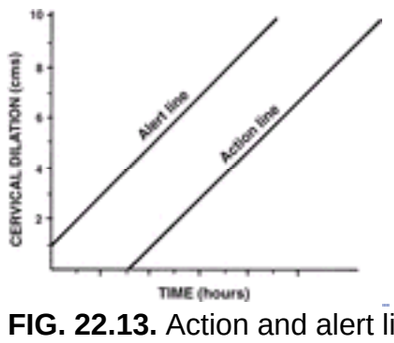

FIG. 22.13. Action and alert lines in the management of labor. This figure depicts the alert and action lines graphically. This type of labor curve has been used successfully to manage labor in many different settings. With this curve, slowing of the labor curve is first marked by an alert that labor is not progressing normally. Then, with further lack of progress, the action line is crossed, mandating that some form of action (medical or surgical therapy) be instituted. (Adapted from Philpott RH, Castle WM. Cervicographs in the management of labor in primigravidae: II. The action line and treatment of abnormal labor. *J Obstet Gynecol Br Commonw* 1972;79:599–602, with permission.)

Amniotomy

Artificial rupture of membranes has been used in the management of slow or desultory labor for decades. This intervention has been deplored by some obstetricians as needless intervention and recommended by others as a useful adjunct. Retrospective studies with relatively small sample sizes suggest that amniotomy could speed normal labor and stimulate abnormal labor to again meet normal milestones. However, large-scale prospective randomized studies do not support the routine use of amniotomy in the management of dystocia (Fig. 22.14). Although normal labor is accelerated modestly, particularly in multiparous women, women in whom amniotomy was routinely used did not have lower rates of cesarean delivery. Additionally, there is a modest increase in the rate of intrauterine infection in women who underwent amniotomy early in the course of labor (e.g., <4 cm dilation). Rupture of the membranes is also associated with variable decelerations of the fetal heart rate as a result of umbilical cord constriction. This problem can, in some cases, be remedied with amnioinfusion of warm saline into the uterine cavity through an intrauterine pressure catheter (IUPC). In such situations, the obstetrician uses one measure to improve outcome (amniotomy) which unfortunately leads to further interventions that otherwise could have been avoided.

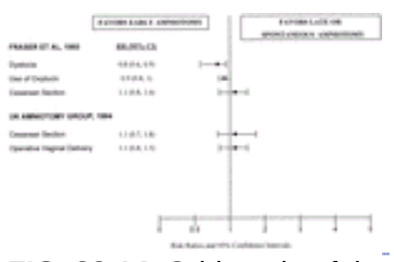

FIG. 22.14. Odds ratio of the effect of amniotomy on labor dystocia. Amniotomy has little effect on the course of labor, the incidence of dystocia, or the incidence of cesarean delivery.

Conversely, there are reasonable indications for amniotomy. Amniotomy is an excellent method for labor induction if the cervix is favorable and the fetal head well applied to the cervix. The judicious use of amniotomy after 5 cm does accelerate labor in the multiparous woman, but less so in the nullipara. Also, oxytocin tends to work more efficiently if the membranes have been ruptured. Disruption of the membranes is required for internal monitoring of the fetal heart rate tracing or of uterine activity. Rupturing of the membranes will detect meconium staining of the amniotic fluid and alert the obstetrician and pediatrician to be prepared for a potentially high-risk circumstance regarding care of the newborn and the prevention of meconium aspiration.

Thus, amniotomy can be a useful adjunct in the management of labor, but only if used wisely and in appropriate circumstances. As long as the parturient is making adequate progress in labor and the fetal heart rate tracing is normal, there is no indication for amniotomy. Spontaneous rupture of the membranes usually occurs at between 7 and 9 cm dilation. Cervical examinations should be minimized after the membranes have been ruptured to decrease the chance of infection because the number of cervical examinations correlates well with the risk of intrauterine infection.

Intrauterine Pressure Catheters

An IUPC is often introduced into the amniotic cavity to help determine the strength of uterine contractions. Application of the catheter requires that the fetal membranes are ruptured, either through spontaneous or artificial rupture of the membranes. Some IUPC require a pressure transducer at the bedside which requires calibration to obtain reliable pressure measurements. More recent devices have the pressure transducer in the tip of the catheter, presumably yielding more reliable pressure measurements. Unfortunately, these pressure readings may be spurious, but more importantly there is a wide range of variation in the duration, strength, and frequency of contractions in normal labor. Thus, quantification of labor using IUPC and applying one standard to all women in labor seems unlikely to lead to favorable maternal outcomes.

Many different quantitative approaches to uterine contractility have been proposed using IUPC technology. For example, the Montevideo unit is the average intensity of the uterine contractions multiplied by the number of contractions over a 10-minute period (expressed as mm Hg/10 min). A total of 200 Montevideo units indicates that there is adequate uterine contractility to effect labor progress. Past studies have suggested that if this level of uterine activity was achieved and no labor progress resulted, then one could state that an adequate trial of labor had been completed and justify cesarean delivery. Other studies ave found that IUPCs increase the rate of

intrauterine infection with no definable benefit. No study to date has shown that the use of IUPC technology improves maternal or perinatal outcome. Therefore, there is no compelling reason to use IUPC in the management of labor. Perhaps the best application for IUPCs is in assisting nursing personnel with the use of oxytocin so that the precise timing of uterine contractions can be determined.

Oxytocin

Oxytocin is a nine–amino-acid peptide (Fig. 22.15) normally produced in the hypothalamus and secreted by the posterior pituitary in a spurting or pulsatile fashion. During normal pregnancy, serum oxytocin concentrations remain essentially unchanged throughout gestation, and there is only modest increase in total serum concentrations before labor. However, with labor, plasma levels increase and then peak in the second stage. Oxytocin receptor expression increases in the decidua in the weeks preceding the onset of labor, and increases sharply just before labor. Oxytocin receptors are expressed primarily in decidua, myometrium, and breast tissue. Myometrial sensitivity to oxytocin parallels expression of oxytocin receptors such that responsiveness begins at about 20 weeks of gestation and then dramatically increases at about 30 weeks of gestation. Oxytocin is cleared from peripheral blood by the liver and kidney and is also significantly metabolized by oxytocinase, an enzyme produced in abundant quantities by the placenta and gestational tissues.

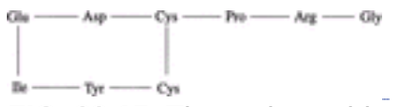

FIG. 22.15. The amino acid structure of oxytocin. Oxytocin is a nine–amino-acid peptide with two disulfide bonds.

Oxytocin may be administered intravenously, subcutaneously, intramuscularly, and buccally. With intravenous administration, there is a concentration-dependent increase in its serum levels but with wide individual variation in responsiveness to the drug. Intravenous administration of oxytocin has effects only on tissues expressing receptors and thus has an excellent therapeutic index. Oxytocin administration results in an increase in the frequency, duration, and strength of uterine contractions. The myometrial response to oxytocin is highly variable, and uterine hyperstimulation may occur at any dose of administered oxytocin depending on the individual patient. Uterine hyperstimulation necessitating discontinuation of the drug or a decrease in the dose being used is the most common side effect of the medication. The only known side effects of oxytocin not related to uterine activity include disturbances in water homeostasis and electrolytes. Oxytocin has approximately 1% the antidiuretic effect of vasopressin, and these side effects are usually seen only at high concentrations of oxytocin infusion (e.g., 40–50 total units administered). Also, intravenous boluses of oxytocin can lead to hypotension and tachycardia as a result of a paradoxical relaxation of vascular smooth muscle.

From the first clinically described use of oxytocin in the 1940s, there has been controversy as to the best and most appropriate regimen for oxytocin use. Table 22.4 summarizes some different acceptable oxytocin protocols currently used. Historically, early regimens of oxytocin administration were highly individualized by physician preference, ranging from relatively low doses to extremely high doses. For example, Seitchik and Castillo found that the most important determinant of the maximum oxytocin dose and the frequency of hyperstimulation was dose-incrementation interval. Those patients who received lower dose increments (every 30–40 min) by 1.0 mU per minute had lower oxytocin doses and less hyperstimulation with good outcomes.

TABLE 22.4. *Acceptable oxytocin protocols*

However, more recent studies have shown that low-dose protocols may result in higher cesarean delivery rates when compared to higher-dose oxytocin protocols. Satin and colleagues used two different methods of oxytocin administration. In one 5-month period, they used a low-dose regimen in 1,251 women where the starting dose of 1 mU per minute was increased by 1 mU per minute every 20 minutes until 8 mU per minute was reached, and then the incremental increase was by 2 mU per minute every 20 minutes up to a maximum of 20 mU per minute. For the next 5-month period (1,537 women), they studied the higher-dose regimen advocated by O'Driscoll in which the starting dose of 6 mU per minute was increased by 6 mU per minute every 20 minutes up to a maximum of 42 mU per minute. Among those patients being augmented, the average maximum oxytocin dose was greater in the high-dose protocol (14.7 mU/min vs. 6.6 mU/min), as was the incidence of uterine hyperstimulation (52% vs. 39%). Notably, there was a significant decrease in the cesarean section rate for dystocia (9% vs. 12%), the use of forceps (12% vs. 16%), rates of neonatal sepsis (8% vs. 12%), and a shorter time from admission to delivery (10.1 h vs. 13.4 h).

In a following study, Satin and colleagues compared two incremental dosing intervals of high-dose oxytocin, comparing a 20-minute dosing interval versus a 40-minute dosing interval. In those women receiving oxytocin for labor augmentation, 603 were in the 20-minute interval group and 564 were in the 40-minute interval group. The results of this study showed that the maximum oxytocin dose, the time from admission to delivery, and the incidence of uterine hyperstimulation were similar in each group. However, women receiving incremental increases in oxytocin at 20-minute intervals had a significantly lower cesarean section rate for dystocia (8% vs. 12%).

A randomized study by Xenakis and associates compared the low-dose protocol of Seitchik and Castillo to a higher-dose protocol in which oxytocin was commenced at 4 mU per minute and increased by 4 mU per minute every 15 minutes. They found a significantly greater number of cesarean deliveries in women receiving the lower-dose regimen (25.7% vs. 10.4%). There were no differences in maternal or neonatal outcome or in the incidence of hyperstimulation. The average maximal dose of oxytocin in the high-dose regimen was only 9 mU per minute, suggesting that achieving a more rapid response with higher doses does not require excessive amounts of oxytocin and that prompt correction of the labor abnormality is critical for success.

These studies suggest that a higher dose of oxytocin will stimulate a higher proportion of patients earlier, resulting in more timely correction of dysfunctional labor and in a lower risk for cesarean delivery (Fig. 22.16). There are numerous factors that can account for the wide variation in responsiveness to oxytocin infusions, including differences in oxytocin receptor expression, differences in oxytocin plasma concentrations, and differences in oxytocinase concentrations and activity.

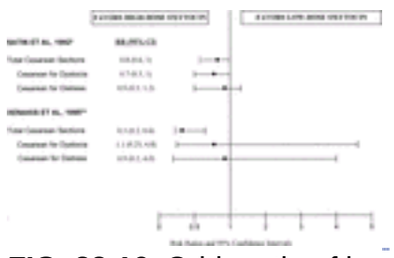

FIG. 22.16. Odds ratio of low-dose oxytocin versus high-dose oxytocin. High-dose oxytocin results in lower overall cesarean delivery rates.

An important unanswered question relates to the safest maximum dose of oxytocin. While some authorities advocate a maximal dose of 42 mU per minute, there are few data upon which to base this recommendation. In a prospective randomized double-masked trial of oxytocin dosage in labor induction and augmentation by Merrill and Zlatnik, two different doses were used. A low- dose regimen of 1.5 mU per minute increasing by 1.5 mU per minute every 30 minutes was compared with a higher-dose regimen of 4.5 mU per minute increasing by 4.5 mU per minute every 30 minutes. Higher-dose oxytocin was associated with a significant shortening of labor, but with no significant differences in cesarean delivery rates. The highest oxytocin dose administered was 117 mU per minute and there were no differences in neonatal outcomes. Hence, no solid recommendations based on data can be made regarding the maximal safe dose of oxytocin.

Regardless of the choice of protocols, clinical judgment should be used when oxytocin therapy is prescribed. There should be no evidence of fetopelvic disproportion based on clinical pelvimetry and estimated fetal weight. If the pelvis is not adequate, or the fetus is large, then the dysfunctional labor may be a sign that vaginal delivery is not safe, and cesarean delivery would be the more appropriate therapy. Additionally, oxytocin should not be used in women with prior classic cesarean section scars because the risk of uterine rupture is high (5%–10%). Care should be taken when women with prior low transverse cesarean sections are being augmented with oxytocin. Although the studies regarding the use of oxytocin and the risk of scar dehiscence are mixed, one should know the total dose given and follow the course of labor carefully. Vaginal birth after cesarean section is addressed more fully in Chapter 24. Oxytocin is an extremely effective drug when used appropriately but can be dangerous for mother and fetus if used inappropriately. Therefore, clinical judgment is required whenever oxytocin is used in the management

of dystocia.

Obstetric Patience

Traditional management of labor has been challenged by some new concepts based on scientific data rather than expert opinion. These new ideas rely on the obstetrician's patience and willingness to allow time for the patient to progress at a somewhat slower rate than has previously been felt to be acceptable. In this regard, these concepts are based on the use of fetal monitoring to ensure that the fetus is tolerating labor well.

Traditionally, an arrest of the active phase of labor with oxytocin augmentation for more than 2 hours was an indication for cesarean delivery. However, studies by Rouse and colleagues question this 2-hour time limit. In their initial study, the Rouse group found that extending the time period of active-phase arrest while on oxytocin from 2 hours to 4 hours was both safe and effective. In their original cohort of 542 normal women presenting with arrest of term labor, 126 demonstrated no labor progress after 2 hours of oxytocin augmentation. However, 101 of these 126 delivered vaginally, decreasing the overall cesarean delivery from 26% (if the 2-hour limit was used) to 8% for the entire study. In those women with presumed adequate labor on the basis of Montevideo units, 32 of 52 delivered vaginally simply by waiting for 4 hours rather than moving to cesarean after 2 hours. These women did have a higher incidence of intrauterine infection, but without increased neonatal morbidity.

In a following study, Rouse and colleagues observed 501 women with a similar protocol. Of these women, 38 had sustained adequate labor for 2 hours based on Montevideo units and no progress in labor. By merely waiting another 2 hours, 23 (or 61%) delivered vaginally and avoided an otherwise indicated cesarean delivery based on traditional criteria. Again, there were no adverse neonatal effects of continuing oxytocin for 4 hours, and there was a higher incidence of intrauterine infection in those women who labored further. Additionally, they found that achievement and maintenance of 200 Montevideo units, the value traditionally noted to represent “adequate” labor, was not predictive of delivery route.

While patient numbers are as yet insufficient to change traditional recommendations on the management of labor arrest, these studies, if confirmed, strongly suggest that allowing more time for oxytocin augmentation is reasonable, effective, and safe. A key issue again is that one management plan should not necessarily apply to all women in labor, as there is considerable individual variation in labor progress and responsiveness to oxytocin.

Two studies have explored different strategies of managing the second stage of labor. These studies have compared two groups of women in the second stage, in which one group of women was encouraged to push promptly with the diagnosis of complete dilation while the other group was encouraged to rest for 1 to 2 hours (or more) before starting pushing efforts. In the study by Fraser and associates, nulliparous women in the delayed pushing group were encouraged to wait at least 2 or more hours prior to pushing. Over 900 women were enrolled in each group. When compared to the early pushing group, women who delayed pushing had a lower incidence of “difficult delivery” (17.8% vs. 22.5%). Difficult delivery was defined as the need for midpelvic delivery, low-pelvic delivery with rotation, any manual rotational delivery, or second stage cesarean delivery. The primary difference was in the incidence of midpelvic delivery (9.3% vs. 13%), while cesarean delivery rates were similar (5.0% vs. 5.7%). Maternal morbidity and neonatal outcomes were similar between the two groups.

The other study of delayed pushing, by Hansen and colleagues, was also a randomized prospective trial comparing immediate versus delayed pushing efforts in over 250 women. In those women randomized to delayed pushing, nulliparas were rested for 120 minutes while multiparas rested for 60 minutes. The investigators found that there were no statistically significant differences in instrumental delivery rate, neonatal outcome, and rates of perineal injury. Women who rested had a longer second stage of labor, but decreased total time pushing, fewer decelerations, and less fatigue. Only three cesarean deliveries were performed, all in the control group. The authors concluded that delayed pushing, up to 4.9 hours, was safe and may be useful in selected patients.

The studies described in this section underscore the value of obstetric patience. While there are average times for the first and second stages of labor, these studies show that traditional and arbitrary time limits may be extended safely in selected patients, with improved maternal outcomes and continued good neonatal outcomes.

Operative Vaginal Delivery

Operative vaginal delivery should only be performed if the following criteria are met: complete cervical dilation, engagement of the fetal head filling the hollow of the sacrum, known position of the fetal head, and sufficient operator experience. Forceps- or vacuum-assisted vaginal delivery should be performed only on behalf of the mother or fetus and not for the convenience of the obstetrician. In the context of dystocia, the primary reason for moving to assisted vaginal delivery is an arrest of descent of the fetal head. This arrest may be due to inadequate uterine contractions, insufficient maternal pushing efforts, abnormal position of the fetal head (OP or deep transverse arrest), or asynclitism of the fetal head. In these situations, the mother often has pushed for 2 hours or more and may be unable to continue with effective pushing efforts because of exhaustion.

Appropriate forceps use or indications for vacuum extraction are dependent on the experience of the obstetrician. Experienced obstetricians skilled in the use of forceps have the judgment to use the appropriate instruments and traction for a successful and safe vaginal delivery. Less experienced providers may find vacuum extraction more successful but vacuum-assisted delivery still requires judgment and skill for a safe delivery. Even with vacuum extraction, prudent use in specific situations will decrease the incidence of maternal and fetal complications. An all too common occurrence is the inappropriate use of operative vaginal delivery with adverse obstetric and neonatal outcomes, usually due to inappropriate application at a higher than expected station. In experienced hands, there are no differences in neonatal outcome in infants delivered by normal vaginal delivery or by outlet forceps.

Cesarean Delivery

If all the previously outlined measures are not successful, then cesarean delivery is likely needed to obtain a good maternal and neonatal outcome. Although one should not move to cesarean delivery before all options are considered, similarly one should not hesitate to operate if a successful vaginal delivery is not possible without potential serious risk or harm to the fetus and neonate. Delay in moving to cesarean delivery when indicated can potentially lead to adverse maternal and neonatal outcomes such as postpartum hemorrhage, uterine rupture, and birth injury. Cesarean section is discussed in detail in Chapter 24.

ACTIVE MANAGEMENT OF LABOR

Since the mid-1960s, an organized approach known as the active management of labor (AMOL) has been developed and advocated by the obstetric staff at the National Maternity Hospital in Dublin, Ireland. Initially conceived by Kieran O'Driscoll, this approach has been modified over the years. The advocates of AMOL cite a continuing low cesarean delivery rate (approximately 10%) with excellent outcomes for mother and infant. The primary goal of AMOL is to prevent prolonged labor. Women are guaranteed that they will either be delivered, or close to delivery, within 12 hours of admission to the labor and delivery unit. The style and content of this labor management have generated much controversy and misunderstanding in the United States. For example, many obstetricians believe that the active part of AMOL is aggressive intervention in the laboring woman or high oxytocin doses, but in fact it refers to the fact that an obstetrician (usually the head of the department) reviews the labor progress of each patient to ensure that optimal outcomes are achieved.

Basic Concepts of AMOL

Table 22.5 lists the primary components of AMOL. Perhaps the hallmark feature of AMOL is that no patients are admitted to the labor and delivery unit unless the diagnosis of labor has been made. Labor is defined as painful, regular uterine contractions with complete cervical effacement, regardless of cervical dilation. The average dilation of the cervix at the time of admission is 2 to 3 cm. AMOL applies only to the nulliparous patient, as multiparous women who have had previous vaginal delivery usually do not have prolonged labor and have a higher risk of uterine rupture with oxytocin administration. After the diagnosis of labor has been made, amniotomy is performed at the time of admission regardless of cervical dilation. The diagnosis of labor is key. If this diagnosis is incorrect, then an induction of labor is being initiated with the attendant increased risk for cesarean delivery.

Comprehensive prenatal education
Admission only after labor is diagnosed
Strict criteria for the diagnosis of labor
Delivery with 12 h of admission
One-on-one nursing care
Immediate amniotomy at admission (if membranes still intact)
Frequent cervical examinations to ensure progress in labor
Prompt intervention if labor progress not confirmed
High-dose oxytocin protocols
Epidural analgesia is available
Midpelvic and rotational forceps not used
Continuous internal audit
“Active” involvement of attending obstetrician

TABLE 22.5. *Key concepts of active management of labor*

On admission, a nurse-midwife or student midwife is assigned to the patient who stays with only this patient throughout her entire labor. There are no provisions for change of nursing shifts. Also, these patients receive detailed instructions on expectations during labor in prenatal birthing classes. One-on-one nursing care, with a clear vision of the ensuing labor, alleviates maternal anxiety and is perhaps the most distinguishing feature of AMOL over other styles of labor management as practiced in the United States.

Cervical examinations to corroborate labor progress are performed by the midwives every 1 to 2 hours. If the patient does not make adequate progress in labor, oxytocin administration is promptly initiated at 6 mU per minute and increased by 6 mU per minute every 15 minutes until 7 to 8 contractions occur every 15 minutes (see Table 22.4). During labor, the patient is never left unattended by the midwife assigned to her care and uterine activity is palpated by the midwife. The midwife assigned to the parturient will then perform the delivery with the head midwife in attendance. The attending obstetrician is asked to intervene only when there is need for an obstetric operation, such as episiotomy, forceps delivery, or cesarean delivery. Midforceps delivery and rotational forceps are not performed.

With AMOL at the National Maternity Hospital, cesarean delivery rates for dystocia are less than 10%. Oxytocin is used in 50% to 60% of nulliparas and only 10% to 15% of multiparas (who are not managed with this program). Delivery occurs in less than 12 hours in 98% of women. Cerebral palsy rates approximate that of the United States, or about 2 per 1,000 births, and birth trauma is rare. Epidural analgesia is allowed and does not impact significantly on the cesarean delivery rate. Clearly, AMOL suits the population served at this hospital well.

Lessons from AMOL

Three prospective randomized trials of AMOL have been conducted in the United States (Table 22.6). Lopez-Zeno and colleagues found a significant decrease in the cesarean delivery rate in nulliparous patients in the AMOL arm of the studies, from 14.1% to 10.5%. Frigoletto and associates randomized over 1,200 to AMOL or traditional management and found no decrease in the cesarean delivery rate but were able to show a modest decrease in the duration of labor in the AMOL arm. In the third study, Rogers and colleagues also found no significant decrease in cesarean delivery rate but confirmed a decrease in the length of labor. These discrepancies may be because AMOL may not significantly reduce the cesarean delivery rate if the baseline rate is 11% or less. In other nonrandomized studies, AMOL has been shown to decrease the primary cesarean delivery rate by 25% to 50%, and a recent meta-analysis by Glantz and McNanley showed that the risk of cesarean delivery for dystocia was decreased on average by 34%. In an analysis of these three randomized trials, AMOL resulted in a lower risk for cesarean delivery (Table 22.6, Fig. 22.17) and a greater incidence of delivery within 12 hours of labor (Fig. 22.18). A prospective randomized study performed at the National Maternity Hospital in New Zealand by Sadler and co-workers found that the cesarean delivery rate was similar in their conventionally managed and actively managed women (9.4% vs. 9.7%), but that women in the AMOL had shorter labors and a lower relative risk for prolonged labor.

TABLE 22.6. *Cesarean delivery incidence in randomized studies of active management of labor*

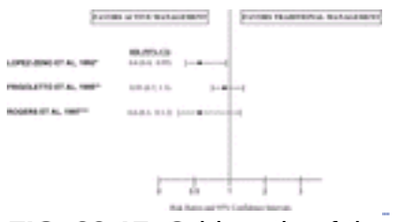

FIG. 22.17. Odds ratio of the effect of active management of labor on cesarean delivery rate. Active management of labor is associated with a lower risk of cesarean delivery in one study but with equivocal results in two studies.

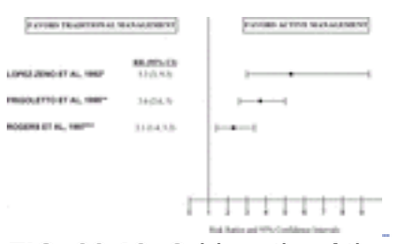

FIG. 22.18. Odds ratio of the effect of active management of labor on delivery within 12 hours. Active management of labor is associated with delivery within 12 hours of presentation to the labor and delivery units in each study depicted.

Many lessons can be derived from the AMOL protocol. First, AMOL is a regimented integrated approach to the management of labor in all nulliparous women admitted to the hospital. In many ways, this philosophy runs counter to the concept of individualizing patient care according to each woman's specific situation. However, application of protocols in some situations, as in clinical practice guidelines, leads to more standardized application of appropriate therapies with concomitant improved outcomes. Whereas much has been made of the use of early amniotomy and the relatively high doses of oxytocin employed in AMOL protocols, a detailed analysis by Thorton and Lilford indicates that the most important component of AMOL in achieving a low cesarean birth rate is one-on-one nursing. And perhaps the most important aspect of nursing care in this setting is the alleviation of maternal anxiety and the prompt diagnosis and treatment of dystocia.

AMOL is an excellent example of how an organized approach to labor management can lead to improved outcomes. Although AMOL cannot be adopted in its entirety in all labor and delivery units in the United States, the principles of AMOL can be adapted in many situations. First, normal women at term with uterine contractions should be admitted only when they are in active labor. Obviously, there are exceptions to this concept, but premature admission with interventions usually implies that an induction of labor is being performed for no clear indication. Second, dysfunctional labor should be promptly diagnosed and treated with appropriate medical therapy. Third, efforts to alleviate maternal anxiety through prenatal education and attentive, sympathetic caregivers should be maximized. Unfortunately, labor and delivery units in the United States would find it impossible to provide one-on-one nursing care throughout labor with the current staffing policies of most units. However, more personal interactions with all caregivers, from nurses to obstetricians, should be encouraged. And last, there is little delay in making the decision to move to cesarean delivery, improving both maternal and neonatal outcomes. Although critics of AMOL cite perceived excessive intervention (based on the use and doses of oxytocin), proponents of AMOL counter that a cesarean delivery rate of 20% to 25% versus less than 10% is the greater intervention.

SUMMARY POINTS

- Dystocia is common, particularly in the nulliparous woman, and is a common indication for cesarean delivery.
- Early amniotomy does not improve labor outcomes. However, amniotomy after 5 cm of dilation can shorten the time of labor but at the expense of a modest increase in infectious morbidity.
- Early application of epidural analgesia can contribute to labor abnormalities, particularly in the second stage, and can lead to an increased need for operative vaginal delivery.
- Active management of labor (AMOL) protocols can decrease the cesarean delivery rate in some populations.
- Oxytocin protocols using higher doses (3–6 mU/min and increasing concentrations every 15–20 min) decrease the need for cesarean delivery for dystocia with adequate safety for mother and fetus.
- All authorities agree that the primary goal in managing women in labor is to obtain healthy babies with minimal maternal morbidity. However, the methods used to achieve these goals elicit a great deal of controversy among obstetricians. Nevertheless, following the principles of labor management as outlined in this chapter should ensure good maternal and fetal outcomes.

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Chapter 23

Michael A. Belfort

Operative Vaginal Delivery

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The enthusiasm for operative vaginal delivery peaked in the early 20th century when almost 50% of all deliveries were with forceps. Over the last three decades this has changed and worldwide there has been a decrease in the use of operative techniques. This has been accompanied by a relative increase in abdominal delivery. There are various explanations for this trend including the development of more effective anesthesia techniques, the introduction of antibiotics, the effective use of blood products, and the development of improved surgical techniques. Thus, cesarean section has become the most commonly performed surgical procedure of our time and operative vaginal delivery rates have significantly decreased. When operative vaginal delivery is performed now, it is more commonly carried out with a vacuum extractor than with forceps and in some parts of the world (Scandinavia), forceps are hardly ever used. In the United States and increasingly in Europe, medicolegal concerns have reduced enthusiasm for operative delivery and the teaching thereof. This is an unfortunate situation since, for the correct indication, and in well-trained hands, operative vaginal delivery is safe and effective and reduces the incidence of abdominal delivery and its attendant complications. The objectives of this chapter are two-fold: first, to outline the basic knowledge that should be required of those wishing to perform operative vaginal deliveries, and second to discuss selected important topical issues that have recently been highlighted in the literature.

APPLIED MATERNAL PELVIC ANATOMY

The art of ante- and intrapartum clinical assessment of the maternal pelvis is slowly disappearing from many training programs as this aspect of obstetric evaluation continually receives less emphasis. In many instances, the argument that labor is the best test of the cephalopelvic relationship is a reasonable one. The counter argument, however, is that accurate clinical maternal pelvimetry may reveal findings that would prevent an unnecessarily difficult labor in a case of obvious cephalopelvic disproportion.

A knowledge of the female pelvis and its different configurations is important. Figure 23.1 shows the four parent types of maternal pelvis, defines their major characteristics as described in the Caldwell-Moloy classification, and lists the percentage of women with each type of pelvis. Table 23.1 lists some important diameters of the maternal pelvis. Detailed clinical knowledge of the type of pelvis and the relative dimensions of that pelvis and the fetal presenting part attempting passage through that pelvis, should form the foundation of any decision to undertake operative vaginal delivery. To this end, the following sections present applied anatomy of the maternal pelvis and fetal head.

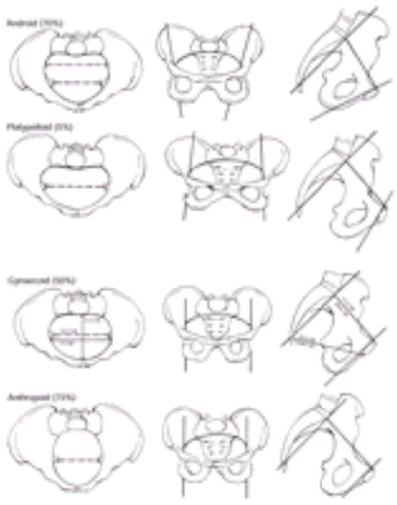

FIG. 23.1. The four major types of female pelvis.

Region of the pelvis	Measurement (cm)
Brim (inlet): AP	11.5 cm
Brim: Transverse	13.0 cm
Midcavity (midpelvis: AP and transverse)	12.0 cm
Cavity: AP and transverse	10.5 cm
Outlet: AP	12.5 cm
Outlet: Transverse	11.0 cm

AP, anteroposterior.

TABLE 23.1. *Diameters of the female pelvis*

PERFORMING CLINICAL PELVIMETRY

The pelvis is usually assessed in terms of the inlet, midcavity, and outlet.

Inlet

The inlet can only be adequately evaluated prior to engagement of the fetal head, since once the head occupies the midcavity the posterior inlet cannot be accessed. The examiner first assesses the anteroposterior (AP) diameter of the inlet by measuring the diagonal conjugate (distance from the undersurface of the symphysis pubis to the sacral promontory). The obstetric conjugate (the narrowest AP diameter of the inlet) is estimated by subtracting 2 cm from the diagonal conjugate. The transverse diameter of the inlet cannot be measured clinically. An idea of the shape and the extent of the circumference of the inlet can be gained by sweeping the examining fingers laterally along the pelvic brim. If more than two thirds of the brim can be easily palpated, and especially if the posterior portions of the brim can be felt, there may be a contracted inlet.

Midcavity (Midpelvis)

The midcavity of the pelvis is evaluated by assessing the shape of the sacrum (curved or straight), the width of the sacrosciatic notch, and the prominence of, and distance between, the ischial spines. A contracted midpelvis characteristically shows a flattened forward projecting sacrum, prominent ischial spines with a narrowed interspinous distance, and a shortened sacrospinous ligament which is less than two fingerbreadths long.

Outlet

Evaluation of the outlet consists of:

- determining the distance between the ischial tuberosities (normally approximately 10 cm)
- palpating the coccyx to determine its orientation and mobility (normally mobile and not protruding into the pelvic cavity)
- evaluating the subpubic angle (>90 degrees) and retropubic angle (flattened in a platypelloid pelvis and sharply angulated in an android pelvis)
- determining the convergence or divergence of the pelvic sidewalls (see Fig. 23.1).

During labor, clinical pelvimetry can be combined with fetal parameters such as head position, molding, caput succedaneum, asynclitism, maternal and fetal soft tissue edema, presence of meconium, descent of the head, and fetal heart rate response, with contractions or pushing. By assimilating the information from repeated examinations an idea of how the fetal head is progressing through the pelvis can be gained. In this way the operator is afforded a more complete estimation of the chances of a successful vaginal delivery using forceps.

The use of the term “adequate pelvis” is to be discouraged since it is very nonspecific. Clinical assessment of the maternal pelvis prior to an operative vaginal delivery is a prerequisite and the findings should be documented in more definite terms with mention being made of the nature of the pelvic inlet, the midpelvis, and the outlet. Since each delivery is a separate event, and applies to a specific fetus, the best time to assess the adequacy of a particular patient's pelvis is during labor and delivery. In this way the relationship between the pelvis and the fetal head can be better evaluated.

Some important definitions of clinical pelvimetry are given in Table 23.2.

Engagement:	The widest diameter of the fetal presenting part (in most cases the bi-parietal diameter of the fetal head) is at or below the plane of the maternal pelvic inlet. The best method of determining this is a combination of abdominal and pelvic examination.
Station:	The relationship between the leading bony part of the fetal presenting part (usually the cranium) and the maternal ischial spines. Usually, but not always, the fetal bi-parietal diameter is engaged when the leading portion of the skull is felt at 0 station. The most common source of error in assessing station is caused by the cephalopelvic disproportion. In circumstances where severe caput succedaneum precludes accurate diagnosis of the station, operative vaginal delivery should not be contemplated.
Attitude:	The relationship of the fetal head to the fetal spine. The head may be flexed, extended, or in a neutral attitude ("military attitude").
Position:	The relationship of the denominator of the fetal presenting part to the maternal pelvis. In a cephalic presentation the denominator is the occiput while in a breech presentation it is the sacrum. The position is always described in relation to the maternal left and right sides of the pelvis.
Presentation:	The relationship between the leading fetal part and the maternal pelvic inlet. The fetus may have a cephalic, breech, or shoulder presentation.
Lie:	The relationship between the fetal and maternal longitudinal axes, which may be longitudinal, oblique, or transverse.
Asynclitism:	The relationship between the anterior and posterior parietal bones and the sagittal suture. When neither of the parietal bones precedes the sagittal suture the head is synclitic. If the anterior parietal bone precedes the sagittal suture there is anterior asynclitism, and when the posterior parietal bone precedes the sagittal suture there is posterior asynclitism.
Molding:	This term describes the phenomenon of abutment or overlapping of the fetal skull bones caused by excessive pressure on the fetal head. In general the occipital and frontal bones slip under the parietal bones when molding occurs.

TABLE 23.2. *Important definitions of clinical pelvimetry*

American College of Obstetricians and Gynecologists' Classification of Station

In 1988 forceps operations were redefined by the American College of Obstetricians and Gynecologists (ACOG). The new classification uses the level of the leading bony point of the fetal head in centimeters at or below the level of the maternal ischial spines (0+ to 5+) to define station instead of the previously used method of describing the birth canal in terms of thirds (0+ to 3+).

APPLIED FETAL CEPHALIC ANATOMY

A knowledge of term fetal skull anatomy is important for anyone performing operative vaginal deliveries since different head positions present different diameters which significantly impact the rate of success in terms of delivery. Figure 23.2 shows important landmarks, and Figure 23.3 presents relevant diameters of the fetal skull. Table 23.3 shows the diameters and circumferences of the fetal head that will need to negotiate the maternal pelvis in specific fetal head positions.

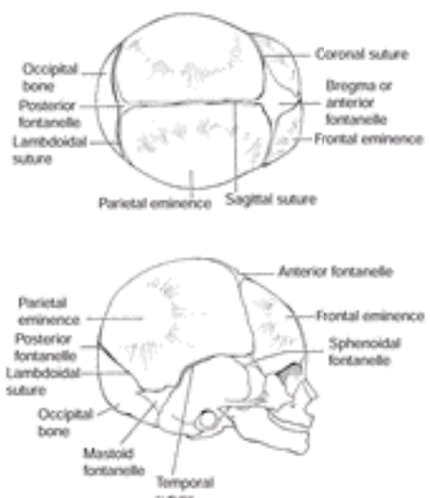

FIG. 23.2. Important landmarks of the fetal skull.

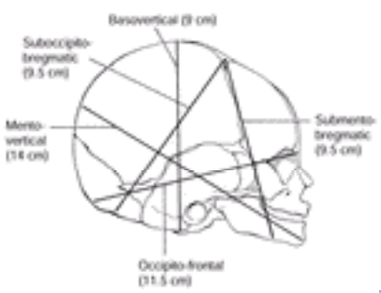

FIG. 23.3. Important diameters of the fetal skull.

Diameter	Measurement (cm)
Suboccipital-Bregmatic Nape of neck to center of bregma	9.5 cm
Submental-Bregmatic Below chin to center of bregma	9.5 cm
Mentum-Vertical Point of chin to above posterior fontanelle	14.0 cm
Basal-Vertical Base of skull to most distant point of vertex	9.0 cm
Occipital-Frontal Root of nose to occipital protuberance	11.5 cm
Bi-parietal Between two parietal eminences	9.5 cm
Bitemporal Greatest distance between the two halves of the coronal suture	8.5 cm

Circumference	Measurement (cm)
Suboccipital-Bregmatic × Bi-parietal Well-flexed vertex	28 cm
Occipital-Frontal × Bi-parietal Deflexed vertex and occipital posterior positions	33 cm
Mentum-Vertical × Bi-parietal Brow presentation (largest possible diameter)	35.5 cm

TABLE 23.3. *Diameters and circumferences of the fetal head that will need to negotiate the pelvis with the head in specific positions*

A number of terms are applied to swellings seen on the neonate's head. Some such as *caput succedaneum* are expected and do not pose a risk to the neonate, and some are pathologic and need immediate attention. Figure 23.4 shows these swellings schematically.

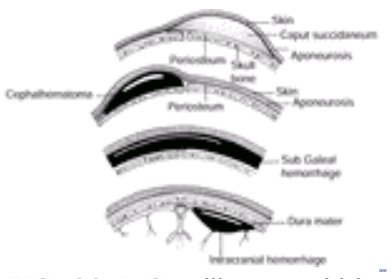

FIG. 23.4. Swellings and bleeds associated with normal and operative vaginal delivery.

Caput Succedaneum

Commonly referred to as caput, caput succedaneum describes edema of the scalp (serous effusion between aponeurosis and periosteum) overlying the leading part of the skull. This is a normal occurrence, the result of pressure from the cervix interrupting venous and lymphatic drainage from the scalp during labor. There are varying degrees of caput and these are described subsequently. Caput usually disappears within hours after birth.

Caput succedaneum should be differentiated from two life-threatening bleeding differential diagnoses: cephalhematoma and subgaleal (subaponeurotic) hemorrhage.

Cephalhematoma A cephalhematoma is a collection of blood between the periosteum and the skull bone. The extent of the bleed is limited by the periosteal attachments at the suture lines but can still be significant. Cephalhematomas usually take hours to develop and weeks to reabsorb.
Subgaleal (Subaponeurotic) Hemorrhage This occurs when emissary veins are damaged and blood accumulates in the potential space between the galea aponeurotica (epicranial aponeurosis) and the periosteum of the skull (pericranium). Since the subaponeurotic space has neither containing membranes nor boundaries, the subgaleal hematoma may extend from the orbital ridges to the nape of the neck. This condition is dangerous because of the large potential space for blood accumulation and the possibility of life-threatening hemorrhage. Subgaleal bleeding presents with diffuse swelling of the head and signs of hypovolemic shock (e.g., pallor, hypotension, tachycardia, and increased respiration rate). The signs may be present at delivery or may not become clinically apparent until several hours or up to a few days following delivery. The swelling is usually diffuse, shifts dependently when the infant's head is repositioned, and indents easily on palpation. However, in some cases the swelling is difficult to distinguish from the edema of the scalp. On occasion, the hypotension and pallor are the dominant signs while the cranial findings are unremarkable.

Molding Molding is an expected deformation of the fetal head that occurs during the delivery process. A small amount of occipitoparietal molding is normal during the second stage of labor but excessive skull bone molding (particularly parieto-parietal molding) is abnormal during the first stage of labor. Molding can be classified in the following way (Fig. 23.5):

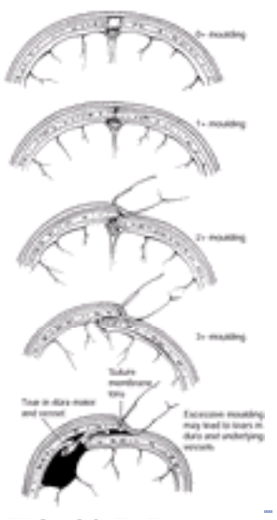

FIG. 23.5. Degrees of molding of the fetal head.

0+ = suture easily felt between the two bones
1+ = no suture felt but the bones can be separated easily with minimal digital pressure
2+ = overlap of bones but they can be separated with digital pressure
3+ = overlap of bones that cannot be separated with digital pressure.

FETAL HEAD POSITION AND ITS DETERMINATION

Knowledge of the position of the fetal head is essential in order to safely perform an operative vaginal delivery. The obstetrician should be able to determine the relationship of the fetal cranial bones and fontanelles to one another, and using this information, plan and execute the procedure. It should be remembered that caput succedaneum, molding, asynclitism, and maternal and fetal soft tissue edema can all combine to mask the true fetal head position. However, an attempt at determining the position of the fetal head should become a reflex action during a vaginal examination in labor. In difficult cases, ultrasound can be used, either translabially or transabdominally. It is axiomatic that until the exact head position is known, forceps should not be applied.

Abdominal Examination as Part of the Routine Assessment Prior to Operative Vaginal Delivery

Examination of the abdomen should be included in the assessment of a patient prior to vaginal examination and any attempt at operative vaginal delivery. This evaluation will help in a number of ways. First, it will confirm the lie and give an idea of where the fetal back is in relation to the uterine midline. If the fetal back is not felt or is palpated laterally, there is a higher likelihood of the baby being in an occipitoposterior or transverse position. Often this knowledge will help the examiner make sense of an otherwise difficult vaginal examination. Second, fetal weight can be assessed and, in experienced hands, this has been shown as to be accurate as intrapartum ultrasound evaluation. Third, and possibly most important, the amount of fetal head palpated above the pelvic brim can be assessed (Fig. 23.6). This is an important observation, and one that is more frequently used in Europe than in the United States. Crichton described a method of assessing the level of the fetal head clinically in terms of “fifths of the fetal head palpable above the maternal pubic symphysis” ([1]) (Fig. 23.7). No more than two-fifths of an unmolded fetal head should be palpated abdominally once the occiput is felt at the ischial spines. If a significant proportion of the fetal head (more than three fifths) is still palpable above the pubic symphysis, regardless of the fact that scalp is felt at the ischial spines, the head should be regarded as unengaged and an operative delivery should be avoided.

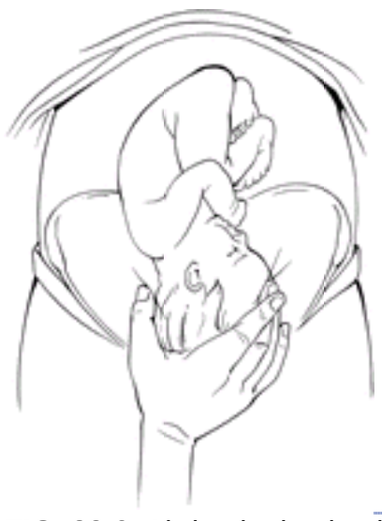

FIG. 23.6. Abdominal palpation and the determination of the amount of fetal head still above the pelvic brim.

FIG. 23.7. The rule of three's. See text for complete description.

PREREQUISITES FOR OPERATIVE VAGINAL DELIVERY

Prior to embarking on any operative vaginal delivery it is important to ensure that the procedure will meet with the greatest possible chance for success. To this end a number of prerequisites have been suggested ([2]). Table 23.4 presents a mnemonic that I have found useful in ensuring the best chance of success for an operative vaginal delivery. Some of the most important prerequisites for a non-rotational operative vaginal delivery can be easily remembered with the use of this mnemonic (F-O-R-C-E-P-S).

F	**F**avorable head position (OA/AP ±45 degrees from the AP diameter)—unless intended rotational delivery **F**etal assessment (weight and status)
O	**O**pen Os (completely dilated cervix)
R	**R**ule of three's, **R**uptured membranes
C	**C**ontractions present, **C**onsent (verbal or written)
E	**E**ngaged head, **E**mpty bladder, **E**pidural or other form of adequate anesthesia
P	**P**repared for cesarean section, if needed **P**repared for neonatal resuscitation, if needed **P**elvimetry (clinical) adequate **P**reoperative note written
S	**S**tirrups and lithotomy position with attention paid to pressure points and prevention of hyperflexion at the hips (to avoid femoral nerve apraxia)

AP, anteroposterior; OA, occipital-anterior.

TABLE 23.4. *Prerequisites for an operative vaginal delivery*

PREPARATION OF THE PATIENT

Preparation for a forceps delivery is very important and can influence the delivery outcome significantly. Essential aspects include:

- proper positioning
- adequate anesthesia
- understanding of the process
- recheck that prerequisites have been satisfied
- “ghosting”

Proper Positioning

Proper positioning will usually be in a modified lithotomy position with the patient sitting up in a way that she can view and remain actively involved in the delivery. In special cases (such as cardiac disease) this should be modified with the patient in a Fowler position with her feet on small stools below the level of her hips. The legs should be abducted but not to the point where excessive tension is placed on the perineal body since spontaneous tearing or unanticipated extension of an episiotomy may occur during delivery. In cases where a direct application of the Kielland forceps is being attempted, the patient's buttocks should overhang the edge of the table (Fig. 23.8). This will allow the shank and handle of the anterior branch to be perpendicular to the floor during the initial application of the blade which may be essential to obtain correct positioning (discussed later in this section). Care should be taken not to overflex the hips, although sufficient flexion to approximate a McRoberts position is useful during the delivery itself. Once the delivery is accomplished the patient should be repositioned to prevent pressure on or stretching of the nerves.

FIG. 23.8. Positioning for an operative vaginal delivery.

The most common nerve injuries noted following vaginal delivery with prolonged lithotomy positioning and their putative mechanisms are listed in Table 23.5. The patient's hands should be positioned on handles attached to the table during the delivery to allow her to support herself and maximize maternal pushing efforts during traction.

Femoral nerve (L2, 3, and 4)	Presentation: Quadriceps paralysis and impaired knee extension, loss of patellar reflex, hypoesthesia over the front of the thigh and medial aspect of calf, numbness of the anterolateral area of thigh Etiology: Hyperflexion of the hips with traction or compression injury of the nerve, prolonged lithotomy position with lanking at Poupart ligament, mid-forceps delivery, retractions at CS, epidural anesthesia
Lateral femoral cutaneous nerve (L2 and 3)	Presentation: Numbness over anterolateral thigh Etiology: Compression of the nerve under the inguinal ligament from prolonged or incorrect lithotomy position, retractions at CS
Common peroneal nerve (L4 and 5, S1 and 2)	Presentation: Foot drop, hypoesthesia over anterolateral aspect of lower calf, foot, and toes Etiology: Compression of the nerve at the lateral aspect of the knee where it is very superficial by a lithotomy pole, has also been reported after epidural anesthesia
Lumbosacral trunk (L4 and 5)	Presentation: Paralysis of the dorsiflexors of the ankle with footdrop, hypoesthesia over the lateral aspect of the calf and foot, slight weakness of the quadriceps (L4), slight weakness of the hip adductors (L4, L5) Etiology: Compression of head against sacrum, more common in midcavity operative vaginal delivery, has been reported after epidural anesthesia
Sciatic nerve (L4 and 5, S1, 2, and 3)	Presentation: Inability to flex leg, pain from gluteal region down to the foot Etiology: Traction injury from lithotomy position, metforcaps, incorrect intramuscular injection
Obturator nerve (L2, 3, and 4)	Presentation: Inability to adduct leg, hypoesthesia medial thigh Etiology: Lithotomy position, acute flexion of hip, hematoma, trauma from forceps blades
Saphenous nerve (L2, 3, and 4)	Presentation: Hypoesthesia medial foot and anteromedial lower leg Etiology: Lithotomy position

CS, cesarean section.

TABLE 23.5. *Common nerve injuries, presentation, and etiology*

Adequate Anesthesia

Optimal analgesia for forceps operations is provided by epidural or spinal conduction anesthesia. Frequently, however, the situation does not allow this, and in such cases a pudendal block and perineal infiltration should be instituted if possible. General anesthesia may occasionally be indicated.

Understanding of the Process

Full understanding of the process will help the patient participate and cooperate in the delivery. Explaining each step as it happens, encouraging her, and communicating one-on-one with her as the operation is performed will allay the patient's anxiety and allow her to feel part of the delivery. This is important since patients often feel quite apprehensive about the procedure.

Recheck that Prerequisites Have Been Satisfied

One of the most important prerequisites to recheck just before placing the forceps is the fetal head station and position. This may change during the preparation of the patient and in some cases forceps may no longer be required.

“Ghosting”

Assembling the forceps or vacuum extractor prior to use will enable the operator to check that, in the case of the forceps the two branches are from the same set and that they articulate well, and that in the case of a vacuum extractor all parts fit together and function. The instrument can then be held in a way that simulates the intended application.

THE VACUUM EXTRACTOR

The vacuum extractor is a device made up of a vacuum cup (of various shapes and designs), a method of developing a vacuum within the cup, and a handle used to apply traction to the cup (and via the cup to the fetal head) (Fig. 23.9). It is beyond the scope of this chapter to describe all of these devices in detail but some description of the more commonly seen vacuum extractors is appropriate.

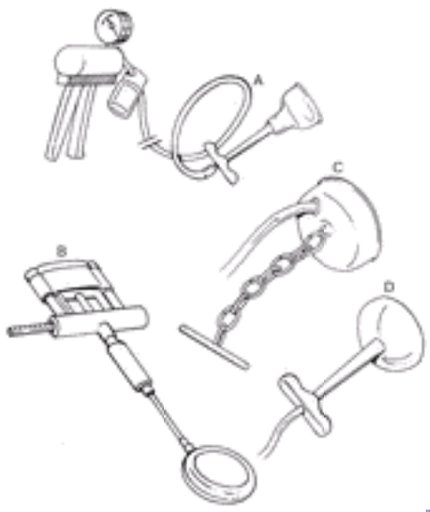

FIG. 23.9. Vacuum extractor cup designs.

Malstrom designed the stainless steel vacuum cup in the 1950s and this revolutionized the practice of operative vaginal delivery. The device works on the principle of creating an artificial caput (chignon) within the suction cup that enables the cup to hold firmly onto the fetal scalp allowing traction thereon. In the U.S. the stainless steel cups have almost completely been replaced by plastic and Silastic soft cup extractors (Kiwi extractor, Silastic cup, Mityvac M-cup, and plastic versions of the original Malstrom design, see Fig. 23.9). Suction is developed using either an electrical pump system or a handheld device.

There have been arguments about the relative success rates and trauma incidence of the different vacuum extractor models. Johanson and Menon reviewed nine trials involving 1,375 women for the Cochrane Database ([3]). They report that soft cups are significantly more likely to fail to achieve vaginal delivery (odds ratio [OR] 1.65, 95% confidence interval [CI] 1.19–2.29). However, the soft cups were associated with less scalp injury (OR = 0.45, 95% CI = 0.15–0.60). There was no difference between the two groups in terms of maternal injury. The authors concluded that metal cups appear to be more suitable for “occipitoposterior,” transverse, and difficult “occipitoanterior” position deliveries. The soft cups seem to be more appropriate for straightforward deliveries. There are some design issues that may be important in the choice of device for specific situations. The relatively rigid rod connecting the handle and cup in most plastic extractor designs precludes accurate placement of the instrument on deflexed or posteriorly positioned heads; this contributes to failure. However, high success rates with a rigid but plastic “M” (mushroom) cup (similar to the original Malmstrom stainless steel cup) have been reported in operations involving these common cranial malpresentations.

CHOICE OF INSTRUMENT FOR CEPHALIC PRESENTATIONS

Outlet Operations/Low-pelvic Operations (Rotation 45 Degrees)

With adequate analgesia, the vacuum extractor and forceps are equivalent instruments. If a vacuum extractor is chosen, any of the previously mentioned instruments can successfully be applied.

Low-pelvic Operations with Rotation More Than 45 Degrees and Midpelvic Operations

Procedures that do not involve significant cranial asynclitism are equally well managed by any of the vacuum instruments discussed. For cases in which there is an asynclitic head in a transverse position, the appropriate cup choices include an occipitoposterior (OP) metal cup (e.g., Bird design, O'Neil design) and a plastic OP design (e.g., Kiwi, Mityvac “M”).

If vacuum extraction is performed using a direct OP cup, appropriate choices include an OP metal cup (e.g., Bird design, O'Neil design) or a plastic OP design (e.g., Kiwi, Mityvac “M”) (see Fig. 23.9). Rotational delivery with a vacuum extractor, or delivery of the fetal head in an OP position, can prove difficult and there is a significant risk of maternal soft tissue injury. These types of procedure should be restricted to the experienced surgeon only.

It should always be remembered that high-pressure vacuum generates large amounts of force and that inexpert use will result in poor outcome regardless of the instrument used.

INDICATIONS AND CONTRAINDICATIONS FOR VACUUM EXTRACTION

Maternal and fetal indications for vacuum-assisted delivery are listed in Table 23.6. Relative contraindications for vacuum extraction are given in Table 23.7. The precise gestational age at which a fetus is considered too premature for vacuum extraction delivery is controversial. Bofill and colleagues ([4]) use a gestational age of 34 weeks as the cutoff point. Morales and colleagues, however, found no significant difference in neonatal morbidity rates following vacuum extraction of preterm infants (birth weights of 1,500 to 2,499 g [3 lbs, 4 oz to 5 lbs, 6 oz]) and full-term infants.

Maternal indications
Need to avoid voluntary maternal expulsive effort (e.g., the mother has cardiac or cerebrovascular disease)
Inadequate maternal expulsive efforts
Maternal exhaustion or lack of cooperation
Fetal indications
Nonreassuring fetal heart tracing
Prolonged second state of labor
Failure to progress in second stage of labor

TABLE 23.6. *Indications for vacuum-assisted delivery*

Operator inexperience
Fetal prematurity (<34 wks of gestation)
Fetal scalp trauma
Unengaged head
Incomplete cervical dilation
Uncertain fetal head position
Active bleeding or suspected fetal coagulation defects
Suspected macrosomia
Inability to achieve proper application
Prior failed forceps delivery
Nonvertex presentation or other malpresentation
Cephalopelvic disproportion
Delivery requiring rotation or excessive traction
Inadequate anesthesia

TABLE 23.7. *Relative contraindications for vacuum extraction*

Placement of the Soft-Cup Vacuum Extractor

A proper vacuum extraction depends upon (a) the accuracy of cup application, (b) the traction technique, (c) the fetal cranial position and station at the time of

application, (d) the cup design, and (e) the fetopelvic relationship.

Prior to use of the vacuum extractor, the prerequisites for any operative vaginal delivery should be satisfied (see Table 23.4).

Cup Application Correct cup placement is paramount and determines the likelihood of success to great extent. The patient is usually placed in the dorsal lithotomy position and adequate anesthesia can usually be provided with an epidural, spinal, or pudendal block. Prior to cup placement the fetal presentation, amount of fetal head palpable above the symphysis pubis, fetal head position, and station should again be confirmed. In cases where fetal head position is difficult to determine, transabdominal or transperineal ultrasound can be of benefit. The soft cup is introduced by spreading the patient's labia, compressing the cup, and inserting it gently by pressing inward and downward with the inferior edge over the posterior fourchette. Some operators use surgical soap or lubricant to moisten the edge of the cup to help form an effective seal. When correctly applied, the vacuum cup is positioned centrally over the point of cranial flexion, or the pivot point (Fig. 23.10). When the vector of traction force is directed through this pivot point, the fetal head is flexed and not twisted obliquely or extended as the extraction proceeds. Anatomically, the pivot point is an imaginary spot over the sagittal suture of the fetal skull, located approximately 6 cm posterior to the center of the anterior fontanelle or 1 to 2 cm anterior to the posterior fontanelle. When a standard 60-mm cup is used this translates into a position where its edge is approximately 3 cm or 2 fingerbreadths behind the center of the anterior fontanelle in the midline over the sagittal suture. Thus, in vacuum extraction operations, the anterior fontanelle becomes the reference point for checking the instrument application because access to the posterior fontanelle is partially blocked once the extractor cup is in place, rendering this familiar landmark unusable. The farther the cup is placed from the midsagittal position on the fetal head over the cranial pivot or flexion point, the greater the failure rate. Oblique applications result in cranial deflexion or asymmetry as traction is applied. This increases the work of extraction by presenting a larger cranial diameter to the birth canal than would occur had the application been correct.

FIG. 23.10. Optimum placement of the vacuum extractor cup on the fetal head.

Correct cup placement maintains flexion of the fetal head and avoids traction over the anterior fontanelle (which aggravates fetal neck extension). After positioning the cup, but before inducing the vacuum, the edge of the cup should be palpated circumferentially to detect any entrapment of maternal soft tissue between the cup and the fetal head. Apart from causing significant vaginal or cervical tears with resultant maternal hemorrhage, entrapment of maternal tissue will cause “pop-off” and a failed procedure. Once the surgeon is convinced of an appropriate placement, full vacuum is applied (i.e., 550–600 mm Hg) and traction follows. The degree of vacuum determines the traction forces (see Fig. 23.3). Effective traction usually requires a pressure of at least 0.6 kg per cm^2 (440 mm Hg). Although more negative pressures reduce the risk of cup detachment, lowering the pressure beyond 0.8 kg per cm^2 (588 mm Hg) increases the risk of fetal scalp and cerebrocranial trauma. During traction, the operator places the nondominant hand within the vagina, positioning the thumb on the extractor cup and one or more fingers on the fetal scalp. The dominant hand is used to grasp the handle of the instrument. When positioned like this, the surgeon follows the descent of the presenting part and can better judge the appropriate angle for traction while gauging the relative position of the cup edge to the scalp. This helps to detect cup separation while preventing rocking motions or torque (which should be avoided). Once vacuum is applied, the cup should not be twisted. Twisting the cup may lead to “cookie-cutter” or semi-circumferential laceration of the fetal scalp, although this is less likely to occur with the soft cup than with the metal cup. Traction should be in line with the pelvic axis and coordinated with maternal expulsive efforts. In some situations the vacuum extractor can be used to aid rotation of the fetal head during traction efforts (discussed subsequently). Descent must begin with the initial traction effort; failure to achieve a change in station mandates prompt reassessment of the procedure. Two common vacuum extraction traction techniques exist: continuous vacuum with maintained traction efforts throughout the procedure versus intermittent vacuum with the vacuum and the traction efforts released between contractions. These techniques have been studied in a randomized controlled trial. No differences were detected between the two groups with regard to the rapidity of delivery, rate of instrument failure, or maternal or fetal outcomes. Thus, the use of either technique is acceptable. Some authors suggest that continued moderate traction may aid in maintaining the progress made in descent of the fetal vertex. If the cup is dislodged, it is reapplied only after careful inspection of the fetal scalp for injury. Traction is continued until the head is crowned. As the head clears the pubic symphysis, the vertex is pulled upward at an approximate angle of 45 degrees to the floor. Once the head is delivered, suction is released, and the cup is removed. Delivery then proceeds as usual. Although no “standard of care” currently exists regarding the duration of a vacuum extraction attempt, the number of traction attempts permitted, or the number of “pop-offs” that should be tolerated, common sense decrees certain limits. *Most experts suggest that vacuum extraction should not be attempted for more than 20 to 30 minutes, that traction attempts should be limited to four to five, and that the procedure should be abandoned after three cup detachments.* Approximately 85% of births requiring vacuum extraction are delivered with four or fewer than four pulls. Thus, if a prolonged extraction with any instrument occurs, the obstetrician must carefully consider if progress truly is taking place. Procedures leading to multiple cup pop-offs or procedures requiring a large number of traction efforts are best abandoned because it is believed that this practice risks injury as the obstetrician strains to overcome disproportion. Finally, the procedure should also be abandoned if there is any evidence of fetal scalp trauma. No data exist dealing with how long one should persist in the face of fetal bradycardia. I would advise that unless delivery is assured and imminent, operative vaginal procedures should not be performed or should be abandoned in favor of a cesarean section when there is persistent bradycardia. It is very reasonable to attempt an operative vaginal delivery while preparations are being made for cesarean section if it seems highly likely that the procedure will be successful. Detailed documentation of the operative delivery in the medical record is very important and is discussed in the following section.

Advisory Letter

On May 21, 1998 the U.S. Food and Drug Administration (FDA) released an advisory letter to alert individuals who use vacuum extractors and inform them that these devices may cause serious or fatal complications such as subgaleal (subaponeurotic) hematoma and intracranial hemorrhage. This letter was in response to an increased incidence of reported vacuum-related fetal injuries. The FDA also wanted to ensure that those responsible for the care of neonates are alerted when a vacuum-assisted device is used so that they may adequately monitor for the signs and symptoms of device-related injuries ([5]). The letter made the following points as to technique:

The vacuum extractor should only be used when a specific indication exists.
The operator should be versed in its use and aware of indications, contraindications, and precautions.
The operator should follow manufacturers' recommendations regarding cup placement, vacuum strength, cumulative duration of applications, and number of extraction attempts.
Rocking movements or torque should not be applied to the device and only steady traction in the line of the birth canal should be used.
Neonatal care providers should be alerted that a vacuum has been used.
Neonatal staff should be educated about the specific complications associated with vacuum devices.
Adverse events and complications associated with vacuum-assisted devices should be reported to the FDA under the auspices of the Safe Medical Devices Act of 1990.

Following publication of the advisory there was significant discussion at both the organizational and lay level. In some instances draconian restrictions were placed on the use of the vacuum extractor and, in response, ACOG published a committee opinion expressing specific concerns that (a) the advisory letter was based on a very low risk of adverse events, and that (b) reaction to the advisory may result in a higher cesarean section rate, or alternatively in the increased use of forceps by those not trained to use them. The ACOG committee strongly recommended that there be continued use of vacuum-assisted delivery devices in appropriate clinical settings ([6]).

Subsequent to the ACOG committee opinion, Ross and colleagues studied the effect of the FDA advisory letter on the reporting of vacuum-related injuries ([7]). They noted a 22-fold increase in reported events within the first 6 months after publication, when compared with the rate prior to the advisory letter—5 per year before versus 110 per year after the advisory letter. There were 10 neonatal deaths, 30 life-threatening events, 12 non–life-threatening events, and 3 equipment failure reports. Of note is that the increased number of reports was due to a significant increase in reports from vacuum device manufacturers (8%–43%). There was a decrease in the number of “voluntary” reports (56%–20%). The authors believe that the sudden increase in reports represents better compliance with reporting, increased awareness of the dangers, and a continued increase in the use of the vacuum extractor. They suggest that that the device may not be as innocuous as was once thought and that many adverse events were going unreported prior to the advisory letter.

In support of this contention is a retrospective chart review from the University of Miami conducted on patients delivered between 1995 and 1999. There were 355 patients in each group who were matched for age, ethnicity, parity, estimated gestational age, and birth weight. Vacuum extraction was 600% more likely to have occurred when the patient had an epidural anesthetic (OR = 6.6 [range, 2.6–16.6]). Following delivery with a vacuum extractor neonates were almost four times more likely to go to a neonatal intensive care unit (OR = 3.7 [range, 1.3–9.6]). There were no differences in the rates of maternal lacerations or meconium-stained fluid.

Whether or not the babies were admitted for observation or whether the increased rate of admission truly represented increased risk of injury is unclear.

OBSTETRIC FORCEPS

Anatomy of Forceps

Forceps are a paired instrument made up of two branches that are usually attached to each other in some way by a locking mechanism. In general, the branches are side-specific and the left branch is applied to the left side of the maternal pelvis using the left hand. The right branch is applied to the right side of the maternal pelvis using the right hand. One exception to this rule is the Salinas forceps which has branches that may be applied without concern to side specificity. Application techniques are described subsequently.

Classic forceps have branches that are made up of a handle, shank, lock, and blade (Fig. 23.11). The tip of the blade is referred to as the toe, the base of the handle is referred to as the heel, and the portion where the shank runs into the blade is termed the shoulder. In some cases an additional part is included to aid in traction and this is termed a traction bar (De Lee forceps) (Fig. 23.11).

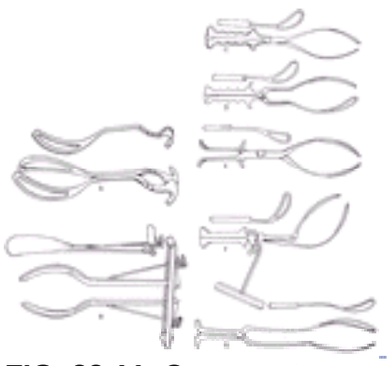

FIG. 23.11. Common types of obstetric forceps.

Handle Most forceps in current usage have some form of handle that incorporates finger grips or lateral flanges. In some cases, the handle may be very small (Laufe divergent forceps and Wrigley forceps, see Fig. 23.11) or rather bulky as in the Salinas forceps. Classic Elliot forceps have a screw and wheel built into the heel of the instrument that allows adjustment of the distance between the heels in order to limit head compression during use.
Shank The shank connects the blade to the handle and usually incorporates the locking mechanism. The shanks may be parallel, overlapping, or divergent, and vary in length from very short (Laufe) to rather elongated (Piper, Kielland, Bailey-Williamson forceps). They may also be straight or have varying degrees of curvature (Piper forceps).
Lock The lock (Fig. 23.12) is usually built into the left-sided shank (or at the junction of the shank and handle) except in the case of the Salinas forceps where the lock forms part of the handle itself. The lock may be:

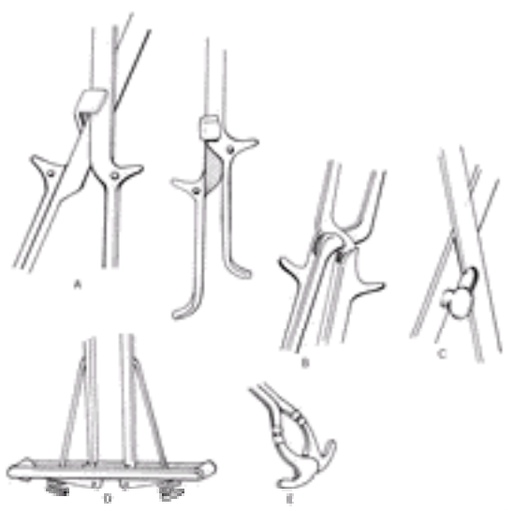

FIG. 23.12. Types of locks: Sliding, English, French, handle.

- sliding (only found on the left shank and allows sliding of the shanks while locked—Kielland forceps)
- English (which is formed by the mating of a tongue and slot mechanism—Simpson, Elliot, Neville-Barnes, Anderson forceps)
- French (which has a nut that is tightened to fix the lock)
- pivot (forms part of the finger grip and tends to force the blades apart as traction is applied—Laufe forceps)
- handle (Salinas forceps).

Blade The blade is the portion of the forceps that grasps the fetal head. Blades may be fenestrated (Simpson, Elliot, Neville-Barnes), pseudo-fenestrated (Luikart-Simpson), or solid (Tucker-McLane, Salinas). Fenestrated blades are purported to cause more maternal tissue damage during rotation. Solid blades are thought to reduce maternal injury by reducing friction but they are associated with increased fetal head slippage. Most forceps have a rigid blade that does not deform; the Salinas forceps however does allow some deformation of its shape because of its minimal thickness. Most forceps have two curvatures: A pelvic curvature which is usually concave upward to approximate the maternal pelvic curve of Carus, with the tip of the blade usually about 3 inches above the level of the handles; and a cephalic curvature designed to fit snugly around the fetal head with a diameter of no less than 7.5 cm at its widest portion. Blades best suited to a molded fetal head tend to be those that are elongated and have a more shallow cephalic curvature (Simpson, De Lee forceps). In cases where the fetal head is less molded a shorter blade with a more rounded cephalic curvature may be more suitable, although either type of forceps may be safely used under both circumstances. Kielland and other rotational forceps, including the Salinas forceps, have almost no pelvic curvature, and this allows safe placement and rotation of the blades in transverse head positions. Rotation of a fetal head using a forceps with a pelvic curvature mandates use of the Scanzoni maneuver (whereby the heel follows the circumference of a large circle during the rotation in order to negate the pelvic curvature of the blade). Some forceps have a reverse pelvic curvature (Piper and Hawkes-Dennen forceps) in order to allow use during vaginal breech delivery.
Traction Bar Some forceps (Hawkes-Dennen) have a built-in device to allow the handles to rotate as the head descends through the birth canal. The idea is to optimize the outward and downward vectors so that the head follows the curve of Carus with the least soft and hard tissue friction. This principle of axis–traction can also be obtained using a traction bar (see Fig. 23.11) which fits onto the handle flange of some forceps.

Mechanical Aspects of Obstetric Forceps

From a mechanical point of view, forceps have four potential actions:

1. Correction of deflexion, asynclitism, or positional abnormalities of the fetal head that impedes or retards descent, rotation, and accommodation within the pelvis.
2. Extraction, which includes augmenting or replacing the expulsive force generated by uterine contractions and voluntary pushing.
3. Reduction of the friction between the fetal head and the birth canal.
4. Transient, artificial enlargement of the soft tissue of the birth canal which reduces the resistance of the outlet.

An understanding of the mechanical forces and principles involved in a forceps delivery is important since it allows the operator to better judge the chances of success in each individual case.

Type of Forceps Delivery

Two main parameters determine the successful outcome and associated morbidity of operative vaginal delivery. These are (a) the station at which the procedure is

performed, and (b) the degree of rotation required. Based on the new definition of station, the types of forceps delivery were reclassified by ACOG in 1988 (Table 23.8). This new classification has been validated in a comparative study of 357 forceps deliveries classified using both systems. Allowing for up to 45 degrees of rotation in an outlet forceps delivery, and classifying any delivery from 0 to 2+ station as midforceps, regardless of rotation, did not increase morbidity.

Outlet forceps:
1. Scalp is visible at the introitus without separating labia
2. Fetal skull has reached pelvic floor
3. Sagittal suture is in AP diameter or right or left OA or OP position
4. Fetal head is at or on perineum
5. Rotation does not exceed 45 degrees
Low forceps:
Leading point of fetal skull is at station + or ≥2 cm and not on the pelvic floor
a. Rotation = or <45 degrees (left or right OA to OA, or left or right OP to OP)
b. Rotation >45 degrees
Midforceps:
Station above +2 cm but head engaged

AP, anteroposterior; OA, occipital-anterior; OP, occipital-posterior.

TABLE 23.8. *Classification of forceps deliveries*

Indications As the specialty has evolved, so have the uses and indications for forceps. We no longer accept stimulation of contractions, artificial molding of the fetal head, forceful dilation of the cervix, or delivery from a high station as indications for forceps. The indications for operative vaginal delivery may be divided into standard and special indications (Table 23.9). It must be understood that regional and international practice differences wilS apply and that no indication for operative vaginal delivery is absolute.

Standard indications: apply to the patient in whom the fetal head is engaged and the cervix is fully dilated
1. Delayed second stage
a. This is defined in the ACOG technical bulletin (No. 196, August 1994) and is different for nulliparous and multiparous women.
i. Nulliparous—lack of continuing progress for 3 h with regional anesthesia, or 2 h without regional anesthesia.
ii. Multiparous—lack of continuing progress for 2 h with regional anesthesia, or 1 h without regional anesthesia.
2. Suspicion of immediate or potential fetal compromise.
3. Elective shortening of the second state for maternal and fetal benefit
a. Need to avoid maternal expulsive effort (as in certain maternal cardiac pulmonary, ocular, and cerebrovascular conditions).
b. Need to augment maternal expulsive effort (as in certain maternal neuromuscular diseases, maternal exhaustion, and lack of cooperation or excessive sedation/analgesia).
c. Selective shortening of the second stage when the head is on the perineum and oriented within 45 degrees of the AP diameter.
d. Selective shortening of second stage to avoid potential fetal and maternal complications resulting from persistent pushing efforts when there is a malposition of the fetal head.
Special indications:
1. Delayed second stage due to malposition or asynclitism of the fetal head where there may be correctable borderline disproportion due to the abnormal head position.
2. Prolapse of the umbilical cord at complete dilation.
3. Nonobstetric indications, which include the extraction of vaginal and rectal foreign bodies, including drugs. (refs)
It is generally understood that a higher level of judgment and skill are necessary when operative vaginal delivery is carried out for special indications. A good understanding of the indication(s), and documentation of this prior to the procedure, will help the obstetrician plan the delivery. In addition, it will help ancillary personnel understand the urgency or need for the procedure and allow them to orchestrate their involvement (anesthesiologist, neonatologists, nursing, and OR personnel).

ACOG, American College of Obstetricians and Gynecologists; AP, anteroposterior; OR, operating room.

TABLE 23.9. *Indications for operative vaginal delivery*

Contraindications

Under certain circumstances operative vaginal delivery should be avoided, or at least carefully considered in terms of relative maternal and fetal risk. The specific reason for the procedure should be carefully documented. Accepted contraindications to forceps delivery are listed in Table 23.10.

1. A noncooperative patient, or one who refuses operative vaginal delivery
2. A fetus with a known bone demineralization condition (e.g., osteogenesis imperfecta) or bleeding diathesis (e.g., alloimmune thrombocytopenia, hemophilia)
a. An unengaged fetal head
b. An unknown position of the fetal head
3. A prior failed operative vaginal delivery attempt (unless there is an obvious reason for the failure unrelated to cephalopelvic disproportion which is unlikely to occur again, and there is justification for a second attempt)
a. A known fetal weight in excess of 4,500 g

TABLE 23.10. *Contraindication to forceps delivery*

Choice of Instrument

There are approximately 700 different types of forceps described. Most authors subscribe to a classification system that divides forceps into classic and specialized subtypes.

The classic subtype includes such forceps as the Simpson, Elliot, Neville-Barnes, Anderson, Tucker-McLane, and Naegle. These forceps would be suitable for most general prophylactic indications (outlet forceps).

The specialized subtype, which includes the Kielland (see Fig. 23.3), Barton (see Fig. 23.4), and Piper (see Fig. 23.5) forceps, is employed for specific tasks such as rotational deliveries (Kielland and Barton), correction of asynclitism (Kielland), and delivery of the aftercoming head in a breech delivery (Piper).

A novel type of forceps has been introduced into the U.S. from Mexico. The Salinas forceps has two identically shaped, nonfenestrated blades with minimal pelvic curvature which can be used interchangeably (see Fig. 23.11). The Salinas forceps also has a lock at the heel of the forceps and the blades are convergent. The blades are kept in place by maternal tissue and no compressive force is generated by the forceps. The operator holds the locked base of the forceps in both hands and applies gentle traction to effect delivery. The blades will slip off if excessive force is applied. The Salinas forceps can also be used for rotation of the fetal head.

The choice of one instrument over another depends on the indication, the training of the obstetrician, the instruments available, and the situation at hand. A comparison of the perceived advantages/disadvantages of forceps versus vacuum extraction is shown in Table 23.11. There are some who choose their forceps based on the condition of the maternal soft tissue (nonfenestrated blade when there is a lot of edema and potential for tearing; overlapping rather than parallel shanks for a patient with a narrow introitus), fetal head molding (Simpson forceps for a molded head and an Elliot-type forceps for a nonmolded head to allow a better fit of the forceps blade to the fetal head shape), or fetal presentation (Piper forceps for the aftercoming head). The need for a rotation or correction of asynclitism also may dictate the type of forceps used (i.e., Kielland, Luikart-Simpson, Barton, or Salinas forceps). Delivery of the aftercoming head in a breech delivery using Piper or Laufe-Piper forceps will permit flexion of the head without excess traction on the fetal spine and reduce the incidence of spinal cord injuries. Face presentation is another unique situation and, in general, mentum-anterior presentations can be delivered using Kielland or Simpson forceps. Rotation of the mentum- posterior/mentum-transverse face presentation to a mentum-anterior presentation has been described but few choose to perform these maneuvers.

Vacuum extractors:
Easier to learn
Quicker delivery
Less maternal genital trauma
Less maternal discomfort
Fewer neonatal craniofacial injuries
Less anesthesia required
Forceps:
Fewer neonatal injuries, including cephalohematoma, retinal hemorrhage, and transient lateral rectus palsy
Higher rate of successful vaginal delivery

TABLE 23.11. *Comparative advantages of vacuum extractors and forceps*

Application of Forceps Correct insertion of the forceps into the vaginal canal and application to the fetal head is paramount to a successful procedure. The forceps

should be placed between contractions. In almost all cases one of two methods will allow good application of the forceps: direct and wandering. Application of the forceps blades should be a gentle and smooth process requiring minimal force. In most cases, if the blade is correctly inserted and positioned, gravity should be sufficient to allow the forceps blade to fall into place. During training it is a good idea to learn to apply the forceps using only the index finger, middle finger and thumb to grasp the shank (Fig. 23.13). The blade should be positioned using the index and middle fingers placed under or on the edges depending on the method employed. No force should be required and if there is resistance the blade should be removed and reapplied. In this way maternal and fetal injury will be minimized. A lubricant such as K-Y jelly placed on the blade may reduce friction and facilitate placement.

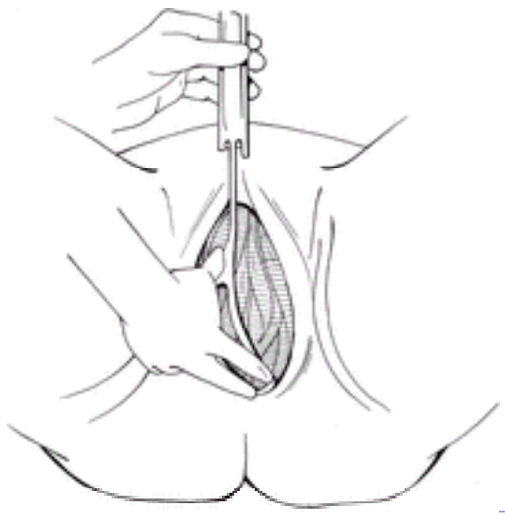

FIG. 23.13. Grasp of forceps.

Direct Placement With this method, the left blade (i.e., the blade that lies on the maternal left) is conventionally placed first. The operator holds the shank at the level of the lock, and the blade is placed into the vagina in the approximate position that it will ultimately lie. The right middle finger is used to support the edge of the blade at the introitus and the right index finger is used to gently apply the upper border of the blade onto the fetal head. The fingers or hand are not placed deep into the vagina. The practice of placing a hand into the vagina to “protect” the vaginal wall is probably not beneficial since this reduces the available space and increases the force required to place the blade. Once the left blade is correctly positioned, minimal force with the left hand will be required to slide it further into the birth canal and into its correct final position. The index and middle fingers of the right hand “walk” along the upper and lower borders of the blade as it enters the birth canal gently pushing it in and adjusting its position. When correctly placed the branch should be firmly held by the fetal head and maternal tissue (not immovable) and the shank and handle should be in the position expected from the “ghosting.” If the position is different from that anticipated the branch should be gently removed by reversing the movements required to initially place it, and the fetal head position should be checked (if necessary, by a more experienced operator). If the anticipated shank and handle angle are incorrect, attempting to place the right hand branch and forcing the two together is absolutely contraindicated. This will only result in maternal and fetal injury. Once the left branch is placed, an assistant can be asked to hold the branch in position or it can be briefly left unattended while the right branch is placed. Holding the right branch with the right index finger, middle finger and thumb, the right branch is placed into the vagina in the approximate position that it will ultimately lie. The right branch should be above the left in order to ensure correct locking. The left middle finger is used to support the edge of the blade at the introitus and the left index finger is used to apply slight pressure onto the fetal head. Once the right blade is correctly positioned, minimal force with the right hand will be required to slide it further into the birth canal and into its correct final position. The index and middle fingers of the left hand “walk” along the upper and lower borders of the blade as it enters the birth canal gently pushing it in and adjusting its position to complement that of the left branch. No force should be used to lock the instrument and the final shank and handle position should be the same as that expected from the “ghosting”. Once both branches are placed, the fetal head position and the application of the forceps should be checked prior to any traction efforts.

Wandering Placement With this method the left branch is also placed first. The operator holds the shank at the level of the lock, and the blade is placed into the vagina with the toe of the blade at the posterior fourchette and the branch held straight upward. The right index and middle fingers are used to support the edge of the blade (Fig. 23.14) at the introitus and to apply slight pressure onto the fetal head. The fingers or hand are not placed deep into the vagina. Once the left blade is correctly positioned, minimal force with the left hand will be required to begin sliding it further into the birth canal. Usually gravity and the weight of the branch is all that is required. As the blade moves into the birth canal the right index and middle fingers (which are held on the maternal left and right edges of the blade, respectively) gently push the blade laterally (maternal left) and “wander” it into position using successive small finger movements and without placing the fingers deep into the vagina. The handle will move in an arc from an initial vertical position to a horizontal position. Once learned, this is a smooth and seamless process. The position is checked as previously described. Once the left branch is placed, an assistant can be asked to hold the branch in position or it can be briefly left unattended while the right branch is placed. Holding the right branch with the right index, middle finger and thumb, the right branch is placed into the vagina in the same way as was the left branch. Once correctly positioned, minimal force with the right hand will cause the blade to move into the birth canal. The left index and middle fingers (which are held on the maternal right and left edges of the blade, respectively) gently push the blade laterally (maternal right) and “wander” it into position in the same way as was done with the left blade. The right branch should be kept above the left during this process to enable correct locking. No force should be used to lock the instrument and the final shank and handle position should be the same as that expected from the “ghosting”.

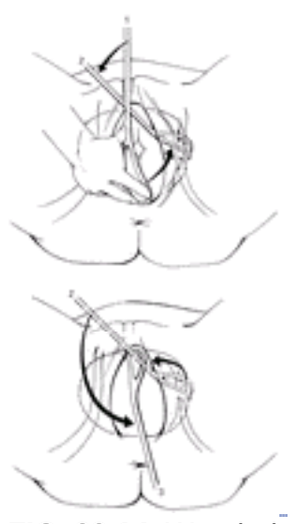

FIG. 23.14. Wandering placement of forceps.

Once the blades are placed, their positioning should be checked. The blades are correctly placed when they are situated against the sides of the fetal head in the spaces between the orbits and the ears (Fig. 23.15). The toe of the blade should reach slightly beyond the malar eminences in order to allow even pressure distribution and to concentrate traction and compression forces on one of the less vulnerable regions of the fetal head. Prior to applying rotational or traction forces the operator should check the following:

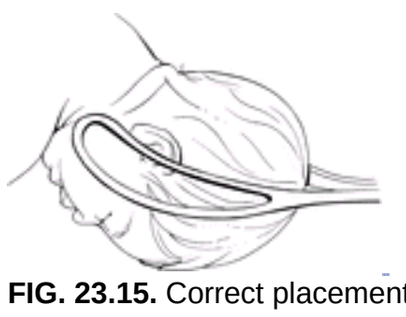

FIG. 23.15. Correct placement of the forceps blades on the fetal head.

The forceps have not accidentally penetrated the side wall of the vagina (any sudden vaginal bleeding after forceps placement should prompt immediate assessment).
The sagittal suture should be palpated symmetrically and perpendicularly between the two blades.
The posterior fontanelle should be palpable close to (about 2 cm) the plane of the shanks but not within the borders of the blade.
The handles, which should not require any more than minimal pressure to close completely, should be pointing straight out and not to either side.
No significant part of the fenestration of either blade should be palpable in front of the fetal head.

Occipitoanterior Positions

Placement of the forceps in a direct occipitoanterior (OA) position can be accomplished as described above. Minor modifications are required when the head is in a left or right OA position. The exact location of the sagittal suture and posterior fontanelle should be known and the final arrangement of the forceps branches should be “ghosted” prior to insertion.

In left occipitoanterior (LOA) positions the left blade should be placed first using either a direct or a wandering approach. Once the left blade is correctly aligned, the right blade can also be placed using either approach. Under most circumstances the wandering approach will work well. The operator must remember that the blade will need to be maneuvered around the sinciput. Careful digital manipulation with the left index and middle fingers will be required to avoid injury to maternal and fetal soft tissue. If the handles do not lock easily the application is incorrect and should be checked. When this occurs the most common cause is that the blade has not been wandered far enough to clear the fetal brow, or has not advanced enough to lie flat against the fetal cheek. Gentle manipulation with index and middle fingers can be tried after unlocking the blades, but frequently the best action is to remove the blade and reintroduce it.

In an upright occipitoanterior (ROA) position, either blade can be placed first using the direct or wandering approach. If the right blade is placed first, once the left blade is positioned the handles will need to be separated and crossed over in order to lock the branches. If the left blade is placed first, the operator will need to manipulate it to a greater extent than in an LOA placement. In either case, care should be taken to prevent soft tissue injury. Rotation from ROA or LOA to direct OA is usually automatic as traction is gently applied and no deliberate elevation of the fetal head is needed.

Traction

Once the forceps have been applied and the position of the blades checked, traction is usually initiated with maternal contractions. The birth canal has a definite curve and this should be kept in mind when applying traction during a forceps delivery. In order to minimize friction, the traction forces on the fetal head should be maintained perpendicular to the axis of the pelvis. This necessitates following of the curve of Carus. The higher the forceps are applied, the greater the initial downward pull required to negotiate the pelvic curve. As the head descends in the birth canal the angle of traction moves forward (in the supine patient), ultimately turning upward at the outlet.

In order to optimize traction efforts the operator should stand slightly to the side of the patient. It is recommended that a right-handed individual stand to the maternal right with the right hand facing upward and the shanks of the closed forceps between the index and middle fingers (Fig. 23.16). The index and middle fingers are curved around the flange of the handle loosely in a forceps with crossed shanks or a sliding lock. In a Simpson-type instrument the middle finger can be placed in the space between the shanks with the index and ring fingers being placed on the handle flange. This hand will apply the outward traction force. Because the traction occurs at the level of the lock (as opposed to the end of the handles) compression of the fetal head will be limited. By angling the body sideways the major muscle group involved is the deltoid. This acts as a natural limited to the amount of traction that is applied. If the operator was standing directly in front of the patient the much more powerful biceps group would be supplying the majority of the traction force. By only using two fingers the operator will further limit the amount of force applied.

FIG. 23.16. Methods of hand placement and stance.

The left hand is placed palm down on the shanks of the forceps and exerts a downward force. This is known as the Pajot maneuver. The combined outward and downward forces can be adjusted to produce a vector that follows the curve of Carus (axis–traction). Similar axis–traction can be applied using the Saxtorph maneuver (see Fig. 23.16) in which the operator is seated and uses the fingers of the left hand to pull the locked shanks downward. Simply pulling in the direction of the handles with a classic-type forceps (Simpson or Elliott) will cause the fetal head to be pulled up under the symphysis pubis. This is because the pelvic curvature of the forceps results in the handles being in a plane that is anterior to the plane of the pelvis in which the fetal head is present. When using an instrument with no pelvic curvature, or a reverse pelvic curvature, it is important not to elevate the handles more than 45 degrees above the horizontal in order to reduce the potential for sulcus tears from the toe of the blade.

A large amount of research has gone into determining what forces constitute safe levels for traction and compression. It has been calculated that during normal spontaneous delivery of the fetal head, second stage expulsive forces range between 8.6 kg and 15 kg. During forceps operations traction forces have been estimated to range from 16 kg to 23 kg. The traction forces are reduced by 25% and 50% by the use of forceps with crossed shanks.

Delivery of the fetal head in an OP position has been associated with increased traction and compression forces probably due to the larger presenting diameters of the fetal head.

Traction should be released between contractions in order to reduce the intracranial pressure differential to which the fetus is exposed. In addition, by releasing the pressure between contractions the vagally induced bradycardia that often accompanies traction efforts will be somewhat alleviated. Because of the potential for fetal heart rate abnormalities during delivery, the fetal heart rate should be continuously monitored during forceps deliveries.

Once the head crowns the handles of the classic-type forceps they can be elevated until they are almost perpendicular to the floor. The hand on top of the shanks will now be pulling almost directly outward. At this point the delivery can be completed with the forceps, or the branches can be disarticulated and the delivery can be completed using a modified Ritgen maneuver.

Occipitotransverse Positions

Occipitotransverse (OT) head position frequently results in a deep transverse arrest and resultant cephalopelvic disproportion. In most cases, this requires rotation of the fetal head to OA or OP to allow vaginal delivery, but occasionally, patients with a platypelloid pelvis will spontaneously deliver a baby with a transverse head position. The options open to the modern obstetrician faced with a deep transverse arrest in an OT position include:

- digital or manual rotation
- rotation with traction using a vacuum extractor (see Chapter XX)
- rotation with forceps
- cesarean section

Unless the operator has had sufficient training and experience with rotational delivery using forceps, cesarean section is frequently the most prudent choice.

DIGITAL OR MANUAL ROTATION

In some cases, particularly if the operator has a small hand, digital or manual rotation can be successfully used to rotate the fetal head from an OT position to an OA position. The digital method entails placing the tips of the index and middle fingers onto the edge of that part of the anterior parietal bone that overlaps the occipital bone in the area of the posterior fontanelle. Pressure is then exerted with the tips of the fingers in an attempt to rotate the posterior fontanelle upward and toward the symphysis pubis (see Fig. 23.6). In a manual rotation the whole hand is introduced into the birth canal and the fingers are placed under the posterior parietal bone. The

thumb is positioned on the anterior parietal bone and the head is rotated (Fig. 23.17). Care should be taken not to completely disengage the fetal head. These maneuvers are difficult for people with large hands; instrumental rotation may be preferred in these circumstances.

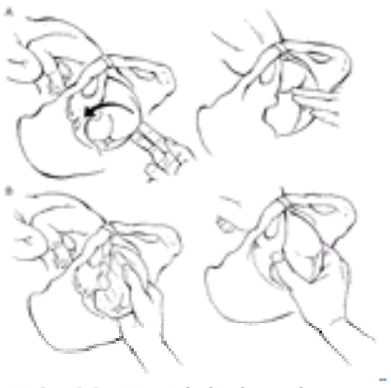

FIG. 23.17. Digital and manual rotation.

If digital or manual rotation is successful, the patient should be encouraged to push in order to increase descent of the fetal head and to stabilize the fetal head position. If the delivery is to be completed using forceps, the fingers should be kept on the fetal head while the forceps are placed (see Fig. 3.17).

ROTATION WITH TRACTION DURING VACUUM EXTRACTION

The vacuum extractor has been promulgated as an instrument with which to effect rotation of the fetal head. While this is true to some extent, it must be remembered that such rotation should only be accomplished by traction in the axis of the pelvis and not by twisting or rotational motions with the vacuum cup. By applying traction in the correct plane, the head is forced to rotate by virtue of the architecture of the soft tissue and bones of the pelvis. The operator should assess the position of the fetal head and take into account the malposition and the attitude and asynclitism of the presenting part. By applying the traction force in an appropriate direction to correct the flexion and asynclitism of the head, rotation will occur automatically as the head descends. The use of a twisting motion is contraindicated because of the risk of cephalhematoma and scalp laceration imposed by the significant shearing force that can be delivered to the soft tissue of the head. This effect is more pronounced when using the metal cup systems than with the Silastic cup. In most situations where rotation is required, choice of an appropriate forceps method will be more likely to result in successful rotation than use of the vacuum extractor.

ROTATION WITH FORCEPS

Rotation of the fetal head from a transverse position to an OA position is one of the most demanding (and satisfying) obstetric operative procedures. It is also one of the most technically demanding. Forceps rotation can be accomplished using classic forceps (i.e., Elliott, Tucker-McLean, Neville-Barnes), specific rotational forceps (Kielland, Barton), or Salinas forceps. The blades may be applied using the classic method, the wandering method, or the direct method.

When using a forceps with no, or minimal, pelvic curvature (Kielland, Salinas), I prefer using the direct method to apply the blades to a head in a deep transverse arrest (Fig. 23.18). In my experience this method involves the least manipulation. If performed correctly, the blades will be correctly positioned with the minimum potential for fetal and maternal injury. The wandering method is a better choice when using a classic-type forceps. I do not believe that a forceps with a pronounced pelvic curvature should be applied using the classic method and I therefore only describe the classic method using a Kielland forceps. When performing a rotational delivery my preference is to use a forceps designed for rotation rather than a classic-type forceps.

FIG. 23.18. Direct application of Kielland forceps for rotation.

Occipitoposterior Positions

An occipitoposterior position may be managed by delivery as a direct OP, by digital or manual rotation, by instrumental rotation, or by a combination of these methods. In general, a well-flexed head in an OP position can be delivered as a direct OP. If the head is extended or only minimally flexed then attempting a direct OP delivery may result in an increased risk of maternal and fetal trauma. This is because of the greater traction required to deliver the head due to the larger diameter presented. There is also the chance that traction on a deflexed head will exaggerate the extension and worsen the situation. Under these circumstances I prefer to rotate the head to an OA position, and this will usually help flex the head as well.

Digital or Manual Rotation

This is performed similarly to that described previously for OT positions except that the arc of rotation is greater.

Instrumental Rotation

Forceps or vacuum extraction can be useful for rotating an OP to an OA position. Either classic-type forceps or an instrument designed for rotation (Kielland or Salinas forceps) can be employed.

If a classic-type forceps is used the blades are placed in the same way as for an OA position (described previously). If the head is in a right OP position the forceps are applied as for a left OA and vice versa. Once the branches are locked the posterior fontanelle should be felt approximately 2 cm below the shanks, with the sagittal suture midway, and perpendicular, between the two blades. The head is then rotated into an OA position with the direction of rotation toward the side of the fetal back. As described earlier, the handles of the forceps should describe a wide arc in order to limit the arc of the toes of the blades. Once the rotation is complete, the now upside-down forceps branches should be removed and replaced in the correct orientation. The easiest way to do this is to have two sets of forceps available for use. As the upside-down forceps branch is removed it can be replaced with the appropriate blade from the other set of forceps. The remaining upside-down blade keeps the head in the OA position during the changeover. Once the replacement branch is correctly positioned the remaining upside-down branch can be removed and replaced with the second branch of the replacement set of forceps. The delivery is then completed as previously described.

If Kielland forceps is used, the blades are applied as for an OA (or LOA/ROA) position using the technique described earlier. The buttons on the handles should face the fetal occiput. The rotation is carried out as already described except that the head is rotated through 180 degrees rather than 90 degrees. The handles should

rotate on their axis since there is no pelvic curvature to contend with. It may be necessary to elevate the head during the rotation and if this is the case the operator may need to lower the handles toward the floor in order to better the forceps with the birth canal. The same slow, controlled maneuvers and precautions should be used as described previously. There is no need to reverse the blades after the rotation and once the head is OA, traction can be applied for delivery. Alternatively, there are some who place the forceps with the buttons facing the sinciput (upside-down application) for the rotation and then remove and replace the forceps for the delivery (either with the Kielland or with a classic-type forceps).

POST-DELIVERY MANAGEMENT

Following operative vaginal delivery the flexion of the patient's hips should be relieved in order to minimize the risk of nerve injury from prolonged pressure or stretching. The episiotomy repair should be performed as expeditiously as possible to limit blood loss and tissue exposure. The birth canal and cervix should be inspected for lacerations and tissue damage. I prefer not to repair minor lacerations that are not bleeding since they will usually heal very quickly. Even cervical tears that are not bleeding are best left alone under close observation. Care should be taken to inspect the periurethral and perianal/rectal areas after any repairs to exclude perforating sutures. Any complaint of anal pain after a forceps delivery should prompt a careful inspection for a vaginal or vulval hematoma. Any sudden drop in hematocrit should indicate a search for continued bleeding either obvious (vaginal or vulval) or occult (retroperitoneal hemorrhage).

Complications of Operative Vaginal Delivery

Complications arise in two main areas:

1. Inappropriate evaluation and underestimation of dystocia.
2. Misuse of an instrument.

It is important to point out that almost all of the complications seen with operative vaginal delivery have also been reported with spontaneous, uninstrumented vaginal deliveries. This should be kept in mind before attempting to link a particular injury directly to an instrumental delivery.

The risks can be divided into maternal and fetal/neonatal.

Maternal Complications Associated with Operative Vaginal Delivery

Lacerations The reported incidence of severe laceration (i.e., third-degree and fourth-degree laceration) during vacuum extraction procedures ranges from 10% to 30%. Operative vaginal delivery with forceps is responsible for a higher incidence of third- and fourth-degree perineal lacerations (closer to 50%) than with spontaneous delivery or vacuum extraction. Meta-analysis of available studies has shown that forceps operations are more likely to specifically result in anal sphincter trauma than vacuum extraction. In pooled data from 8 randomized trials studying maternal delivery trauma, a 6% decrease (95% CI = -.10 to -.02) in anal sphincter trauma occurred if a vacuum extractor, and not forceps, was employed.

Stress Urinary and Anal Incontinence Delivery trauma is suspected to predispose the patient to subsequent pelvic floor dysfunction; however, data indicate that the long-term effects of operative vaginal delivery on rectal or urinary incontinence are more complex than originally believed. Interpretation of all the available data is not straightforward. There is a suggestion that vaginal delivery is a major contributor to, but not the sole culprit of, long-term perineal dysfunction. It is believed that the greater the degree of perineal trauma, the greater the likelihood that there will be residual sphincter abnormalities. Arya and colleagues ([8]) retrospectively studied the incidence of new-onset urinary incontinence after forceps and vacuum delivery compared with spontaneous vaginal delivery. They enrolled primiparous women delivered by forceps (n = 90), vacuum (n = 75), or spontaneous vaginal delivery (n = 150). They then followed these women at 2 weeks, 3 months, and 1 year after delivery and showed that incontinence was similar in the 3 groups at 2 weeks after delivery. The proportion of women developing new-onset urinary incontinence decreased significantly over time in the spontaneous vaginal (*P* = .003) and vacuum delivery groups (*P* = .009) but not in the forceps group (*P* = .2). There was no relationship between urinary incontinence and a history of vaginal lacerations, epidural anesthesia, length of second stage of labor, or infant birth weight. These authors concluded that in primiparous women, urinary incontinence after forceps delivery is more likely to persist compared with spontaneous vaginal or vacuum delivery. A Swedish study of three large databases involving 1,559 patients who presented for incontinence surgery later in life (20–40 years after delivery) linked the need for surgery to some independent variables. The study included 189 women who had experienced an operative vaginal delivery (almost all were vacuum deliveries). There were positive associations between diabetes, body mass index, parity, birth weight, epidural, and age at first delivery. Interestingly, in this study, operative vaginal delivery, cesarean section, and episiotomy were shown to be protective against incontinence surgery in later life. Farrell and co-workers (level II-2) studied 690 Canadian primiparas who filled out a questionnaire about urinary incontinence during, and 6 months after, their first pregnancy ([9]). Twenty-five percent delivered by cesarean section, 19% had an operative vaginal delivery, and 56% had a spontaneous vaginal delivery. The median birth weight was 3,489 g. The rate of urinary incontinence at 6 months was 26%. Vaginal delivery was associated with a higher rate of urinary incontinence than cesarean section. Ten percent of women who had a cesarean section and 22% of those who had a spontaneous vaginal delivery reported postpartum urinary incontinence (OR = 2.1 [range, 1.1–-3.7]). Thirty-three percent of those who had a forceps delivery reported postpartum incontinence (forceps [33%] vs. spontaneous vaginal delivery [22%]; OR = 1.5 [range, 1.0–2.3]) and forceps (33%) vs. cesarean section (10%) (OR = 3.1 [range, 1.7–5.9]). Vacuum extraction showed no higher incidence when compared with spontaneous vaginal delivery, but when compared with cesarean section there was a significantly higher rate of postpartum incontinence (vacuum extraction vs. spontaneous vaginal delivery, no significant difference; vacuum extraction vs. cesarean section (OR = 3.5 [range, 1.3–9.1]). The authors concluded that cesarean section performed before or during labor reduces postpartum urinary incontinence. Meyer and co-workers studied 107 Swiss primiparas during their pregnancy and at 10 weeks and 10 months after delivery ([10]). The methods used for collecting data included questionnaire, clinical examination, assessment of bladder neck behavior, urethral sphincter function, and intravaginal/intraanal pressures during pelvic floor contractions. The results did not show any significant differences between the women who had forceps delivery and those who delivered spontaneously in terms of urinary incontinence (20% vs. 15% at 10 months), fecal incontinence (4% vs. 5% at 10 months), and diminished sexual response (12% vs. 18% at 10 months). More women in the forceps group however were shown on objective testing to have a weak pelvic floor (20% vs. 6%; *P* = .05) and low intraanal pressure (*P* = .04). The authors concluded that forceps delivery is not responsible for a higher incidence of pelvic floor complaints, or a greater change in bladder neck behavior or urethral sphincter function. However, they do believe that patients who have had a forceps delivery have a significantly greater decrease in intraanal pressure and a greater incidence of a weak pelvic floor. In terms of fecal incontinence, McArthur and colleagues questioned over 5,000 postpartum women and showed that forceps deliveries are associated with higher risk than vacuum extraction (OR = 1.94; 95% CI = 1.30–2.89) while cesarean section may offer some protection (OR = 0.58; 95% CI = 0.35–0.97). This area of obstetrics remains under-researched and the value of anal manometry and the current methods used in the diagnosis and ascertainment of postpartum anal injury/dysfunction have been questioned. Long-term follow-up studies controlling for prepartum pelvic support status (e.g., preexisting rectal dysfunction or urinary incontinence, length of labor, anesthesia, clinically observed perineal trauma, and delivery method) are required before changes in current practice can be recommended. Patients should be counseled that significant vaginal trauma may be related to long-term sphincter dysfunction, but that a relatively atraumatic operative vaginal delivery (i.e., one that does not cause rectal or sphincter rupture) is not known to cause a higher rate of dysfunction than that which follows spontaneous vaginal delivery.

Nerve Injuries Following Operative Vaginal Delivery An uncommon but distressing complication of vaginal delivery (be it spontaneous or operative) is a nerve injury which is usually the result of incorrect positioning and undue compression or traction on a nerve. Fortunately most of these injuries are apraxias, which recover, but occasionally a neuronotmesis or axonotmesis occurs with long-term disability. The most common cause of these injuries is excessive flexion of the maternal hips at the time of delivery (forced McRoberts position with attendants applying significant pressure to flex the patient's hips) and episiotomy repair (prolonged hyperflexion of the hips). Because the repair of lacerations and the episiotomy may be lengthy, it is advisable that the operator adjust the patient's position after delivery so that there is minimal flexion of the hips. Care should also be directed to pressure points on the patient's legs to avoid nerve compression injuries, and adequate padding and positioning is essential. The common injuries and their causes and presentations are shown in Table 23.5.

Neonatal Injury and Operative Vaginal Delivery

Neonatal Injuries Associated with the Vacuum Extractor

Scalp Bruising/Lacerations Ecchymoses and, uncommonly, scalp slough or lacerations can follow vacuum extraction. Most of these injuries occur when the recommended limits to total cup applications are exceeded. *Subgaleal hemorrhage* is a serious neonatal complication of vacuum extraction. This complication occurred in 1.0% to 3.8% of vacuum extractions in one series but has been much less common in some more recent studies. Approximately half of all subgaleal hemorrhages are related to vacuum extraction. The remainder are associated with forceps operations; less commonly, they occur following spontaneous delivery. This complication has not been reported in recent vacuum extraction meta-analyses, attesting to the rarity of severe scalp injuries, while emphasizing the importance of following strict technical guidelines when performing vacuum extractions/operations. Despite the low incidence of subgaleal bleeding, notification of pediatric personnel whenever an extraction is performed is mandatory, regardless of the immediate condition of the baby because subgaleal hemorrhage may not be clinically apparent until some hours postpartum. Infants with subgaleal hemorrhage present with a boggy scalp, swelling crossing the suture lines, and an expanding head circumference. They may also have signs of hypovolemia, pallor, tachycardia, and a falling hematocrit. Cephalhematoma is another fetal complication of vacuum extraction. This complication is more common with vacuum extraction (14%–16%) than with forceps delivery (2%). Intracranial hemorrhage has been found to occur in one of every 860 vacuum-assisted deliveries compared with one of every 1,900 spontaneous deliveries (a statistically significant difference). Yet, the comparative rate of intracranial hemorrhage is not statistically different when vacuum extraction, forceps delivery, and cesarean section during labor are compared. It is possible that the abnormal labor that necessitated the assisted delivery may be an underlying cause for a portion of the morbidity attributed to operative deliveries. Retinal hemorrhages may be more common in vacuum-assisted deliveries than with forceps (38% vs. 17%) but are most often associated with duration of labor. Because these hemorrhages resolve within several weeks, they are unlikely to be associated with long-term morbidity. Transient neonatal lateral rectus paralysis has been found to occur more frequently in vacuum-assisted deliveries (3.2%) than in forceps deliveries (2.4%), normal spontaneous vaginal deliveries (0.1%), and cesarean sections (0%). Because the paralysis

resolves spontaneously, it is unlikely to be of clinical importance. Vacuum extraction is associated with a higher rate of neonatal jaundice than is spontaneous delivery or forceps procedures, and this is possibly related to the higher rate of cephalhematoma.
Long-term Neonatal Outcomes The few available studies evaluating long-term neurologic sequelae of instrumental delivery have found no differences among children delivered spontaneously and children delivered by either vacuum extraction or forceps. Vacuum extraction has not been found to result in significant intellectual or neurologic disability.
Neonatal Injuries Associated with Forceps (Fig. 23.19)

FIG. 23.19. Forceps-associated injury. (Courtesy of Dr. Gerardo Cabrera Meza.)

Exactly how much neonatal injury can be attributed to a forceps delivery is difficult to assign since it is well known that a protracted spontaneous labor can result in a poor neonatal outcome. The most commonly described neonatal injuries include those described in the following paragraphs.
Superficial Scalp and Facial Markings These will invariably be present and only occasionally are of significance. Obviously correct placement of the forceps blades will prevent tissue damage to sensitive regions such as the eyelids and face. Inappropriate forceps application (sometimes referred to as the fetal grip) can be easily noted by the bruising on the baby's face in the neonatal period. In general, if the parents are prepared for the markings that they see, and it has been explained to them that these are temporary, their acceptance is good. Abrasions and lacerations are not expected or acceptable, and a careful assessment of one's technique should follow any such occurrence. Excessive pressure on the fetal face can result in vesicle formation, lipoid necrosis, and massive face and head trauma. Pressure localized over the mastoid region can result in facial erve injury. Most superficial injuries are short-lived and recovery is uncomplicated.
Facial Nerve Injury Injury to the facial nerve has been reported and is usually the result of compression of the nerve against the rigid cervical spine from a forceps blade at the point where the nerve is superficially placed in the mastoid region. This is usually a transient event, but may result in permanent injury.
Cephalhematoma Cephalhematoma occasionally occurs with forceps delivery (2%) but is more commonly seen after vacuum extraction (14%–16%). Skull fracture, subgaleal hematoma, and intracranial hemorrhage have all been reported after complicated or difficult forceps deliveries. It is difficult to assess the risk, however, since these problems have also been noted after complicated spontaneous deliveries. In addition, no data are available addressing the incidence of these complications in normal vaginal or abdominal deliveries. If a difficult delivery occurs, the neonatal personnel should be advised and the infant should then be appropriately observed and investigated.
Retinal Hemorrhage This complication occurs with forceps deliveries (17%) but is more frequently seen after vacuum extraction (38%; $P < .05$).
Corneal Abrasions/External Ocular Trauma Forceps delivery is associated with an increased rate of eyelid edema (39%) and minor external ocular trauma (17%) when compared with babies born by spontaneous vaginal delivery (eyelid edema = 10%, and external ocular trauma = 6%). Corneal abrasion is possible and corneal edema has been reported. Long-term sequelae are extremely rare and ophthalmologic screening should be reserved for specific cases.
Intracranial Bleeds It is the intracranial hemorrhages and infarcts seen following a difficult operative vaginal delivery that are of great concern. Whether or not a specific neonate suffers cerebrovascular injury due to the underlying condition that precipitated the fetal distress that resulted in delivery with the forceps, or whether the damage was caused directly by the forceps at the time of the delivery, is frequently difficult to discern. The decision to attempt a forceps delivery in the face of fetal distress can often be a difficult one. If the operator is experienced and confident that delivery can be achieved with an uncomplicated procedure, appropriate use of forceps in an emergency situation (while preparations for cesarean section are underway) can significantly reduce the time to delivery and reduce potential fetal injury. In most cases with a bad outcome there is no guarantee that cesarean section would have resulted in any different outcome from an appropriately performed operative vaginal delivery. Abdominal delivery in these situations certainly does not remove the threat of litigation. Therefore it is advised that cesarean section be performed for obstetric reasons and not out of fear of litigation.

FAILED OPERATIVE VAGINAL DELIVERY AND SEQUENTIAL USE OF INSTRUMENTS

A failed forceps/vacuum delivery attempt was, until recently, not thought to significantly worsen the neonatal course or increase morbidity or mortality of the neonate. This impression was based on small series. More recent, large, population-based studies have revealed that a failed operative delivery, or the sequential use of different instruments, does significantly increase morbidity and mortality. Towner and colleagues performed a population study of 583,340 live-born, singleton babies delivered from nulliparous women in California between 1992 and 1994 ([11]). They restricted the study to babies with birth weight between 2.5 and 4.0 kg and breech deliveries were excluded.

Approximately 30% of the deliveries were by operative techniques.

The authors studied the relationship between mode of delivery and the morbidity/mortality of the babies. The study showed that, when compared with spontaneous vaginal delivery, vacuum extraction (OR = 2.7 [range, 1.9 - 3.9]), forceps delivery (OR = 3.4 [range, 1.9 - 5.9]), and cesarean section after abnormal labor (OR = 2.5 [range, 1.8 - 3.4]) resulted in an increased incidence of subdural and cerebral bleeds. Intracranial bleeding occurred with the following frequencies:

- 1:334 failed vacuum extraction or forceps followed by cesarean section
- 1:860 after vacuum extraction
- 1:664 after forceps
- 1:907 after cesarean section during labor
- 1:2,750 after cesarean section without labor
- 1:1,900 normal spontaneous vaginal delivery.

Differences in the rate of intracranial hemorrhage were reported after the use of vacuum extraction or forceps delivery (OR = 1.2 [range, 0.7–2.2]).

One of the surprising findings in this study was that the common risk factor for intracranial bleeding was abnormal labor, rather than simply the mode of delivery.

When compared with successful forceps or vacuum extraction alone, the rate of intracranial bleeding was two to three times higher in babies born after a sequential operative vaginal delivery, or after a failed forceps/vacuum procedure that was followed by a cesarean section. These findings were confirmed by a similar study by Gardella and colleagues who used Washington state birth certificate data linked to hospital discharge records and compared 3,741 vaginal deliveries by both vacuum and forceps, 3,741 vacuum deliveries, and 3,741 forceps deliveries to 11,223 spontaneous vaginal deliveries ([12]). They showed that compared with spontaneous vaginal deliveries, the sequential use of vacuum and forceps had significantly higher rates of intracranial hemorrhage (RR = 3.9 [range, 1.5–10.1]), brachial plexus (RR = 3.2 [range, 1.6–6.4]), facial nerve injury (RR = 13.3 [range, 4.7–37.7]), seizure (RR = 13.7 [range, 2.1–88]), depressed 5-minute Apgar score (RR = 3.0 [range, 2.2–4.0]), assisted ventilation (RR = 4.8 [range, 2.1–11]), fourth-degree (RR = 11.4 [range, 6.4–20.1] among multiparous women) and other lacerations, hematoma (RR = 6.2 [range, 2.1–18.1] among multiparous women), and postpartum hemorrhage (RR = 1.6 [range, 1.3–2.0]). The relative risk of sequential vacuum and forceps use was greater than the sum of the individual relative risks of each instrument for intracranial hemorrhage, facial nerve injury, seizure, hematoma, and perineal and vaginal lacerations.

Based on these two studies, there is now no question that the sequential use of vacuum and forceps is associated with an increased risk of both neonatal and maternal injury. Unless there is a reasonable likelihood of atraumatic vaginal delivery, a “trial of operative vaginal delivery” is something that should be undertaken with caution. The use of the term “failed forceps” should fall out of use as careful preoperative assessment of mother and baby are applied. A failed forceps suggests that a forceps delivery was attempted and that obvious, repetitive, but futile efforts were made to deliver the baby with at least one genuine attempt at rotation or traction that was without success. When the term “failed forceps” is used it implies that the underlying expectation of the operator was to complete the delivery with the chosen instrument.

In a situation where the correct indications and prerequisites apply, and an appropriate, albeit unsuccessful attempt is made, a better term to use when documenting is “abandoned trial of forceps.” This shows that the attempt was justifiable but stopped when the operator recognized a complication such as an inability to properly apply the instrument, inability to correctly rotate the head, or a lack of descent despite a correct application of the instrument. In this case it is clear to anyone reviewing the chart, that the operator sensed a problem and did not persist.

STRATEGIES TO REDUCE INJURY

One of the most important clues as to the potential for successful operative vaginal delivery can be found in the details of the labor course. Use of labor monitoring graphics such as the Friedman curve or the Philpott and Castle “alert and action lines” will lead to early identification of those patients most likely to have dystocia. The combination of the “history” (labor course) and physical examination will usually allow an accurate assessment of the potential for vaginal delivery. The wise obstetrician will very carefully evaluate a patient who is a candidate for a forceps delivery but who has had a protracted labor. Frequently a slow course, or a second

stage arrest, will be associated with an unusually large baby, an unsuitable pelvis, or an unrecognized malposition. These complications may well contraindicate any attempt at instrumental delivery. The fact that a patient can get to complete dilation with a baby whose head appears to be engaged does necessarily mean that the safest route of delivery is vaginal.

Once the decision to proceed with a forceps delivery has been made, the selection of the appropriate instrument, correct positioning of the patient, and satisfaction of the aforementioned prerequisites are important.

The willingness to reassess the decision after application of the forceps blades is also important. Merely applying the blades, or attempting to apply the blades will not cause maternal or fetal damage unless excessive force has been used. At this point, if the application is incorrect or inappropriate, the procedure should be abandoned and the blades gently removed. Whether or not to attempt a second application will again be a judgment call. It is recommended that if this is to occur there should be a careful reevaluation of fetal and maternal condition. If both mother and baby are in good condition, the most experienced individual should be the one to reassess the situation and reapply forceps, if appropriate.

Knowing when to abandon a forceps operation is just as critical as knowing when to attempt one, and reflects the maturity and experience of the operator. This should be an infrequent occurrence since abandoning a procedure almost always indicates incorrect assessment in the first place. However, there will be cases where application of the forceps changes the head position, or results in asynclitism that was not there in the initial evaluation. If, at the traction attempt, there is no descent of the fetal head it is fruitless to continue applying more traction as this is the cause of most fetal injury. The safety of the mother and baby should always be first in the mind of the operator and there should never be a need to complete the operation at all costs. There are no good data addressing the important questions of how many traction attempts are reasonable, or how long the forceps procedure should take. These aspects of obstetrics can only be acquired by clinical training, and are dependent on the experience, skill, and integrity of the operator.

Does Fetal Distress Preclude Operative Vaginal Delivery?

Vintzileos and colleagues demonstrated that in cases where the vacuum extractor was used to deliver babies with suspected fetal distress there were no differences in blood gas parameters when compared with normal spontaneous deliveries. The authors concluded that the use of vacuum extraction is not contraindicated in cases of fetal distress ([13]).

Documentation and Safety Issues

The application and use of forceps is associated with a definite risk profile that should be explained to the patient prior to their use. If the situation allows, it is my practice to write a short preoperative note detailing the following:

1. Indication for the procedure along with the time and date of the note.
2. The amount of head palpable above the pelvic brim.
3. The position and station of the fetal head.
4. The degree of molding of the parietal bones.
5. The amount of caput succedaneum palpable.
6. The estimated fetal weight.
7. A clinical assessment of the maternal pelvis.
8. A statement regarding the fetal heart rate and character.
9. A statement about the maternal contractions.
10. A statement about maternal condition and type of anesthesia to be used.
11. A statement that the mother understands the reason for the procedure and accepts the risks.

After the delivery an operative note should be written or dictated and should contain as much of the following information as possible:

1. Preoperative and postoperative diagnoses along with the time and date of the note.
2. Reiteration of the physical findings (outlined previously) at the time of the procedure, especially if these were different from those detailed in the preoperative note.
3. Number of applications of the forceps, ease of application, and any complications with the application. If possible have a nurse or assistant document the exact times of application and traction.
4. Duration and force of each traction attempt, as well as the number of traction attempts.
5. Complete explanation of a failed or abandoned procedure with reasons.
6. Detailed description of any maternal or neonatal injuries.
7. Cord blood gases if the 5-minute Apgar is less than 7.

Informed Consent for Forceps Operations?

Although not frequently done, I believe that unless there is an emergency situation, a forceps delivery should be discussed with the patient as one would discuss any operative procedure. In this way informed consent can be obtained and the patient can be prepared for what to expect. The risks and benefits of operative vaginal delivery should be explained (and compared with those of cesarean section) and the patient should be aware of her options. I recommend that this be detailed in the patient's chart prior to the delivery. Most lawsuits are generated as a result of lack of communication between the doctor and the patient. Dissatisfaction with an outcome will always be heightened if the patient feels uninvolved with the decision and perceives that she has been misinformed about the risks. The best time to educate the patient is during her prenatal course or on admission to the hospital. When the patient signs her consent forms during the admission process I believe that a consent form for operative vaginal delivery should be included. The information provided should include a description of what forceps look like and that, despite their shape and size, they are specially designed to protect the mother and baby by gently grasping the fetal head and assisting the infant to negotiate the last portions of the birthing canal. The fact that a timely operative delivery will the time and energy required during the birthing process should be explained. The fact that correct forceps use can be lifesaving should be stressed. The patient should, however, also understand that bad outcomes will still occur due to unforeseen problems, and the obstetrician should be prepared to explain the maternal and fetal/neonatal risks specific to forceps operations. The possibility of facial bruising and possible facial nerve or eye injury should be mentioned before the delivery because of the emotional impact of these injuries after the delivery has occurred, especially when the patient or her family makes accusations that these risks were never mentioned. The detractors of informed consent complain that after being informed of the potential risks of operative vaginal delivery most women will elect to proceed with cesarean section and will forgo vaginal delivery. The argument against this point of view is that since cesarean section is a viable option that will allow minimization of fetal injury (and one that is not associated with a prohibitively high incidence of maternal or neonatal injury) patients have the right to choose to avoid potential trauma to their baby. Many authorities fear that by providing more detailed written informed consent the medicolegal risk increases since it is not possible to cover every eventuality and thus the informed consent will be regarded as incomplete or misleading. This is obviously a controversial matter but at this time there is no standard of care in the United States that demands a written informed consent prior to operative vaginal delivery.

Post-Delivery Responsibilities

It is very important that neonatal caregivers be informed of a vacuum or forceps delivery, and that they monitor the infant for signs of any complications.

CONCLUSIONS

Operative vaginal delivery has been an important part of obstetric practice for nearly 400 years. We must make every effort to retain these skills, to modify and improve them in every possible way, and then to pass them on to those who will follow us. It is in this way that women and children of future generations will benefit from the many years of experience that have gone before them.

SUMMARY POINTS

- Adequate assessment of the “pelvis and passenger” is essential prior to attempting an operative vaginal delivery. Careful assessment of the maternal abdomen prior to attempting operative vaginal delivery forms an important part of this assessment. If the fetal head is not felt to be completely engaged and there is excessive molding of the fetal head, the procedure should be avoided. There are important prerequisites, which if satisfied, will reduce the chances of failed operative vaginal delivery procedures.
- Failed operative vaginal delivery and sequential operative vaginal delivery attempts with different instruments significantly increase the risk of neonatal intracranial complications.
- Both forceps and the vacuum extractor are acceptable and safe instruments for operative vaginal delivery. Operator experience should determine which instrument should be used in a particular situation. The vacuum extractor is associated with an increased incidence of neonatal cephalhematomata, retinal hemorrhages, and jaundice when compared with forceps and the neonatal care provider should be made aware of the mode of delivery in order to exclude these complications.
- Large fetal size and prolonged labor are associated with an increased risk of shoulder dystocia and careful consideration should be given to performing operative vaginal delivery under these circumstances.
- Forceps delivery may be preferable to vacuum extraction in small-for-gestational-age babies since it is associated with a lower incidence of intraocular bleeding.
- Operators should attempt to reduce the time between vacuum application and delivery of the baby since cephalhematoma is more likely if the interval exceeds 5 minutes.
- Midforceps operations, if performed under the correct circumstances by an adequately trained individual, should still be considered an appropriate procedure to be used and taught.
- Efforts should be made to train resident obstetricians in the use of operative vaginal delivery techniques since appropriate and safe employment of forceps and vacuum-assisted delivery still is an important part of modern-day obstetrics.

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Chapter 24

T. Flint Porter and James R. Scott

Cesarean Delivery

INDICATIONS
Labor Contraindicated
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Intrapartum Fetal Heart Rate Abnormalities
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SUMMARY POINTS

SUGGESTED READINGS

Cesarean section is a term commonly used in obstetrics to describe the delivery of a viable fetus through an incision in the abdominal wall (laparotomy) and the uterus (hysterotomy). However, the words cesarean and section used together are redundant, because both imply incision. Cesarean birth and cesarean delivery are preferable terms and are used interchangeably in this chapter.

Cesarean delivery has played a major role in lowering both maternal and perinatal morbidity and mortality rates during the past century. The initial purpose of the surgery was to preserve the life of the mother with obstructed labor, but indications have expanded over the years to include delivery for a variety of more subtle dangers to the mother or the fetus. Contributing to its more frequent use is its increased safety, which is largely a result of better surgical technique, improved anesthesia, effective antibiotics, and availability of blood transfusions. Nevertheless, there has been increasing concern over what is considered by many to be an excessive cesarean rate in contemporary obstetrics.

The percentage of babies in the United States delivered by cesarean dramatically increased from less than 5% in 1965 to 25% in 1990. The reasons for this striking increase are multiple. During the 1970s and 1980s, it was assumed that cesarean delivery would be the solution to numerous obstetric problems. Facing increasing medical-legal pressures, obstetricians gradually abandoned most vaginal breech and forceps deliveries, broadened the definition of intrapartum fetal distress, and liberalized the diagnosis of dystocia. Also, a greater number of older women and older primigravidae, whose primary cesarean rates are higher, were having children. Finally, the escalation in primary cesareans increased the overall cesarean rate, because in most subsequent pregnancies, babies were delivered by repeat cesarean.

Although perinatal outcome in the United States improved during the period when the cesarean rate increased, it also improved in other countries where cesarean rates remained low. Moreover, the incidence of cerebral palsy has not declined during the past 20 years because perinatal morbidity and mortality are more often a function of antepartum events, abnormal fetal growth, congenital anomalies, and premature birth. Delivery by cesarean usually is associated with an increased cost for the health care system and the patient when compared with vaginal birth. These factors have led to efforts to reduce the rate of cesarean delivery. Most emphasis has been placed on decreasing the number of repeat cesareans by encouraging vaginal birth after cesarean (VBAC). Accordingly, the percentage of women attempting VBAC increased from less than 10% in 1988 to about 30% in 1996. During this same period, the percentage undergoing cesarean declined to about 20%. Unfortunately, initial enthusiasm for VBAC has been dampened by the results from several studies showing adverse maternal and perinatal outcomes in some women who attempted it. In turn, this has led to a steady decline in the number of women attempting VBAC and an increase in the overall cesarean rate to about 24%.

INDICATIONS

Cesarean birth is necessary whenever labor is unsafe for either mother or fetus, when labor cannot be induced, when dystocia or fetal problems present significant risks with vaginal delivery, and when an emergency mandates immediate delivery. It is not practical to list all potential indications for cesarean delivery or to discuss the numerous changes in obstetric management hat have influenced these over the years (Table 24.1). Many indications are well accepted, a number are subjective or selectively applied in individual patients, and others are more controversial. The majority of cesareans are performed for fetal indications, a few are solely for maternal reasons, and some benefit both fetus and mother. Repeat cesarean accounts for approximately 30% of cesarean deliveries in the United States, dystocia is the indication for up to 30%, and fetal distress, breech, and other conditions are responsible for the remaining cases.

Accepted
Failed induction
Cephalopelvic disproportion
Failure to progress in labor
Proven fetal distress
Placental abruption
Placenta previa
Umbilical cord prolapse
Obstructive benign and malignant tumors
Active genital herpes infection
Abdominal cerclage
Conjoined twins
Controversial (or selective)
Breech presentation
Repeat cesarean
Congenital fetal anomalies, major
Cervical carcinoma
Prior vaginal colporrhaphy
Large vulvar condylomata
HIV infection

HIV, human immunodeficiency virus.

TABLE 24.1. *Common indications for cesarean delivery*

Labor Contraindicated

Uterine contractions can be hazardous to the mother under certain circumstances. These include central placenta previa, previous classic uterine incision, myomectomy transecting the uterine wall, or uterine reconstruction. In these situations, labor and vaginal delivery may result in uterine rupture and hemorrhage, endangering the life or future health of the mother. Conditions in which labor is dangerous to the fetus include placenta previa, velamentous insertion of the cord or other forms of vasa previa, and cord presentation. More recent indications include treatable fetal anomalies such as meningomyelocele and certain degrees of hydrocephaly.

Failed Induction

Conditions such as alloimmunization, diabetes mellitus, intrauterine growth retardation, and hypertensive disorders constitute a threat to the mother or fetus and often

require delivery when the cervix is unfavorable for induction. If attempts to induce labor are inappropriate or unsuccessful, cesarean birth is the only alternative. This is especially true in nulliparous women. More effective methods of softening the cervix before inducing labor preterm may reduce the need for cesarean.

Dystocia

Mechanical problems of the uterus, fetus, or birth canal or ineffective uterine contractions that result in unsuccessful progress of labor and vaginal delivery are referred to collectively as *dystocia.* This term encompasses a variety of commonly used clinical terms, such as failure to progress, cephalopelvic disproportion (CPD), and dysfunctional labor. However, CPD is a relative term. Although fetal macrosomia sometimes causes CPD, most cesarean births for abnormal labor involve a normal-sized infant. Dystocia occasionally is also caused by soft tissue tumors and abnormal fetal presentations.

Intrapartum Fetal Heart Rate Abnormalities

Electronic fetal monitoring improves the chance of detecting fetal compromise, but its inaccuracy (false-positive rate) has also contributed to the increased number of cesarean births. Nonreassuring fetal heart rate patterns and the diagnosis of fetal distress are discussed elsewhere. Many clinicians have replaced vaginal breech deliveries with cesarean delivery to avoid the risk of intrapartum asphyxia or delivery-related trauma from head entrapment and umbilical cord prolapse. An increase in adverse perinatal outcome with singleton vaginal breech delivery was confirmed in one large randomized controlled trial.

Maternal or Fetal Emergency

Certain maternal or fetal conditions require immediate delivery of the baby because vaginal delivery is either impossible or inappropriate. Such circumstances include severe placental abruption, hemorrhage from placenta previa, prolapse of the umbilical cord, active genital herpes, and impending maternal death.

COMPLICATIONS

A variety of postpartum complications—including unexplained fever, endometritis, wound infection, hemorrhage, aspiration, atelectasis, urinary tract infection, and venous thromboembolism—occur in up to 25% of women who undergo cesarean delivery. The frequency of cesarean-related maternal death varies with the institution and with the condition necessitating the procedure. However, rates are less than 1 per 1,000 operations, and many deaths are related to an underlying maternal illness or anesthetic complications.

Late maternal complications of cesarean delivery include intestinal obstruction from adhesions, dehiscence of the uterine incision in subsequent pregnancies, and abnormal myometrial invasion of the placenta (accreta, increta, percreta) in subsequent pregnancies. Both intestinal obstruction and scar dehiscence are more common with the classic incision than with a lower uterine segment incision. The incidence of abnormal myometrial invasion by the placenta (accreta, increta, percreta) increases with each cesarean and can result in severe and intractable hemorrhage at delivery, often requiring cesarean hysterectomy. This should be suspected in all women with a placenta previa and a history of cesarean.

TYPES OF CESAREAN OPERATIONS

Almost all contemporary cesareans are performed using a transperitoneal approach to reach the uterine wall. An extraperitoneal technique was sometimes used in the past in patients with an infected uterus in an attempt to reduce the chance of peritonitis. More effective antibiotics have now made this approach unnecessary.

The two major types of cesarean operations are classified by the location and direction of the uterine incision. The first are those incisions made in the upper segment of the uterus (Fig. 24.1). The vertical incision usually made in the anterior fundus is referred to as a *classic incision.* It is used primarily when it is difficult to deliver the infant through a low uterine segment incision. The second type is characterized by incisions made in the lower portion of the uterus after the bladder has been displaced downward (Fig. 24.2). The preferred and most frequently used is the low transverse incision. A vertical incision may also be made in this area, but it usually involves the upper uterine segment unless the lower segment is quite elongated by labor.

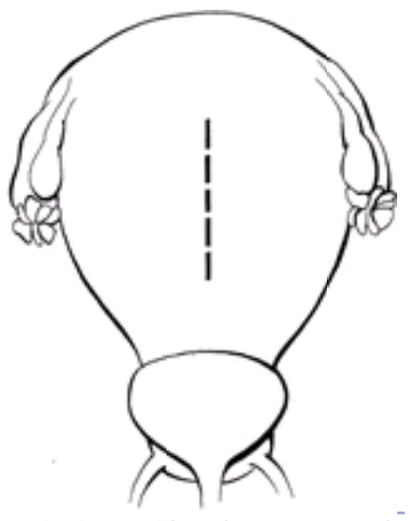

FIG. 24.1. Classic cesarean incision in the upper segment of the uterus.

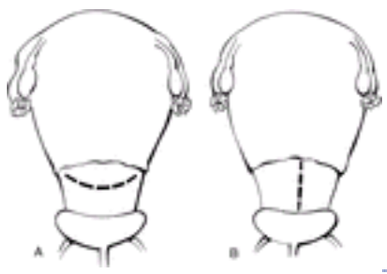

FIG. 24.2. Incisions in lower uterine segment. **A:** Low transverse incision. **B:** Low vertical incision.

Occasionally, variations are used because of unanticipated difficulty (Fig. 24.3). These incisions are best avoided by careful assessment and planning. A J-shaped incision is made when the obstetrician begins a transverse lower uterine segment incision and finds the lower uterine segment to be too narrow. It often is not realized that the incision is inadequate until delivery is attempted. A vertical extension from one end is necessary to avoid extension into the broad ligament. The T-shaped incision is made for similar reasons.

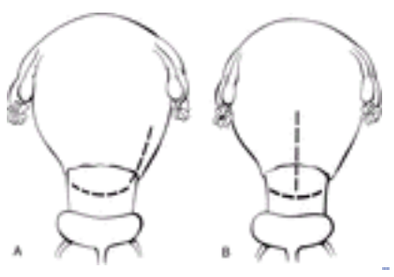

FIG. 24.3. Undesirable variations of uterine incisions. **A:** J-shaped incision. **B:** T-shaped incision.

ANESTHESIA

The choice of anesthetic technique and agents is dictated by a number of factors, as discussed elsewhere in Chapter 3. Most patients requiring immediate delivery because of fetal distress, hemorrhage, or shock are not candidates for spinal or epidural anesthetic techniques. The same is true for women with previous injury or surgery to the spine, skin infections of the lower back, or coagulopathy. Conversely, patients with active pulmonary disease, such as pneumonia or tuberculosis, or in whom intubation is judged difficult, are not good candidates for inhalation anesthesia.

The choice between regional block and inhalation anesthesia should be discussed among the patient, anesthesiologist, and obstetrician and should be based on the urgency of delivery, patient choice, and skill of the anesthesiologist.

Regional anesthesia has the potential to adversely affect maternal and fetal hemodynamics. In the dorsal recumbent position, the gravid uterus compresses the inferior vena cava, resulting in decreased venous return and maternal cardiac output and, eventually, hypotension and reduced uterine perfusion. This is referred to as the *inferior vena cava syndrome.* The weight of the pregnant uterus progressively compresses the aorta as the mean arterial pressure falls, thus also reducing blood flow to the pelvis. Hypotension produced by regional anesthetic techniques compounds this problem. Devices attached to the operating table, inflatable wedges or towels placed under the patient, or tilting the table can be used to displace the uterus to the patient's left in preparation for cesarean delivery. Rapid intravenous infusion of physiologic solution containing sodium immediately before the initiation of regional anesthesia also reduces the incidence of hypotension.

The status of the fetus worsens as the time of exposure to anesthesia lengthens. Progressive fetal depression as induction-to-delivery time is prolonged makes it important to avoid unnecessary delay before and during surgery. The abdomen should be fully prepped, draped, and ready for the incision before general anesthesia is induced. On the other hand, reckless surgical techniques for rapid delivery of the fetus are unwise. An induction-to-delivery time of 5 to 15 minutes is reasonable if maternal oxygenation, blood pressure, and displacement of the uterus are monitored and maintained.

OPERATIVE PROCEDURE

Preparation

Cesarean delivery requires the same preoperative care as any major surgery plus additional consideration for the status of the fetus. A patient who is dehydrated from prolonged labor needs volume correction with intravenous fluids. Because anemia is relatively common in pregnancy, a hemoglobin or hematocrit level should be checked preoperatively. Blood is typed and screened to be available for immediate transfusion. Routine preparation of autologous blood is not cost effective for most cesarean patients, because few are transfused. However, autologous blood can be prepared during the antepartum period if the patient is at high risk for hemorrhage as with placenta previa or accreta. Because the bladder will be in the operative field, it is necessary to place an indwelling catheter before beginning surgery. The patient and her partner should be given an explanation of the details of the operation, the reason it is necessary, and the risks involved. Informed written permission for the procedure, anesthetic, administration of blood, and possible hysterectomy, if necessary, is then signed by the patient.

With elective repeat cesarean delivery, it is the obligation of the physician to obtain evidence of fetal maturity. Documentation by noninvasive techniques is outlined in Table 24.2. If the criteria confirm gestational age assessment on the basis of menstrual dates in a patient with normal menstrual cycles and no immediately antecedent use of oral contraceptives, delivery can be scheduled after 39 weeks by menstrual dates. Ultrasonography is considered confirmatory of menstrual dates if there is gestational age agreement within 1 week by crown-rump measurement obtained at 6 to 11 weeks, or within 10 days by the average of multiple measurements obtained at 12 to 20 weeks. When the fetal gestational age remains uncertain, amniocentesis for amniotic fluid studies should be employed to ensure fetal maturity. Awaiting the onset of spontaneous labor is another option.

Fetal heart tones documented for 20 weeks by nonelectronic fetoscope or for 30 weeks by Doppler
36 weeks since a positive serum or urine human chorionic gonadotropin pregnancy test was performed by a reliable laboratory
An ultrasonographic measurement of the crown-rump length, obtained at 5 to 11 weeks, that supports a gestational age of >39 weeks
Ultrasonography obtained at 12 to 20 weeks that confirms the gestational age of >39 weeks determined by clinical history and physical examination

Source: American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin No. 10. Washington, DC: ACOG, Nov 1999, with permission.

TABLE 24.2. *Fetal maturity assessment before elective repeat cesarean delivery*

Aspiration of the acidic contents of the stomach, a known risk of general anesthesia in pregnant women, can be avoided by pretreatment with any of several medications. Prophylactic antibiotics are administered to reduce the risk of postpartum infection, which is increased with prolonged labor, prolonged rupture of the membranes, and numerous cervical examinations. A single dose of a broad-spectrum antibiotic, such as 1 g of a cephalosporin, usually is given after the umbilical cord has been clamped. However, if an intrapartum infection is apparent preoperatively, therapeutic antibiotics should be given before surgery and continued postoperatively. Preparation of the abdomen includes scrubbing the skin with soap and an antiseptic agent such as nonorganic iodide. The abdomen is then draped, leaving the area for the incision exposed. Personnel trained in neonatal resuscitation should be available.

Surgical Technique

A lower abdominal midline vertical incision and the transverse Pfannenstiel incision are used most commonly for cesarean deliveries. The vertical incision minimizes blood loss and allows extension above the umbilicus, if necessary. It also allows for rapid access to the abdominal cavity because of diastasis of the rectus muscles, common in late pregnancy. Nevertheless, the transverse Pfannenstiel incision is used more frequently because of the cosmetic result preferred by most women. Entry through this incision is relatively rapid in experienced hands, visualization of the pelvis is adequate, and there may be less risk of subsequent herniation.

The abdomen is opened in layers, and any large bleeding vessels are clamped. Meticulous hemostasis is postponed if it will unduly delay delivery of the fetus. The abdominal cavity is inspected briefly, and the direction and degree of rotation of the uterus are noted. Retractors are placed in the abdominal incision for better visualization. The bladder is dissected carefully away from the serosa of the uterus and a small transverse incision is made in the midline of the uterus, a few centimeters below the peritoneal incision (Fig. 24.4A, Fig. 24.4B, Fig. 24.4C, Fig. 24.4D and Fig. 24.4E). Care should be taken to keep the fetal membranes intact. Under direct vision, the incision is extended laterally with bandage scissors in a gentle upward curve using the operator's fingers as a guide (Fig. 24.4F).

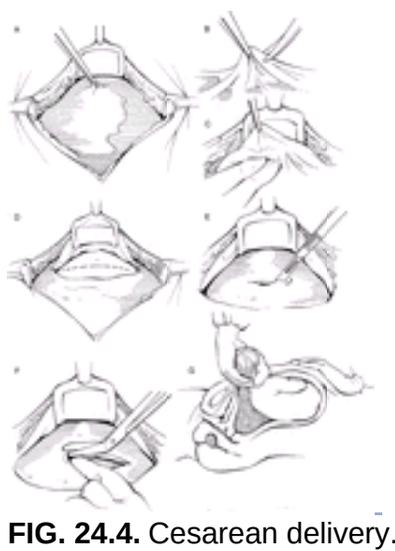

FIG. 24.4. Cesarean delivery. **A:** Reflection of peritoneum from the serosa of the uterus to the bladder is identified. **B:** Peritoneal reflection between the uterus and

bladder is elevated and incised. **C:** The bladder is displaced away from the lower uterine segment. **D:** The bladder is retracted, and the incision is planned to be 2 to 3 cm below the peritoneal incision. **E:** A small incision is made through the uterine wall to the fetal membranes. **F:** A uterine incision is made in a curvilinear shape, using bandage scissors. **G:** The fetal head is elevated through the uterine incision by the operator's hand.

An alternative method of opening the uterus in a woman with an adequately developed lower uterine segment is to make a shallow curvilinear incision through the pubocervical fascia to the fetal membranes. Inserting both index fingers into the opening, the operator pulls laterally, bluntly opening the uterus. The operator ruptures membranes and inserts one hand beneath the lower edge of the uterine incision to feel the presenting fetal part. If vertex, the occiput is identified, and the head is flexed and brought into the uterine incision (Fig. 24.4G). The assistant or operator exerts fundal pressure to deliver the fetal head gently through the incision, after which an assistant suctions the mouth and nares with a bulb syringe while the operator continues to deliver the shoulders gently in a manner similar to that of a vaginal delivery. Specially designed forceps or a vectis also can be used to deliver the head through the uterine incision.

After delivery, the umbilical cord is clamped and divided, and the infant is handed off the operative field. Although spontaneous delivery of the placenta is preferable, it may be removed manually by blunt separation from the uterine wall. The uterine cavity is inspected for any structural abnormality, and retained placental tissue and membranes are removed. Dilation of the endocervical canal from above is usually unnecessary. Following delivery of the placenta, oxytocin should be administered to stimulate uterine contractions and reduce bleeding.

The cut edges of the uterine incision may be grasped with ring forceps or other noncrushing clamps for traction and to control bleeding. The uterine incision may be closed with a one-layer or two-layer technique (Fig. 24.5A and Fig. 24.5B). With the exception of a shorter operating time using the one-layer technique, neither has been found superior to the other. Persistent bleeding in the incision line may be controlled with interrupted figure-of-eight sutures or electrocautery. Inspection of the uterine incision and surrounding organs should be followed by removal of abdominal packs and lavage and suctioning to remove any residual blood, amniotic fluid, or meconium. If desired, surgical sterilization via tubal ligation may be performed at this point. It adds little time or morbidity to cesarean delivery and does not significantly prolong postpartum recovery. The Pomeroy method is the simplest sterilization technique and gives satisfactory results.

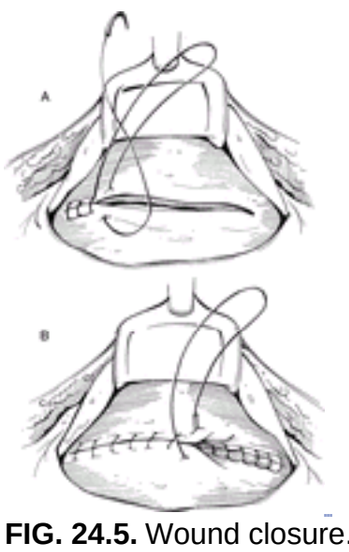

FIG. 24.5. Wound closure. **A:** First layer of closure. **B:** Second layer of closure.

The abdominal incision is closed most commonly with a delayed-absorbable synthetic suture, although a nonabsorbable suture is also acceptable in high-risk groups. A mass-layer closure should be considered for vertical incisions, especially in patients at high risk of disruption.

Postoperative management is similar to that of any patient who has had major surgery, including removal of the urinary catheter on the first postoperative day, oral feedings advanced as tolerated, and early ambulation to avoid thromboembolism. Most women are ready for discharge on the third postoperative day, although hospitalization should be continued if clinically indicated and documented by the physician in the patient's record.

Closure of the Classic Incision

The thickness of the upper uterine wall sometimes requires a three-layer closure to and including the serosa. Continuous suture techniques may be used, but interrupted sutures frequently give a more exact closure. The first layer should include about half the thickness of the wall and can be continuous or figures-of-eight. A second continuous layer is placed to avoid leaving a space between the layers. The third layer should close the serosa in a manner that minimizes exposed raw surfaces using continuous, unlocked absorbable suture. Each bite of the needle should begin on the raw surface of the wound and exit through the serosa a few millimeters from the cut edge. With this technique, sometimes referred to as a baseball stitch, the cut edge is infolded, and the serosa is on the surface.

Techniques for Difficult Cesarean Deliveries

After a prolonged obstructed labor, the fetal head often is impacted in the midpelvis. Manipulation of an impacted fetal head may result in damage to a thinned and elongated lower uterine segment, with extension of the incision into the cervix or broad ligament and laceration of uterine vessels. The vaginally placed hand of an assistant pushing upward can facilitate dislodgement of the fetal head.

Most malpresentations can be delivered safely through a low transverse uterine incision extended widely to deliver the aftercoming head. However, this may impossible with a preterm malpresentation or other circumstances such as placenta previa. If the lower uterine segment is too narrow to accommodate a transverse incision, a vertical incision should be performed, even if it extends into the uterine corpus.

Incision of the uterus through the maternal surface of the placenta can result in considerable hemorrhage. The operator should continue quickly to extend the incision for delivery of the fetus but not cut or fracture the placenta, because disruption of chorionic vessels may result in fetal hemorrhage. Instead, the placenta should be separated from the uterine wall to allow access to the fetal membranes so that rupture may occur and the fetus may be delivered. Occasionally, an internal podalic version and breech extraction are necessary.

POSTMORTEM CESAREAN DELIVERY

Most obstetricians will never be forced to decide whether or not postmortem cesarean is necessary. Nevertheless, all should be familiar with the general principles. First, the certainty of maternal death must be clinically established quickly and preferably confirmed by electrocardiographic or electroencephalographic findings. Documentation of fetal well-being before deciding on delivery may give erroneous information, because the time from apparent fetal death to actual fetal death or serious damage is unknown. Second, the abdomen and uterus should be opened rapidly, ignoring aseptic precautions. Third, the fetus must be delivered quickly, given immediate resuscitation, and transferred to an intensive care nursery. Finally, the placenta should be removed and the uterus and abdomen closed.

The outlook for the infant is improved if delivery occurs before maternal death, and survival continues to be possible if delivery is accomplished within 10 minutes of maternal death. Unfortunately, the degree of damage from cerebral hypoxia is difficult to predict and the prognosis for the fetus is usually ominous. Uncommonly, a mother who opposes fetal intervention dies before giving birth, thereby presenting the obstetrician with an ethical dilemma.

PRIMARY ELECTIVE CESAREAN

Performing a cesarean delivery solely because the patient desires to avoid labor would have seemed unthinkable 20 years ago. However, in recent years a growing number of patients and physicians have supported the notion that women have the right to choose elective cesarean rather than go through the rigors of labor, regardless of any obstetric or medical indication. Proponents reason that women have the right to choose their method of delivery because of the inconveniences of unscheduled labor and the possibility that vaginal delivery may result in pelvic support disorders. The practice of performing primary cesarean delivery for these reasons has gained wide acceptance in some parts of the world among women of higher socioeconomic status.

Although cesarean delivery in modern obstetrics is considered a safe procedure, recovery time and the risk of thromboembolic episodes and infections are still higher with cesarean birth than with vaginal birth. Furthermore, although most elective surgeries are done only once, a primary cesarean often is followed by repeat cesarean deliveries, with morbidity increasing with each birth. The risks of complications such as uterine rupture, placenta previa, and placenta accreta increase proportionately with the number of cesareans performed. All may result in severe hemorrhage, postpartum hysterectomy, urologic and bowel injury, and even maternal death.

The controversy surrounding primary elective cesarean delivery will not be resolved unless adequate controlled studies are performed. Until that time, the decision to perform cesarean delivery on demand should be made only after careful consideration of all of the risks involved.

VAGINAL BIRTH AFTER PREVIOUS CESAREAN

The rising number of women undergoing elective repeat cesarean has been one of the principal reasons for the steady increase in the cesarean delivery rate in the United States during the last 30 years. Not surprisingly, several governmental and professional organizations have advocated a trial of labor (TOL) in all women with a prior cesarean. Based on the results of early studies comparing VBAC with repeat cesarean, VBAC appeared to be successful in 60% to 80% of women undergoing TOL. Uterine rupture, the most serious potential complication of attempted VBAC, appeared to be a rare event with few consequences. However, the results of more recent prospective trials indicate that a decision to undergo a TOL after previous cesarean is not as straightforward as it once seemed.

Safety

Most of the emerging body of literature comparing VBAC with repeat cesarean suggests that a TOL should be offered to thoughtfully selected candidates. Contraindications include a classic scar, a low vertical scar that extends into the upper segment of the uterus, previous uterine rupture, and a T-shaped scar. Other factors that may increase the likelihood of uterine rupture include two or more prior cesarean deliveries, macrosomia, induction of labor, the presence of müllerian anomalies, and postdatism. The patient should be aware that problems could arise during her pregnancy that could necessitate repeat cesarean delivery.

Some minor complications may be more common in women who undergo repeat cesarean. However, the most recent meta-analysis of retrospective and prospective series comparing VBAC with repeat cesarean has showed that most major complications are more likely for women who attempt VBAC (Fig. 24.6). Most complications occur in women with a failed TOL, especially if an emergency cesarean is necessary.

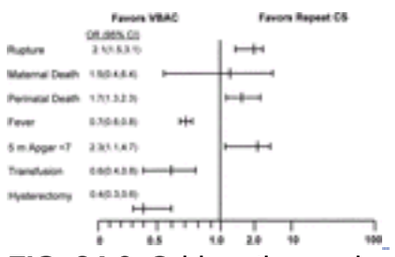

FIG. 24.6. Odds ratio graph comparing morbidity of trial of labor versus elective repeat cesarean delivery.

The degree of perinatal morbidity and mortality after a failed TOL, especially in cases of uterine rupture, has been under-appreciated until recently (see Fig. 24.6). In theory, fetal damage is minimized if delivery can be accomplished expeditiously. However, fetal damage can occur even if delivery occurs less than 18 minutes after uterine rupture. Furthermore, immediate delivery requires around-the-clock in-hospital obstetric and anesthesia coverage, typically available only in large university or tertiary level centers. In one survey, anesthesiologists were available in-hospital on nights and weekends in only 26% of hospitals with 500 to 1,499 births per year, and in only 3% of those with fewer than 500 births per year. Although the absolute risk of perinatal death associated with VBAC is low (12.9 per 10,000), it is significantly greater than with elective cesarean, especially if uterine rupture occurs.

Success of Labor

In most published series, 60% to 80% of women who attempt VBAC have successful vaginal births. However, many of these studies have included only women who meet strict inclusion criteria, excluding those who otherwise would be considered VBAC candidates in clinical practice. Based on the available evidence, the probability of successful VBAC for women whose first cesarean was done for a nonrecurring indication is similar to the probability of vaginal delivery in all laboring patients. Moreover, their probability of success is improved if they also have had a previous vaginal delivery, regardless of whether or not it was before their first cesarean birth or was a successful VBAC. In contrast, successful VBAC is less likely for women whose primary cesareans were performed for labor dystocia (50%–70%).

Vaginal Birth After Cesarean in Obstetric Practice

Counseling Potential Candidates for VBAC Only women who meet specific criteria and who can deliver in appropriate facilities should be offered VBAC (Table 24.3). Initial evaluation includes a search for contraindications to VBAC and review of medical records if the type of previous incision is unknown (Table 24.4). Once this evaluation is complete, thorough, impartial, and factual counseling should be given and reviewed at intervals during pregnancy. Notably, the probability of achieving a successful VBAC and the magnitude of the maternal and perinatal risks associated with a failed TOL should be discussed with each potential candidate and documented in the prenatal record. Support and encouragement should be given regardless of the decision made. Global mandates for TOL after previous cesarean are inappropriate, because individual risk factors are not considered.

1. One or two prior cesarean deliveries
2. Clinically adequate pelvis in relation to fetal size
3. No other uterine scars, anomalies, or previous rupture
4. Patient consent
5. Physician capable of monitoring labor and performing an emergency cesarean delivery immediately available throughout active labor
6. Availability of anesthesia and personnel for emergency cesarean

TABLE 24.3. *Criteria for vaginal birth after cesarean*

1. Prior classic or T-shaped incision or other transmural uterine surgery
2. Contracted pelvis
3. Medical or obstetric complication that precludes vaginal delivery
4. Patient refusal
5. Inability to immediately perform emergency cesarean because of unavailable surgeon or anesthesia personnel, inadequate staff or facility

TABLE 24.4. *Contraindications to vaginal birth after cesarean*

Intrapartum Management A TOL after previous cesarean should be conducted in facilities where anesthesia, obstetric, and blood bank personnel are immediately available. Each hospital should develop a protocol for management of VBAC (Fig. 24.7). One reasonable approach to the initial evaluation of a woman attempting VBAC includes the following measures:

FIG. 24.7. Flow sheet showing one management scheme for vaginal birth after cesarean.

- Intravenous access on admission
- Blood count, type and screen
- Nothing by mouth
- Continuous electronic fetal monitoring
- Alert anesthesia, obstetric, and neonatal personnel

Once labor has begun, women attempting VBAC should be frequently evaluated and monitored. Most authorities recommend continuous electronic fetal heart rate monitoring during labor. Personnel who are familiar with the potential complications of VBAC should be present to watch closely for fetal distress and inadequate progress of labor.
Induction and Augmentation Spontaneous labor is preferable to labor induction and augmentation in any woman who is attempting a TOL after a previous cesarean delivery. Several series have documented increased rates of failure, as well as uterine rupture, in women who have had a previous cesarean and who are undergoing labor induction or augmentation, especially if prostaglandin preparations are employed as cervical ripening agents. The use of misoprostol is of particular concern.
Analgesia There are few contraindications to epidural anesthesia, and adequate pain relief may encourage a greater number of women to choose TOL over repeat cesarean. Epidural analgesia rarely masks the signs and symptoms of uterine rupture, and success rates for VBAC are similar to those experienced by women who receive other types of pain relief.

Uterine Rupture

Uterine rupture, the most serious complication of VBAC, is often life threatening for both mother and baby. Incomplete or partial rupture refers to an opening of the previous scar but not the overlying peritoneum. This includes extrusion of intrauterine contents into the broad ligament. A complete rupture is a separation of the previous scar *and* overlying peritoneum with extrusion of intrauterine contents into the abdominal cavity. Scar dehiscence is defined as an *opening of the previous scar with intact overlying visceral peritoneum and no expulsion of intrauterine contents* (also termed a *window*).

Intrapartum uterine ruptures requiring emergency treatment occur in approximately 0.5% of patients with a transverse low-segment scar. The rupture usually involves the old scar and lower uterine segment but may be stellate and extend intraperitoneally or retroperitoneally. Contributing factors include induction with oxytocin or prostaglandin preparations, dysfunctional labor, more than one prior cesarean delivery, high parity, and even previous perforation of the nonpregnant uterus by curettage, hysteroscopy, metroplasty, and myomectomy.

Diagnosis The signs and symptoms of uterine rupture may be surprisingly subtle. However, the diagnosis soon becomes apparent as the maternal or fetal condition, or both, deteriorate. Fetal heart rate pattern abnormalities are identified with uterine rupture most consistently, although none is specific. A common scenario involves variable decelerations that evolve rapidly into late decelerations, bradycardia, and undetectable fetal heart tones (Fig. 24.8). Hence, all fetal heart rate pattern abnormalities exhibited by women attempting VBAC should be investigated thoroughly.

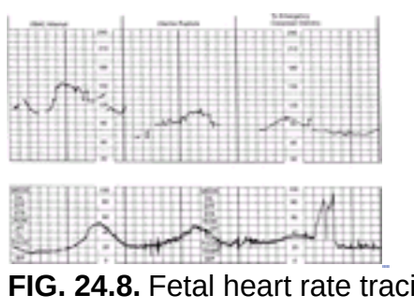

FIG. 24.8. Fetal heart rate tracing shows changes in pattern during uterine rupture.

Other clinical findings of uterine rupture include uterine or abdominal pain, which usually occurs in the area of the previous incision, may range from mild to severe, and sometimes is described as a *tearing* sensation. Uterine contractions often diminish in intensity and frequency, although no rupture-specific pattern has been identified. Vaginal or intraabdominal bleeding is associated with anxiety, restlessness, weakness, dizziness, gross hematuria, shoulder pain, and shock. Loss of station of the presenting part is diagnostic but not essential for the diagnosis.
Management Women who are suspected of having uterine rupture should undergo immediate exploratory laparotomy and cesarean delivery. Perinatal outcome is dependent on the severity of the rupture and its relationship to the placenta and umbilical cord. Damage to the placenta or umbilical cord may lead quickly to hypoxemia, permanent end-organ dysfunction, and fetal death. Fetal extrusion into the abdominal cavity is particularly detrimental. Once delivery has been accomplished, repair of the uterine defect is possible in many cases and may be considered if it appears technically feasible, if the patient wants to retain fertility, or if her condition is not jeopardized by continued hemorrhage. The wound edge should be debrided before reapproximation followed by closure similar to that used for cesarean delivery. Hysterectomy is required if there has been extension into the broad ligament vessels, extensive damage to the uterine myometrium, or in the presence of placenta accreta.
Pregnancies After Uterine Rupture If the site of the ruptured scar is confined to the lower segment, the rate of repeat rupture or dehiscence in labor is 6%. In contrast, if the upper segment is involved, the rate jumps to 32%. Therefore, women with prior uterine rupture are best delivered by repeat cesarean as soon as the fetus is mature or at 36 to 37 weeks of gestation, before the onset of labor.

CESAREAN HYSTERECTOMY

Indications

Occasionally, hysterectomy must be performed immediately after cesarean or vaginal delivery. A useful classification is based on emergency indications (e.g., uterine rupture, uncontrollable uterine hemorrhage, placenta accreta, uterine infection) and nonemergency indications (e.g., for significant uterine pathology such as carcinoma in situ or uterine leiomyomas).

Emergency Indications Uncontrollable uterine hemorrhage may result from uterine rupture, uterine atony, placenta accreta, placental site sinusoids after placenta previa, or a coagulation defect. When surgery is indicated to control hemorrhage of uterine origin, the patient's desire to preserve childbearing capacity and the current danger are assessed. Nonsurgical management is indicated in such circumstances as uterine atony and coagulation defect. Bimanual uterine massage, oxytocin, prostaglandin administration, and blood replacement should be used before surgical intervention is considered. Hemorrhage from lower uterine segment venous sinuses associated with placenta previa sometimes can be controlled with mattress or figure-of-eight 2-0 to 0 absorbable sutures. With uterine atony, surgical interruption of the arterial flow to the uterus may be tried as the first measure of control. The operator may proceed to bilateral ligation of the hypogastric or the uterine arteries. If this is not efficacious, hysterectomy may be necessary. Hysterectomy can also be lifesaving as treatment of severe uterine infection. The patient who has experienced a second-trimester septic abortion with septic shock, peritonitis, or uterine perforation may be saved by prompt hysterectomy. Clostridial infection, dehiscence of a classic incision with uterine infection, or a severe uterine infection unresponsive to antibiotics should also be treated by hysterectomy.
Nonemergency Indications The risks and benefits of hysterectomy for nonemergency indications are much less certain than for emergency conditions. Hysterectomy performed at term is associated with hemorrhage, infection, thromboembolism, and injury to contiguous organs. The declining use of hysterectomy despite an increase in the incidence of cesarean delivery reflects a generally accepted conservative approach in most situations. Tubal ligation is a safer operation at term than is

hysterectomy. When carcinoma in situ must be treated, removal of the cervix at the time of hysterectomy is much more certain and technically less complicated in the nonpregnant state. The decision to perform a nonemergency hysterectomy requires good judgment, which is based on existing skills, facilities, and the needs of the individual patient.

Procedure

The technique for hysterectomy is described elsewhere, but some points are especially pertinent to its performance immediately after cesarean or vaginal delivery. In general, blood is conserved if the uterine wound for cesarean delivery is closed rapidly before beginning the hysterectomy. Normal ovaries should be preserved, and the operator should be aware that the relative shortening of the uteroovarian ligament at term necessitates extra care in the placement of clamps and sutures in this area. The increased vascularity of the pregnant uterus requires considerable care in the correct placement of clamps and sutures.

In the uterus at term, palpation of the portio of the cervix is often difficult, and portions of the cervix may be left behind inadvertently at the time of hysterectomy. This may be avoided by vaginal placement of easily palpated clips or clamps on the cervix prior to surgery. Alternatively, a vertical incision can be made in the lower uterine segment and extended caudad until the limits of the cervix are identified. Drainage of the pelvic cavity may be necessary, depending on the adequacy of hemostasis. In emergent situations or when the patient is unstable, a supracervical hysterectomy is simpler and quicker and may be preferable to total hysterectomy.

SUMMARY POINTS

- Cesarean delivery has played a major role in lowering both maternal and perinatal morbidity and mortality.
- Cesarean birth is necessary whenever labor is unsafe for either mother or fetus, when labor cannot be induced, when dystocia or fetal problems present significant risks with vaginal delivery, and when an emergency mandates immediate delivery.
- A variety of postpartum complications—including unexplained fever, endometritis, wound infection, hemorrhage, aspiration, atelectasis, urinary tract infection, and venous thromboembolism—occur in up to 25% of women who undergo cesarean delivery.
- The risk of late complications of cesarean, including uterine rupture, placenta previa, and placenta accreta, is directly proportional to the number of previous cesarean deliveries.
- The preferred and most frequently used is the low transverse incision.
- The decision to perform cesarean delivery on demand should be made only after careful consideration of all of the risks involved.
- A TOL after cesarean is safest in patients with only previous low transverse incisions.
- A TOL after cesarean preferably is undertaken in facilities where an immediate emergent cesarean can be performed.
- Women whose primary cesarean was performed for a nonrecurring condition have a better chance of success than women whose primary cesarean was performed for labor dystocia.
- Major complications occur more often in women who have a failed TOL after cesarean than in those who have an elective repeat cesarean.
- The most devastating complication of VBAC is uterine rupture, occurring in 0.5% of all women who attempt a TOL after cesarean.
- Uterine rupture during a TOL after cesarean often results in fetal damage or death, even if delivery is accomplished quickly.

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Chapter 25

Steven L. Clark

Critical Care Obstetrics

SHOCK IN PREGNANCY
HYPOVOLEMIC SHOCK
SEPTIC SHOCK
FETAL RESPONSE TO MATERNAL HEMODYNAMIC INSTABILITY
INVASIVE HEMODYNAMIC MONITORING
Determinants of Cardiac Output
Indications
DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC) ASSOCIATED WITH PREGNANCY
Pathophysiology
Diagnosis
Causes
TRANSFUSION THERAPY
Whole Blood
Red Blood Cells
Platelets
Fresh Frozen Plasma
Cryoprecipitate
Transfusion Reactions
ACUTE RESPIRATORY DISTRESS SYNDROME
Clinical Management
AMNIOTIC FLUID EMBOLISM
SUMMARY POINTS

SUGGESTED READINGS

The critically ill obstetric patient presents unique challenges to the clinician. Pregnancy alters the function of virtually every organ system; thus, both the baseline state and the patient's response to physiologic aberrations are different in the pregnant patient compared with her nonpregnant counterpart. In addition, fetal considerations often are important in designing a diagnostic and therapeutic approach to the critically ill gravida. Numerous situations may be encountered in which the physiologic demands of mother and fetus may be opposite. Many of the principles that apply to the critically ill nongravid patient apply in pregnancy, as well. This chapter explores a number of conditions in critical care medicine that are unique to pregnancy.

SHOCK IN PREGNANCY

Shock encompasses various pathophysiologic aberrations that lead to inadequate tissue perfusion and impaired cellular metabolism. Although hypotension often is the most obvious clinical sign in shock of any cause, such blood pressure changes are the final common manifestation of a number of distinct pathologic processes. The successful clinical management of patients in shock depends on the proper definition of the underlying pathophysiology, as well as an understanding of the unique effects of pregnancy on such conditions.

Several types of shock have been defined. This chapter focuses on the pathophysiology, diagnosis, and treatment of hypovolemic and septic shock, the types most commonly encountered in the pregnant patient.

In the nonpregnant patient, hypotension generally is defined as a systolic blood pressure less than 90 mm Hg or a mean arterial pressure less than 60 mm Hg. During pregnancy, this definition has less value, because blood pressures as low as 80/50 mm Hg commonly are seen in healthy pregnant women. Further, although a mean arterial pressure of 60 mm Hg may be adequate for perfusion of the adult heart and brain in a nonpregnant adult, the effects of a given blood pressure on uteroplacental perfusion cannot easily be generalized but are related to gestational age and placental condition. Whereas a blood pressure of 80/50 mm Hg may be adequate in one pregnant woman, another woman with pregnancy-induced hypertension and uteroplacental insufficiency may suffer inadequate placental perfusion and fetal distress with a diastolic blood pressure of 90 mm Hg. During pregnancy, shock is more reliably diagnosed on the basis of the overall clinical picture, including heart rate, mental status, urine output, and fetal condition, than on the basis of any absolute arterial pressure.

HYPOVOLEMIC SHOCK

Despite the availability of modern blood banking techniques, hemorrhage remains a major cause of maternal mortality. Pertinent physiologic changes that affect a woman's response to hemorrhage during pregnancy include a 50% increase in plasma volume with slightly lesser increases in circulating red blood cell mass. These changes, as well as an increase in resting heart rate of 10 beats per minute, result in about a 50% increase in resting cardiac output in the term gravida compared with her nonpregnant counterpart. Such changes are accompanied by a decrease in systemic vascular resistance, resulting in a net decrease in mean arterial pressure during the second trimester. At term, an average of 500 milliliters of blood is lost with vaginal delivery, compared with a mean blood loss of 1,000 milliliters with cesarean section. Such losses usually are well tolerated by the pregnant woman because of the physiologic hypervolemia.

Early in the course of massive hemorrhage, there are decreases in mean arterial pressure, cardiac output, central venous pressure, pulmonary capillary wedge pressure (PCWP), stroke volumes, and oxygen consumption and increases in arterial venous oxygen content difference. These changes are accompanied by compensatory increases in heart rate, systemic and pulmonary vascular resistance, and myocardial contractility. In addition, the redistribution of cardiac output and blood volume result in diminished perfusion to the kidneys, gastrointestinal tract, skin, and uterus, with relative maintenance of blood flow to the heart and brain. In the pregnant patient, such redistribution may result in fetal hypoxia and distress, even in the absence of an overt maternal hypotension. To some extent, the fetus acts like a miner's canary: regardless of absolute maternal blood pressure, significant maternal shock is virtually never seen in the presence of a reassuring fetal heart rate pattern. During this initial phase, initial oxygen extraction by the maternal tissues is increased. Further maldistribution of blood flow results in local tissue hypoxia and metabolic acidemia. If not promptly corrected, such shunting of blood from the renal and splanchnic beds may result in acute tubular necrosis and may contribute to pulmonary capillary endothelial damage, resulting in the adult respiratory distress syndrome (ARDS) even if resuscitation eventually is successful. In a similar manner, such tissue hypoxia and damage may give rise to thromboplastin release resulting in disseminated intravascular coagulation (DIC). Hemorrhagic shock also has been demonstrated to suppress bone marrow hematopoiesis. Once such shock has progressed to the point of end-organ failure, secondary consumptive coagulopathy, and depressed hematopoiesis, survival may not be possible even with adequate replacement of volume, red blood cells, and clotting factors.

As the blood volume deficit exceeds 25% to 30%, the compensatory mechanisms begin to become inadequate to maintain cardiac output and blood pressure. At this point, additional losses of blood may result in rapid clinical deterioration that produces a cycle of cellular death and vasoconstriction leading to organ ischemia, loss of capillary membrane integrity, and additional loss of intravascular fluid volume to the extravascular spaces. Thus, time is of the essence in restoring hemodynamic and oxygenation parameters to normal if survival is to be optimized.

The management of the patient in hemorrhagic hypovolemic shock is directed toward two goals: restoring circulating blood volume and eliminating the source of hemorrhage. The management of the most common causes of obstetric hemorrhage (e.g., lacerations, retained placenta, uterine atony) is described in detail elsewhere. The therapeutic restoration of circulating blood volume begins with a rapid infusion of crystalloid solution and packed red blood cells. These maneuvers form the cornerstone of therapy for hemorrhagic shock. Patients with normally functioning hearts may respond better to hypovolemic shock with blood volume replacements that are 500 to 1,000 milliliters in excess of their predicted norm. Such expansion dilates the constricted capillary networks that persist from the initial hypotensive phase and assists in resolving acidosis at the cellular level.

Continued replacement of blood with crystalloid solutions and packed red blood cells alone results in eventual depletion of labile clotting factors and platelets and may result in a dilutional coagulopathy which, itself, may contribute to further bleeding. This is to be distinguished from the consumptive coagulopathy which also may arise secondary to shock and tissue damage. A fibrinogen level below 100 milligrams per deciliter or prolongation of the prothrombin and active partial thromboplastin times in a bleeding patient are indications for fresh frozen plasma infusion. Platelet transfusion should be guided by platelet counts. One unit of platelets raises the platelet count by 8,000 to 10,000 per cubic millimeter and should be considered in a bleeding patient with a platelet count below 30,000 per cubic millimeter.

SEPTIC SHOCK

The incidence of septic shock appears to be increasing. Septic shock accompanies up to 50% of bacteremias caused by Gram-negative organisms and 5% of those caused by Gram-positive organisms. In the overall hospital population, once clinical shock is evident, the mortality rate is 40% to 50%. Although pregnancy classically has been considered a factor that predisposes a patient to septic shock, data to support this are lacking. It seems more likely that such older observations stemmed from delayed diagnosis and treatment in the pregnant patient. In obstetrics, septic abortion, chorioamnionitis, pyelonephritis, and endometritis are the most common conditions associated with septic shock. Postpartum infection with group A streptococcus is increasingly recognized as an uncommon, but potentially lethal, complication of the puerperium, a condition made more serious by the virulent nature of this infection and its rather protean clinical manifestations. Although it may be presumed that with a younger population, the mortality with septic shock is somewhat less than in the overall population, this condition continues to account for a significant percentage of maternal mortality.

Septic shock in obstetrics most commonly is associated with infection caused by endotoxin-releasing Gram-negative aerobic coliform organisms. Endotoxin, a complex cell wall–associated lipopolysaccharide, is released into the circulation at the time of bacterial death, resulting in multiple hemodynamic effects. The subsequent activation of lymphocytic T cells and mast cells results in histamine and kinin activation, as well as the activation of kallikrein and a decrease in kallikreinogen and kallikrein inhibitor. These changes result in the release of bradykinin, a potent arterial dilator. Complement activation and the release of arachidonic acid metabolites, nitric oxide, endorphins, and other endogenous mediators play a major role in the pathophysiology of septic shock. In addition, septic shock results in a marked reduction of vasopressin (antidiuretic hormone) levels, further impairing the body's vasoconstrictive response and capacity for intravascular fluid retention. This generalized inflammatory response, similar to that seen with other conditions such as anaphylaxis, is responsible for much of the pathophysiology seen with these conditions and has been termed the systemic inflammatory response syndrome.

Early septic shock is a classic example of distributive shock, related to a systemic maldistribution of relatively normal, or even increased, cardiac output. Clinical findings include hypotension, fever, and chills. Initial hemodynamic findings include decreased systemic vascular resistance and high-normal or elevated cardiac output. The continued maldistribution of cardiac output leads to local tissue hypoxia and the development of lactic acidosis and end-organ dysfunction. This decrease in systemic vascular resistance is caused by the release of vasoactive substances, as well as by vascular endothelial cell injury, which promotes capillary plugging secondary to complement-induced leukocyte aggregation. These factors lead to increased arteriovenous shunting.

The treatment of septic shock in this early phase involves optimizing preload by restoring relative intravascular volume with crystalloid infusion, as well as aggressively treating the underlying infection. Although some authorities advocate the use of colloid solutions for volume replacement, there is no convincing evidence that the use of such solutions decreases the incidence of pulmonary edema or ARDS. If the offending organism is known, single-agent antibiotic therapy may be used. More commonly in obstetrics, the infection is polymicrobial, and broad-spectrum coverage for Gram-negative and Gram-positive aerobic and anaerobic organisms is most appropriate. If an abscess is involved, prompt surgical drainage after initial resuscitation is mandatory.

If the process continues, the patient may enter a second hemodynamic phase of septic shock. Of primary importance in this late phase is the development and progression of myocardial dysfunction leading to ventricular failure. Although commonly viewed as a late finding, studies assessing stroke work index and ventricular ejection fraction have demonstrated depressed intrinsic ventricular function even in the early stages of septic shock, when increases in heart rate are compensatory and associated with a normal or high cardiac output. This myocardial depression is a direct effect of myocardial depressant substance in the serum of patients with septic shock. When ventricular function has deteriorated to the point in which cardiac index is frankly depressed (i.e., <3–4 L/min per m^2 in pregnancy) in the presence of adequate preload, the prognosis is extremely grave. Pulmonary hypertension, another important hemodynamic alteration often associated with septic shock, may have additional profound hemodynamic consequences.

For most pregnant patients in septic shock, maximal ventricular function is obtained by means of optimizing Starling forces with a PCWP of about 16 mm Hg. Patients who remain hypotensive after such preload manipulation require treatment with pressor agents such as dopamine hydrochloride. This agent, in dosages of less than 5 micrograms per kilogram per minute, improves renal blood flow by way of dopaminergic mesenteric vasodilation; in dosages of 5 to 30 micrograms per kilogram per minute, a positive inotropic effect also is seen. In dosages that exceed 30 micrograms per kilogram per minute, the favorable effect on blood pressure is principally one of a-adrenergic vasoconstriction. Additional inotropic or vasoconstrictive agents may need to be administered in refractory septic shock. Treatment with vasopressin has been effective in improving urine output, decreasing pulmonary vascular resistance, and reducing the need for additional pressor agents. Initial studies suggest the infusion of methylene blue (an inhibitor of nitric oxide synthesis) may prove effective in counteracting myocardial depression, maintaining oxygen transport, and reducing the need for additional adrenergic support. The use of glucocorticoids in septic shock continues to unfold. Original enthusiasm for early, high-dose steroid treatment in patients with septic shock was followed by well-designed studies demonstrating not only a lack of benefit, but potential harm, from such therapy. More recently, the demonstration of an altered hypothalamic–pituitary–adrenal axis in patients with septic shock have led to additional investigations suggesting that lower-dosage replacement therapy with hydrocortisone may be beneficial, by interfering with the physiologic expression of the systemic inflammatory response syndrome.

The hemodynamic manipulation of patients whose hypotension fails to respond rapidly to volume infusion may, at times, be assisted by pulmonary artery catheterization, allowing the clinician to achieve optimal preload before the institution of inotropic or vasoconstrictive therapy.

Patients who recover from the initial hemodynamic instability of septic shock may suffer prolonged morbidity secondary to endotoxin-mediated pulmonary capillary injury and noncardiogenic pulmonary edema (i.e., ARDS). Such lung failure is a major cause of death in patients with septic shock. Similarly, pregnant patients whose hypotension was prolonged may experience acute tubular necrosis. Endotoxin-mediated endothelial cell injury and associated thromboplastin-like activity, as well as prolonged shock from any cause, may also lead to activation of the coagulation cascade and to a clinical picture of DIC. Even in the absence of frank tissue hypoxia, septic stimuli may lead to coagulation abnormalities.

Of special interest to obstetricians is the demonstration that, in patients in septic shock, *adult* heart rate variability is diminished; such observations have been suggested as potentially useful in the diagnosis of adult septic shock.

FETAL RESPONSE TO MATERNAL HEMODYNAMIC INSTABILITY

Fetal well-being depends principally on the maintenance of maternal oxygenation and uterine blood flow. During severe fetal hypoxia, cardiac output decreases and pulmonary vasoconstriction occurs, with redistribution of the fetal circulation favoring blood flow to the brain, heart, and adrenals at the expense of splanchnic and even placental blood flow. Although Starling's law is operative in the fetus, ventricular stroke work varies over a much smaller range of end-diastolic pressures. Changes in cardiac output manifest themselves primarily by changes in fetal heart rate alone. As maternal arterial PO_2 falls, there appears to be no corresponding fall in fetal PO_2 as long as the maternal PO_2 exceeds 60 mm Hg. Because the fetus operates on the steep portion of the oxygen dissociation curve (Fig. 25.1) (i.e., normal fetal PO_2 range, 10–33 mm Hg), further falls in maternal and fetal PO_2 result in dramatic decreases in fetal oxygen saturation and fetal hypoxia. Unfortunately, observations using the fetal pulse oximeter have demonstrated that the administration of oxygen to the mother using most readily available oxygen delivery methods does not result in improvement in fetal oxygen saturation.

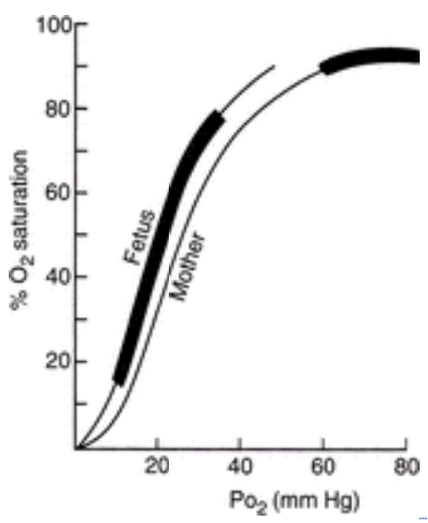


FIG. 25.1. Oxygen dissociation curves for human maternal and fetal blood, indicating the physiologic range of PO_2 and O^2 saturation for mother and fetus. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:343, with permission.)

Near term, uterine blood flow approaches 500 milliliters per minute and accounts for about 10% of total maternal cardiac output. The uterine arteries show little capacity for autoregulation; thus, uterine and placental blood flow fall in direct proportion to maternal systemic arterial pressure. In the hypotensive mother, compensatory maternal vasoconstriction aimed at maintaining circulation to the heart and brain decreases uterine blood flow even further. Thus, maternal hypotension, whether caused by supine venacaval compression, conduction anesthetic, or even amniotic fluid embolism (AFE), may be first heralded by fetal bradycardia. Because maternal compensatory mechanisms maintain systemic arterial pressure at the expense of uterine blood flow, such abnormal patterns may be seen even in the absence of overt maternal hypotension. Thus, during the critical course of a gravely ill mother, careful monitoring of fetal well-being is essential. Even in a medical or surgical intensive care setting, continuous electronic fetal heart rate monitoring is often an important part of the care of the critically ill and unstable pregnant patient.

INVASIVE HEMODYNAMIC MONITORING

Since its introduction into clinical medicine in the early 1970s, the pulmonary artery catheter has come to play an important role in the management of critically ill patients with hemodynamic instability. Several prospective trials demonstrate the benefits of this technique in select, critically ill patients, including a reduction in morbidity and mortality in some subsets. On the other hand, the risk–benefit ratio of invasive monitoring in the general population of seriously ill patients has been questioned. When obstetric patients require such monitoring, optimal patient outcome is predicated on the clinician's understanding of the hemodynamic changes associated with pregnancy, as well as a working knowledge of indications for invasive hemodynamic monitoring. Although invasive hemodynamic monitoring rarely is required in the pregnant patient, an understanding of the hemodynamic principles derived from such techniques may assist the obstetrician–gynecologist in the noninvasive management of less critically ill patients.

The pulmonary artery catheter is a multilumen catheter placed most commonly through the internal jugular or subclavian vein (Fig. 25.2). As the catheter is advanced through the great vessels and heart, its location can be determined precisely by observing characteristic pressures and waveforms (Fig. 25.3). When the catheter is placed correctly, the lumens terminate in the pulmonary artery and the superior vena cava or right atrium and allow direct assessment of central venous pressure, PCWP, and pulmonary artery pressure. S_xO_2 and cardiac output can be computed either continuously or intermittently using a fiberoptic thermistor system. These measurements may be combined with mean arterial pressure and body surface area and heart rate to calculate additional important hemodynamic indices, such as systemic vascular resistance and left ventricular stroke work index (Table 25.1). In critically ill obstetric patients, discrepancies often are seen between measurements of PCWP and central venous pressure. In such circumstances, clinical use of the central venous pressure measurement alone would be misleading and possibly deleterious. With rare exceptions, the complications seen with pulmonary artery catheterization are associated with obtaining central venous access and are similar whether a central venous pressure line or pulmonary artery catheter is used. For these reasons, in a modern perinatal intensive care unit, central venous pressure monitoring alone seldom is indicated.

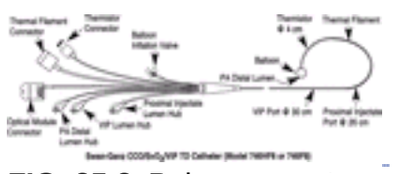


FIG. 25.2. Pulmonary artery catheter. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:63, with permission.)

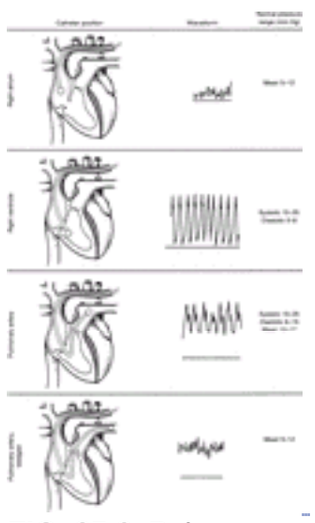


FIG. 25.3. Pulmonary artery catheter placement. Catheter position, corresponding waveforms, and pressures are shown. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:67, with permission.)

TABLE 25.1. *Derived hemodynamic parameters*

Determinants of Cardiac Output

In addition to heart rate, important determinants of cardiac output are preload, afterload, and an assessment of myocardial contractility.

Preload Preload represents the volume or pressure generated within the ventricles at end diastole. According to Starling's law, ventricular output is directly proportional to ventricular preload. Clinically, right ventricular preload is measured as central venous pressure, and left ventricular preload as PCWP. Because the left side of the heart perfuses the myocardium, brain, and uteroplacental unit, PCWP is the preload measurement of interest in clinical practice. When central venous pressures are used, it is done with the tacit assumption that the preloads of the right and left sides of the heart are equivalent. In a critically ill patient, this often is not the case, thus further limiting the usefulness of central venous pressure in the hemodynamically unstable obstetric patient.
Afterload Afterload describes the resistance to the flow of blood during ventricular systole. It is not measured directly; rather, after the measurement of cardiac output, central venous pressure, and mean arterial pressure, afterload is calculated as systemic vascular resistance. Cardiac output fluctuates inversely with systemic vascular resistance. Septic shock and preeclampsia are examples of frequently encountered conditions in obstetrics that may markedly influence systemic vascular resistance.
Ventricular Stroke Work Index Ventricular stroke work is also a calculated parameter (see Table 25.1). The assessment of ventricular stroke work on a modified Starling curve (Fig. 25.4) allows the clinician to directly assess the intrinsic contractility of the left ventricle and to classify myocardial function as normal, hyperdynamic, or hypodynamic. After preload has been optimized, ventricular function may be further affected by the administration of inotropic agents such as dopamine. The use of such agents may shift the intrinsic contractility of the ventricle from the hypodynamic to the normal range, resulting in improved cardiac performance (Fig. 25.5).

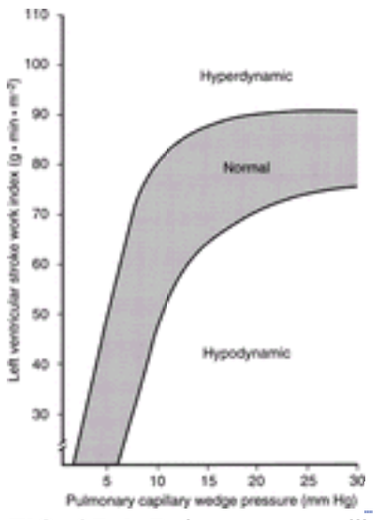


FIG. 25.4. Pulmonary capillary wedge pressure versus left ventricular stroke work index. Normal relationship is represented by the *shaded area.* (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:399, with permission.)

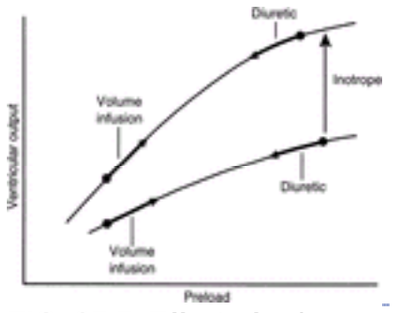


FIG. 25.5. Effect of volume manipulation and inotrope administration on ventricular output in two patients with septic shock. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:181, with permission.)

Indications

The indications for pulmonary artery catheterization in pregnancy include many of the conditions common to all critical care medicine. These include severe cardiac disease during labor and delivery, septic shock, and hemodynamic instability in patients with uncertain volume. Select patients with complicated severe preeclampsia form a subset unique to pregnancy. It has been suggested that patients with severe hypertension unresponsive to conventional antihypertensive medication, those with pulmonary edema of unknown cause, and those with persistent oliguria may benefit from invasive hemodynamic monitoring. In contrast, hemodynamic monitoring seldom is indicated in cases of hypovolemia associated with obstetric hemorrhage. Normal values for invasively obtained hemodynamic indices have been described and often are valuable in managing the critically ill obstetric patient (Table 25.2).

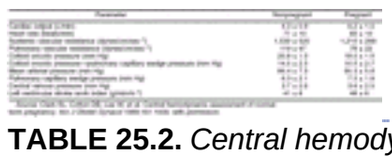


TABLE 25.2. *Central hemodynamic changes*

DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC) ASSOCIATED WITH PREGNANCY

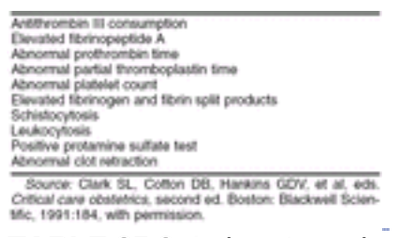
DIC is not a distinct clinical entity; rather, it represents a manifestation of various disease processes that have in common activation of intravascular clotting and fibrinolysis, resulting in excess consumption of soluble coagulation components. In obstetrics, secondary fibrinogenolysis commonly dominates the clotting aberration and results in the circulation of fibrin and fibrinolytic split products, which further accentuate the clinical picture of hemorrhage. In addition, sometimes a dilutional coagulopathy is encountered in pregnancy. This condition occurs when massive hemorrhage is replaced only by red blood cells and crystalloid solution, resulting in a dilutional depletion of platelets and soluble clotting factors. From both a clinical and a laboratory standpoint, dilutional coagulopathy may be confused with a more classic process of intravascular consumption and fibrinolysis. In practice, the hemorrhage associated with dilutional coagulopathy often results in hypotension and shock. The tissue hypoxia that accompanies shock of any cause is well known to potentially activate the coagulation–fibrinolysis cycle associated with DIC. Thus, it is not always possible to draw a clear distinction between dilutional and consumptive coagulopathy.

Pathophysiology

A number of conditions in obstetrics may trigger the intravascular coagulation–fibrinolysis sequence. All have in common some form of endothelial disruption or release of tissue thromboplastins into the central circulation. Thus, clotting may occur by either the intrinsic or the extrinsic coagulation pathways. After activation of the clotting cascade, fibrin monomer polymerizes, forming insoluble fibrin. Serum plasminogen simultaneously begins the degradation of fibrin. The breakdown products of fibrin and fibrinogen (i.e., fibrinolytic split products) then bind the soluble fibrin monomer to prevent further polymerization. In addition, plasmin inactivates factors V, VIII, IX, and XIII and inhibits the platelet-mediated primary phase of coagulation. The fibrin monomer that does polymerize is filtered within the microvasculature, resulting in fibrin plugs. Such plugging reduces blood flow, which causes tissue hypoxia and organ schemia. The subsequent endothelial damage further enhances the clotting cascade. Thrombocytopenia results from both consumption and destruction secondary to fibrinolytic split products in the microvasculature, a process that also results in microangiopathic hemolytic anemia. The release of thromboplastic material from damaged red blood cells and complement activation further propagate the vicious cycle of intravascular coagulation–fibrinolysis (see Fig. 25.5).

Diagnosis

DIC is suggested clinically by excess bleeding from surgical incision sites or the postpartum uterus. In severe cases, spontaneous bleeding from intravenous sites and other mucous membranes also may be seen. Table 25.3 lists some laboratory abnormalities that may be present in DIC. The prothrombin and partial thromboplastin times are relatively insensitive indicators of clotting status, because results are not prolonged until 40% to 50% of the clotting factors have been consumed. Although levels of fibrinolytic split products and paracoagulation tests are thought to be sensitive indicators of DIC, values may be normal in 10% to 15% of patients with acute DIC.



Antithrombin III consumption
Elevated fibrinopeptide A
Abnormal prothrombin time
Abnormal partial thromboplastin time
Abnormal platelet count
Elevated fibrinogen and fibrin split products
Schistocytosis
Leukocytosis
Positive protamine sulfate test
Abnormal clot retraction

Source: Clark SL, Cotton DB, Hankins GDV, et al, eds. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1991:184, with permission.

TABLE 25.3. *Laboratory abnormalities in disseminated intravascular coagulation*

Causes

Numerous causes of DIC may be encountered in obstetrics (Fig. 25.6). The most common are placental abruption and dead fetus syndrome. AFE, a rare obstetric catastrophe, often is associated with DIC. Preeclampsia, commonly associated with thrombocytopenia, is not itself a cause of clinical DIC, unless complicated by substantial placental abruption. Other conditions not unique to obstetrics, such as septic shock and transfusion disorders, also may be associated with DIC in obstetrics. The management of acute DIC in obstetrics principally involves resolution of the underlying pathophysiologic process. Although possibly severe, the DIC associated with abruption, dead fetus syndrome, or AFE usually is self-limiting, and its resolution may begin with delivery of the fetus and placenta. In most cases, the replacement of soluble clotting factors or platelets is effective in preventing clinical hemorrhage for the short term while delivery is accomplished; little evidence exists to support the use of heparin or fibrinolytic agents in obstetric DIC syndromes. One exception may be dead fetus syndrome, in which low-dose heparin therapy (5,000 U subcutaneously twice daily) may correct moderate coagulation abnormalities during delivery. When there is bleeding or if surgery is planned, platelet transfusion should be considered for patients with a platelet count less than 30,000 per cubic millimeter, and fibrinogen replacement with fresh frozen plasma is appropriate for the bleeding patient with a fibrinogen level less than 100 milligrams per deciliter or prolonged prothrombin and partial thromboplastin times. In the nonsurgical patient without clinical hemorrhage, clotting abnormalities associated with a mild to moderate intravascular coagulopathy may simply be observed while delivery is accomplished.

FIG. 25.6. Obstetric disorders that initiate disseminated intravascular coagulation. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:182, with permission.)

TRANSFUSION THERAPY

Indications for blood or component transfusion include restoration of circulating volume, improvement in oxygen transport, and correction of coagulation disorders. The third indication has been addressed in the preceding paragraphs. This section addresses blood and component transfusion considerations in the patient with massive blood loss.

The incidence of blood transfusion in patients undergoing vaginal delivery is less than 1%, whereas 2% to 12% of patients undergoing cesarean delivery receive blood. To anticipate the potential for peripartum blood loss, blood often is sent for type and screen and, occasionally, type and crossmatch. To type and screen blood, first the ABO group and Rh(D) type of the patient's cells are determined. Her serum is then mixed with reagent red blood cells that contain the antigens with which most clinically significant antibodies will react. An antibody-enhancing solution, such as bovine serum albumin, may be added at this point to enhance the detection of nonagglutinating antibodies. After incubation and washing, the appearance of an agglutination indicates the presence in the recipient serum of antibodies to one or more antigens in the reagent blood cells.

Type and crossmatch procedures are similar to those described for typing and screening, except that potential donor red blood cells are used rather than standard reagent erythrocytes. If blood that has been screened but not cross-matched is used, a transfusion reaction might take place if the recipient serum contains an antibody to an antigen present on the donor cells that was not present on the reagent red blood cells. Because only 0.03% to 0.07% of patients who were determined not to have antibodies on type and screening subsequently are found to have preexisting antibodies determined by crossmatch, the type and screen approach has been about 99% effective in preventing incompatible transfusions. Type and screen testing is much less costly than typing and cross-matching blood and allows blood to be made available for more than one potential recipient, thus decreasing the wastage of banked blood. Therefore, this method is appropriate for both vaginal delivery and most cases of cesarean section and, under these circumstances, is preferred to typing and cross-matching.

Whole Blood

A unit of whole blood contains about 450 milliliters of blood. One unit of whole blood can raise the recipient's hematocrit by 3% to 4%. When stored for longer than 24 hours, whole blood retains few functioning granulocytes or platelets. Clotting factors are maintained in adequate concentrations for the life of the unit, except levels of factors V and VIII, which may be reduced. Because whole blood is not readily available, whole blood transfusion is uncommon in modern obstetric practice; red blood cells plus component replacement is preferred.

Red Blood Cells

Packed red blood cells are prepared from whole blood by separating the cells from plasma by centrifugation or sedimentation. They have a hematocrit of about 70% to 75% (160–275 cc red blood cells per unit). A unit of packed cells contains the same number of erythrocytes as a unit of whole blood; thus, it can raise the recipient's hematocrit by 3% to 4%. Packed red blood cells provide the same oxygen-carrying capacity as whole blood in about one half the volume.

Platelets

Platelets are prepared from whole blood by centrifugation and then are resuspended in 50 to 70 milliliters of plasma. Unlike red blood cells, they cannot tolerate prolonged storage; under special circumstances, however, they may be stored for up to 5 days. The donor plasma in which the platelets are suspended must be ABO compatible with the recipient's red blood cells. A unit of random donor platelets should raise the platelet count by 8,000 to 10,000 per cubic millimeter. Platelets are available in packs of 8 or 10 units. No consensus has been reached regarding minimal platelet levels that indicate the need for transfusion. In the nonbleeding or nonsurgical patient, platelet transfusion seldom is indicated with a platelet count that exceeds 10,000 per cubic millimeter, because antibody formation and platelet destruction are rapid. In the bleeding or surgical patient, the platelet count should be maintained above 30,000 per cubic millimeter to prevent further hemorrhage.

Fresh Frozen Plasma

Fresh frozen plasma contains all soluble clotting factors, similar to those found in whole blood. In addition, it contains significant amounts of factors V and VIII. The plasma is first separated from whole blood and then frozen. The volume of a unit is about 250 milliliters. Fresh frozen plasma is indicated for patients with a consumptive or dilutional coagulopathy in whom replacement of soluble clotting factors, including fibrinogen, is indicated. In the bleeding patient, a fibrinogen level less than 100 milligrams per deciliter associated with prolonged prothrombin and partial thromboplastin times is an indication for fresh frozen plasma infusion. By definition, each milliliter of fresh frozen plasma contains 1 IU of each coagulation factor. One unit will raise the serum fibrinogen level by approximately 25 milligrams per deciliter.

Cryoprecipitate

A unit of cryoprecipitate is prepared by thawing a unit of fresh frozen plasma, removing the supernatant plasma, and then refreezing the precipitate. Cryoprecipitate contains factor VIII:C, factor XIII, von Willebrand factor, fibrinogen, and fibronectin. The sole advantage of cryoprecipitate over fresh frozen plasma is the ability to infuse relatively large amounts of factors in a small volume. In practice, volume restriction seldom is desirable for the hemorrhaging patient; thus, fresh frozen plasma nearly always is preferable to cryoprecipitate in the management of obstetric hemorrhage associated with consumptive or dilutional coagulopathy.

In cases of dilutional coagulopathy, bleeding is more likely to be secondary to thrombocytopenia than to factor deficiency. All the blood and clotting factors contained in cryoprecipitate and fresh frozen plasma carry with them the risk of blood-borne disease transmission, although such a risk is minimal in properly screened and donated blood.

Transfusion Reactions

Acute transfusion reactions are seen in about 5% of blood recipients, and delayed transfusion reactions in up to 7% of recipients. Nonhemolytic febrile reactions may accompany 1% of all transfused units. Most nonhemolytic febrile and allergic reactions are unavoidable. Most hemolytic reactions may be prevented by proper attention to cross-matching procedures.

Hemolytic transfusion reactions may be acute or delayed. Acute intravascular hemolysis most commonly results from the transfusion of ABO-incompatible blood. Such errors are the most frequent cause of fatalities resulting from blood transfusion and usually are related to technical errors in blood specimen labeling and in patient identification. Such hemolysis is complement mediated. Signs and symptoms of acute hemolytic reaction include lumbar pain, facial flushing, chest pain that may be accompanied by fever, tachycardia, hypotension, and shock. In severe cases, DIC associated with oliguria and pulmonary edema may be seen. Acute tubular necrosis or ARDS may be encountered in patients who survive the acute episode. The key laboratory findings in the diagnosis of intravascular hemolytic transfusion reaction are a decrease in the plasma haptoglobin level with an increase in free serum hemoglobin. These findings typically are accompanied by hemoglobinuria if plasma levels exceed 25 milligrams per deciliter.

Acute extravascular hemolytic reactions are not mediated by complement but by the development of immunoglobulin G (IgG) antibodies to antigens such as D or Kell. Clinical findings are less severe and often manifest by simply a fever and hemolytic anemia. Severe clinical symptoms are infrequent.

Delayed hemolytic reactions occur within 3 to 7 days of a blood transfusion. These reactions are caused by a serum antibody that is present in low, undetectable levels at the time of transfusion. The clinical parameters are similar to those seen with acute extravascular hemolysis but are not as severe.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome is a complex pathophysiologic process resulting from either primary lung epithelial injury by way of the airways or capillary endothelial injuries initiated by way of the pulmonary vasculature. Such injury results in increased pulmonary capillary permeability, loss of lung volume, and shunting with resultant arterial hypoxemia. The physiologic criteria required for the diagnosis of ARDS are listed in Table 25.4. In pregnancy, the incidence of ARDS is approximately 1 in 6,000. Sepsis, preeclampsia, viral pneumonic processes, hypovolemic shock, and aspiration pneumonia are the most common causes of ARDS.

P_{O_2} <50 with F_{iO_2} >0.6
Pulmonary capillary wedge = 12 mm Hg
Total respiratory compliance <50 mL/cm (usually 20–30 mL/cm)
Functional residual capacity reduced
Shunt (Q_s/Q_t) >30%
Dead space (V_D/V_T) >60%
Alveolar—arterial gradient on 100% oxygen = 350 mm Hg

F_{iO_2}, fraction of inspired oxygen; P_{O_2}, partial pressure of oxygen; Q_s, blood flow to nonventilated areas; Q_t, total blood flow to both ventilated and nonventilated areas; V_D, dead space volume; V_T, tidal volume.

Source: Clark SL, Cotton DB, Hankins GDV, et al, eds. *Critical care obstetrics*. third ed. Boston: Blackwell Scientific, 1997, with permission.

TABLE 25.4. *Physiologic criteria for adult respiratory distress syndrome*

ARDS represents a final common pathway of a cascade of events initiated by the alveolar, epithelial, or endothelial injury (Fig. 25.7). After the initial injury to alveolar epithelial cells or vascular endothelial cells, the complement system, leukocytes, macrophages, and platelets may all play important roles in perpetuating the injury. During the initial lung injury, phospholipids are released from red blood cell membranes, resulting in a secondary mechanism of injury. Free arachidonic acids serve as a substrate for the synthesis of both prostaglandins and thromboxanes by way of the cyclooxygenase system and, possibly, leukotrienes by way of the lipoxygenase system. All of these arachidonic acid metabolites have been implicated in perpetuating the injury of ARDS.

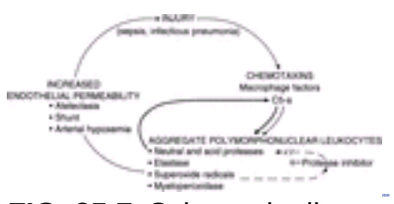


FIG. 25.7. Schematic diagram of the proposed mechanism of lung injury. After the cycle is established, loop 1 feeds back on itself to perpetuate the injury. Amplification of the first loop is provided by the neutral and acid proteases *(bold line);* disruption of the amplification loop is prevented by myeloperoxidases *(dashed line).* PMNs, polymorphonuclear leukocytes. (From Clark SL, Phelan JP. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1990:343, with permission.)

Clinically, the course of ARDS can be divided into four phases. Each is distinguishable by histologic changes in the lungs and reflected in various physiologic parameters in the patient. In phase I, hyperventilation is the only physiologic aberration seen, and arterial oxygenation remains adequate. During phase II (i.e., the latent period), there may be minor auscultatory and radiographic evidence of pulmonary disease. Mild decreases in lung compliance and increases in intrapulmonary shunting of blood are common. Histologically, these stages are characterized by progressive alveolar and interstitial edema formation and the movement of inflammatory cells into the interstitium. Damage to type I alveolar cells occurs, and hyaline membrane formation begins. Phase III is characterized by acute respiratory failure with severe dyspnea, tachypnea, and arterial hypoxemia. During this phase, lung volume is lost, resulting in the deterioration of pulmonary compliance and an increase in intrapulmonary shunting. Chest x-ray films taken during this stage demonstrate marked abnormalities, including bilateral lung opacification. During phase III, intubation and assisted ventilation are required. Histologically, phase III is characterized by thickening of the alveolar septum and marked infiltration by leukocytes, plasma cells, and macrophages. Hyaline membranes begin to form and organize during this phase, and the proliferation of fibroblasts and type II alveolar cells is prominent. In phase IV, interpulmonary shunting in excess of 25% results in hypoxemia refractory to all measures. Dead space during this period may exceed 60% of tidal volume. Metabolic and respiratory acidemia may be found and may result in increased myocardial excitability, which often leads to terminal dysrhythmia. Intraalveolar fibrosis is severe, and pathologic and physiologic derangements are irreversible.

Clinical Management

Four considerations are essential in understanding the clinical management of the pregnant patient with ARDS. These are oxygen delivery and tissue extraction, pulmonary compliance, interpulmonary shunt fraction, and eradication of the underlying cause.

Oxygen delivery is directly proportional to cardiac output; it is also influenced by the oxygen-carrying capacity of the blood. Thus, oxygen delivery can be optimized by maintaining cardiac output and correcting anemia. In the presence of suboptimal cardiac output or significant anemia, marked increases in the inspired concentration of oxygen have little effect on actual oxygen delivery. However, high inspired concentrations of oxygen are toxic to the lung. The goals in caring for a patient with severe ARDS are first to optimize cardiac output and hematocrit and then to maintain a PO_2 of 60 to 70 mm Hg. Because increased body temperature and metabolic acidosis produce a rightward shift in the oxyhemoglobin dissociation curve, these conditions may favorably affect peripheral oxygen delivery. Thus, the patient should not be chilled either in the operating room or through the administration of large volumes of intravenous fluids or blood that is below body temperature. Further, respiratory alkalosis should be corrected. Indeed, a mild metabolic acidemia may result in better tissue oxygen delivery than would be obtained with complete correction of the patient's acid–base status.

Arterial–venous oxygen content difference may be used to assess the adequacy of oxygen delivery. During pregnancy, the arterial–venous gradient narrows.

In the critically ill patient who is receiving assisted ventilation, pulmonary compliance can be calculated by using parameters obtainable from the ventilator. With severe ARDS, pulmonary compliance may fall from a normal value of about 75 milliliters per cm H_2O to as low as 20 milliliters per cm H_2O. Serial calculation of compliance may be useful in evaluating the effects of various therapeutic maneuvers, including positive end-expiratory pressure (PEEP). Longitudinal evaluation of pulmonary compliance may serve as a useful method of following the resolution or progression of ARDS.

The normal shunt in the healthy gravida is 2% to 5% of cardiac output. Mild pulmonary dysfunction may result in shunting of 10% to 15%. A shunt that exceeds 25% suggests and, in the absence of other causes, may be diagnostic of ARDS. The shunt may be estimated either by analyzing an arterial blood sample alone or by analyzing simultaneously obtained arterial and pulmonary artery blood samples. In the former method, the greatest accuracy is obtained by having the woman breathe 100% oxygen. In a patient who is intubated and receiving 100% inspired oxygen, the arterial oxygen pressure should exceed 500 mm Hg; values below 300 mm Hg suggest severe shunting.

During initial treatment of the pregnant gravida with ARDS, the physician should simultaneously conduct an aggressive search for and attempt to eliminate the underlying cause of the lung injury. Early intubation is essential for the patient in incipient respiratory failure (Table 25.5). Mechanical ventilation requires a volume-cycled ventilator. Appropriate initial settings may include a rate of 12 breaths per minute, a tidal volume of about 15 milliliters per kilogram of body weight with a sigh volume of 200 to 400 milliliters above tidal volume, a PEEP of 5 cm H_2O, and 100% inspired oxygen. Fifteen to 30 minutes after the initial therapy, an arterial blood sample is analyzed, and the ventilator settings are adjusted to obtain a PaO_2 of 60 to 70 mm Hg with a PCO_2 of 35 to 45 mm Hg. The level of PEEP often must be increased to optimize PO_2 and oxygen saturation. The use of high levels of PEEP is preferable to the continued use of toxic concentrations of oxygen. If possible, the FIO_2 should be reduced to less than 60% to minimize the potential for long-term oxygen toxicity. The criteria for using higher levels of PEEP include a static compliance less than 40 milliliters per centimeter of water, a shunt fraction exceeding 20%, or an alveolar–arterial oxygen gradient on 100% oxygen exceeding 400 mm Hg. At high levels of PEEP (>20 cm of water), cardiac output may fall; thus, invasive hemodynamic monitoring often is useful in assessing the cardiac output response to high levels of PEEP. Fluid therapy in patients with ARDS may also be facilitated by the use of invasive hemodynamic monitoring, and the PCWP should be maintained as low as is consistent with adequate cardiac and urine output.

	Normal	Intubate
Respiratory rate	12–20	>35
Vital capacity (mL/kg)	65–75	<15
FEV_1 (mL/kg)	50–60	<10
Inspiratory force (cm H_2O)	75–100	<25
Pa_{O_2} (mm Hg)	100–75 air <70 mask	0.4 <300 F_{iO_2}
$Paco_2$ (mm Hg)	35–45	>55
V_D/V_t	0.25–0.40	>0.6

FEV_1, forced expiratory volume in 1 second; F_{iO_2}, forced inspiratory oxygen concentration; H_2O, water; $Paco_2$, arterial carbon dioxide pressure; Pa_{O_2}, arterial oxygen pressure; V_D/V_t, ratio of dead space volume to tidal volume.

Source: Clark SL, Cotton DB, Hankins GDV, et al, eds. *Critical care obstetrics*, second ed. Boston: Blackwell Scientific, 1991:357, with permission.

TABLE 25.5. *Guidelines for instituting ventilator therapy*

The management of the patient with ARDS often is a long-term process. Ventilation and circulation may be supported by using some of the techniques outlined in this section. After the underlying cause of ARDS has been eliminated, therapy involves support of respiration and circulation while allowing the lungs time to heal. Despite aggressive and optimal management, the mortality rate for pregnant patients is approximately 40%. When ARDS is secondary to sepsis, higher mortality is seen. In many instances, such patients may expire despite optimal therapy. Surfactant replacement as well as nitric oxide therapy have shown promise in the treatment of severe ARDS; however, the use of these agents remains investigational.

AMNIOTIC FLUID EMBOLISM

AFE is an uncommon obstetric catastrophe with a mortality as high as 80%. It is a biphasic process that is triggered by the sudden embolization of amniotic fluid or debris of fetal origin into the maternal venous circulation. The initial physiologic disturbances involve profound alterations in hemodynamics and oxygenation, often followed by the development of a consumptive coagulopathy. Either of these phases may predominate and, occasionally, bleeding may be the initial manifestation. The most common clinical picture consists of sudden dyspnea and hypotension, commonly followed within minutes by cardiorespiratory arrest. In up to 50% of these cases, these initial events may be accompanied by seizure activity. Common signs and symptoms of AFE are presented in Table 25.6. One half of all patients with AFE die within 1 hour after the onset of symptoms; in survivors, neurologic damage or brain death secondary to the initial severe hypoxia is not uncommon. Data from the National AFE Registry suggested an overall mortality rate of 61%; only one half of those who survive do so without significant neurologic sequelae. Women with AFE generally exhibit left ventricular dysfunction or failure accompanied by elevated PCWP and, in most cases, depressed left ventricular stroke work index. Systemic vascular resistance is decreased. Elevations of pulmonary artery pressure and pulmonary vascular resistance often are in the range attributable to left ventricular failure. The existence of an initial but transient phase of pulmonary hypertension and elevated right ventricular pressure is supported by some animal and clinical data. A component of noncardiogenic pulmonary edema (i.e., ARDS) often is present and may become the predominant clinical problem in survivors.

Signs or symptom	No. of patients	%
Hypotension	43	100
Fetal distress	30	100
Pulmonary edema or adult respiratory distress syndrome	28	93
Cardiopulmonary arrest	40	87
Cyanosis	38	83
Coagulopathy	38	83
Dyspnea	22	49
Seizure	22	48
Uterine atony	11	23
Bronchospasm	7	15
Transient hypertension	5	11
Cough	3	7
Headache	3	7
Chest pain	1	2

Source: From ref. 48.

TABLE 25.6. *Signs and symptoms noted in patients with amniotic fluid embolism*

A hemorrhagic phase is reported in at least 50% of patients with AFE. This problem commonly is compounded by the simultaneous occurrence of uterine atony, perhaps as a direct result of a myometrial depressant effect of amniotic fluid. Although AFE has been reported under many conditions, most cases have occurred during labor. In the past, a pattern of vigorous labor or hypertonic uterine contractions associated with oxytocin infusion had often been implicated in the pathogenesis of this condition. Evidence of this association was anecdotal and is clearly invalid. Placental abruption is present in up to 50% of cases, with fetal death reported in some cases before the acute clinical onset.

Early studies suggested that meconium or particulate matter in amniotic fluid is the pathologic agent, but more recent data suggest that a humoral substance, rather than particulate matter, is responsible for the observed hemodynamic changes. It is also clear the infusion of clear amniotic fluid, per se, is innocuous, both in the human and in animal models. Further, the marked similarities between the clinical manifestations of AFE and both septic and anaphylactic shock suggest the involvement of endogenous mediators in the pathophysiology of this condition. Thus term *amniotic fluid embolism* is a misnomer, because the syndrome is not caused by amniotic fluid per se, nor are clinical manifestations those commonly seen with embolic events. Rather, this is yet another example of the increasingly recognized systemic inflammatory response syndrome which characterizes other types of critical illness such as anaphylaxis and sepsis (Fig. 25.8).

FIG. 25.8. Proposed pathophysiologic relationship among amniotic fluid embolism, septic shock, and anaphylactic shock. Each syndrome may also have direct physiologic effects (e.g., fever in endotoxin-mediated sepsis).

Classically, the definitive diagnosis of AFE has been made at autopsy with the demonstration of fetal squamous cells, mucin, hair, or vernix in the pulmonary artery vasculature. More recently, it has been demonstrated that squamous cells and other debris of presumed fetal origin may be demonstrated in blood aspirated from the central venous or pulmonary artery circulation of living patients with AFE. Studies of pregnant women undergoing pulmonary artery catheterization for various medical

indications have suggested that the detection of squamous cells in the maternal pulmonary artery circulation is a common phenomenon that may, in part, be attributable to contamination with adult squamous epithelium from the site of central venous access. Further, such debris is detected in only 50% to 75% of patients with clinical AFE, even when examined with special stains and techniques. Thus, the detection of squamous cells in the maternal pulmonary artery circulation during life is neither sensitive nor specific for the diagnosis of AFE. Such a diagnosis must be made principally on the basis of clinical picture. The differential diagnosis of AFE includes septic shock, aspiration pneumonitis, acute myocardial infarction, pulmonary thromboembolism and, in cases in which coagulopathy is a dominant feature, placental abruption.

Treatment revolves around three goals: oxygenation, maintenance of cardiac output and blood pressure, and resolution of what usually is a self-limiting, albeit severe, coagulopathy. Hypotension usually is on the basis of cardiogenic shock; treatment involves initial optimization of cardiac preload by rapid crystalloid administration followed by pressor support, as necessary. Administer component therapy to treat bleeding secondary to DIC. Packed red blood cells and fresh frozen plasma are the mainstay of such therapy.

It is axiomatic in obstetrics that when maternal and fetal therapeutic interests are divergent, maternal considerations must be primary. Thus, in the presence of an unstable mother, delay in delivery is often necessary despite ongoing fetal asphyxia. On the other hand, once the mother has suffered frank cardiac arrest, maternal prognosis is sufficiently grave to warrant emergency cesarean delivery. Delivery of the fetus beyond 15 minutes from the time of maternal cardiac arrest generally results in newborn death or neurologic impairment.

In patients who survive AFE, recurrence during subsequent vaginal or cesarean delivery has not been reported.

SUMMARY POINTS

- Successful management of the critically ill gravida requires an understanding of both unique maternal physiology, as well as fetal response to critical illness.
- Prompt recognition and aggressive management of shock during pregnancy is essential for optimal maternal and fetal outcomes.
- Invasive hemodynamic monitoring rarely is indicated in the pregnant woman. However, principles learned from such techniques often assist the clinician in the management of critically ill patients without resorting to invasive procedures.

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Chapter 26

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Office Gynecology

PREVENTIVE HEALTH CARE
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The female population of the United States is estimated to grow by approximately 17% over the next 25 years. The over-40 female population will increase by approximately 27% between 2000 and 2020, with the 65- to 80-year-old female population increasing by 52%. Gynecologists have a major role in the provision of primary health care for women, with changes in health care technology, patient expectations, managed care, and health care delivery formats providing new challenges in the area of women's health.

Gynecologists provide more office-based general medical examinations to women 15 years and older than either family practitioners or internists, particularly in those ages 15 to 44. When fellows of the American College of Obstetricians and Gynecologists (ACOG) were queried as to whether they considered themselves primary care providers or specialists, 48.3% designated the former. Office visits to gynecologists and the number, percentage, and characteristics of patients who receive care exclusively from gynecologists are increasing. Thus, gynecologists represent an important resource for general medical examinations, the first step in the provision of health care services for women. However, gynecologists differ significantly from other primary care specialists with respect to the frequency of diagnostic and screening tests that they provide during general yearly examinations. Thus, the complexity and details of the gynecologic history and examination are of great importance in women's health care.

PREVENTIVE HEALTH CARE

Gynecologists spend the majority of their time in the office, and a significant proportion of their patient visits can be classified as preventive medicine visits. A great deal of health care is dependent on the principles of preventive medicine, such as population characteristics, risk profiles, epidemiology, and statistics as they pertain to screening programs. In reviewing the major points of a history and physical examination, gynecologists can address the components of preventive care based on patient demographics, cost, and risk factors. Annual examinations may be recorded on data sheets containing “check-off” lists for preventive services. An example of a form such as this is available at the ACOG Web site (Fig. 26.1). Reminder systems for follow-up visits for Papanicolaou tests (Pap smears) and mammograms can help to integrate disease prevention and health maintenance into gynecologic practice. In addition, gynecologists play a major role in screening for domestic violence, depression, injury, and other psychosocial concerns, as well as sexual dysfunction. Counseling practices for sexually transmitted diseases (STDs) and human immunodeficiency virus (HIV) infection has changed markedly over the past two decades. In addition, genetic testing is becoming an important part of gynecologic practice, including determination of risk for genetic diseases affecting women's reproductive and menopausal care. Rapid advances in genetics, particularly through screening for breast and ovarian cancer, ultimately will result in the assimilation of genetics into the routine gynecologic office practice. In addition, postmenopausal women have a variety of preventive health needs including breast and cervical cancer screening, and general medical needs such as cholesterol screening and smoking advice. Thus, gynecologists have an important role in making preventive recommendations and can make a significant difference in the delivery of women's health care. The beginning of this health care interaction begins with the gynecologic history and follows up with physical examination, along with office diagnostic procedures.

FIG. 26.1. Gynecologic intake history form (http://www.acog.com/).

PATIENT HISTORY

Women want to be actively involved in decisions regarding their gynecologic care and usually expect physicians to use the history to obtain information concerning, not only medical issues, but also concerns regarding family history, cancer risk, sexual partners, or significant personal and social issues. The quality of the medical care provided by a physician, as well as the type of the relationship between the physician and patient, may be determined largely by the depth of the gynecologic history.

New Patients

Time must be taken to obtain a comprehensive history and to perform a comprehensive physical examination for each new patient. It is important to establish a database on each patient, along with a physician–patient relationship based on good communication. Office scheduling should permit dedicated time for new patient bookings to allow sufficient time to obtain the information, perform an examination, provide the management plan, allow for health education, and complete the encounter. Many preprinted history and physical examination forms exist, some of which may be obtained at the ACOG Web site.

Some physicians prefer to use patient-directed history forms, others use an assistant or nurse, and still others prefer to take the history personally. Multiple studies documented that personally directed questioning is more productive than patient questionnaires. Understanding of the predictive health care needs for preventive medicine based on family history, patient history and lifestyle, integrated functional medical investigations, and treatments and development of personal preventive programs all impact the ongoing health and wellness relationship with the gynecologist.

Established Patients

A good database already has been recorded for an established patient, and updates should include any changes in gynecologic or pregnancy history. Additional surgery, accidents or hospitalizations, or new medications should be added. Any changes in family history should be noted. This type of history taking, both for new and established patients, results in a well-organized, problem-oriented medical record. Besides obtaining the historical details, it is important to understand why the patient is seeking care in the gynecologist's office. In addition to understanding and meeting patients' needs, physicians must be prepared to do a medical evaluation in a physically and emotionally comfortable setting, making the visit as comfortable and informative as possible so that women leave the office calm and with their questions answered. This is achieved by an understanding attitude and an ability to listen.

History Taking

Physicians can do several things to obtain a detailed history and reduce patients' anxiety with respect to history taking.

- The history should be obtained in as comfortable and private a setting as possible. Some patients prefer to be clothed and seated at the same level as the physician, especially if they are meeting for the first time. Other patients may choose to change into an examination robe before seeing the physician if the visit is for a follow-up examination. Under most circumstances, patients should be interviewed alone. Exceptions may be made for children, adolescents, and mentally impaired women or at the specific request to have an attendant or a family member present. Even in these situations, it is usually a good idea to give patients the opportunity of speaking privately.
- The initial portion of the interview should be designed to put patients at ease. This often can be accomplished by discussing neutral and nonmedical subjects, such as recent recreational activities, employment, and family. The discussion should be viewed, not merely as a means of relaxing patients, but also as an opportunity for gathering information about their psychological and social backgrounds.
- Physicians should not make assumptions about patients' backgrounds. For example, a clinician usually assumes that all adult female patients are sexually active and heterosexual. Either assumption or both may be incorrect. By asking neutral, open-ended questions (e.g., “Are you sexually active?” and “Are you having sex with men?”), physicians let patients know that these assumptions have not been made.
- An appropriate length of time should be scheduled to allow a patient to tell her story without being hurried or interrupted. Interruptions from phone calls or office staff should be avoided, if at all possible, so that the patients has the physician's undivided attention.
- Patients should be made to feel that they have the respect of the physician. This means that they will have the opportunity of sharing in the decision-making process, will not be forced to endure unwanted pain, will have what they tell the physician held in strict confidence, and are free to ask questions.

In addition to these aspects of the patient–clinician interaction, patient satisfaction is related to the time required to get an appointment, the patient mix in the reception area, the length of waiting time in the reception or examination room, the attitude of the office staff, and the billing procedures.

EFFECTIVE COMMUNICATION

In this age of rapidly expanding medical knowledge, the development of simpler, safer, and more effective techniques of diagnosis and treatment, and an emerging emphasis on preventive health care, it is ironic that there is widespread dissatisfaction in physician–patient relationships. There is increasing evidence that a physician's attitude influences not only patient compliance but also the ultimate effect of therapy. These factors suggest that clinicians must understand the techniques of effective communication.

The first step in effective communication is establishing a good relationship with the patient. Research in human relations has demonstrated that a rapport is most readily established if physicians possess and display certain qualities, including empathy, respect, nonpossessive warmth, genuineness, nonjudgmental acceptance, kindness, and interest. These qualities are common to all effective counselors and can be learned by most clinicians.

Merely possessing the qualities described is not enough; physicians must be able to communicate them to patients through both verbal and nonverbal messages. Physicians convey empathy and respect by listening intently and giving undivided attention. They reinforce these qualities by summarizing their understanding of patients' problems in terms patients can understand.

The communication of warmth, kindness, and interest is, for the most part, nonverbal. Examples of nonverbal communication that convey these qualities include the following measures:

- Maintaining eye contact
- Having a relaxed, open posture
- Facing the patient
- Leaning toward the patient
- Showing a facial expression consistent with the patient's predominant emotion
- Having a modulated, nonmechanical tone of voice

However, forced or excessive expressions of warmth during the early stages of the patient–clinician relationship may be counterproductive and inappropriate.

Once a physician has developed the qualities described and has learned to express them, he or she must put them together to become an effective counselor. The steps involved in doing this are as follows:

- Listening effectively
- Creating a nonthreatening atmosphere in which the patient feels free to express herself
- Creating a relationship based on mutual trust and caring
- Responding to the patient in verbal and nonverbal ways that convey empathy, respect, and warmth by reflecting accurately and fully the patient's feelings, communicating acceptance of the patient as a person, and showing attentiveness and caring through nonverbal behavior
- Defining and agreeing with the patient about the exact role of the physician in the counseling situation

TAKING THE HISTORY

Overview

The history provides information about the total patient and is perhaps the most important part of the gynecologic evaluation. It enables patients to become acquainted with their physicians in a nonthreatening situation. In most cases, it provides the data to establish a tentative diagnosis before the physical examination. In many respects, physicians taking a history are like detectives who keep the various clues that are pertinent and discard those that are deliberately or inadvertently misleading. If the gynecologic history is sufficiently comprehensive, it should in almost all cases permit a physician to narrow the likely possibilities to one or at most two probable diagnoses. The preliminary opinion may not always be correct, but the history-taking session should not end until a tentative diagnosis has been made.

Like a hospital chart, the office chart is a legal, as well as a medical, record. As such, it is subject to subpoena, and whatever is recorded in it may someday need to be defended in court. It should not contain extraneous or casually written material, and the notes should be sufficiently complete that the case can be reconstructed readily.

The gynecologic history should include the following information:

I. Chief complaint
   A. Primary problem
   B. Duration
   C. Severity
   D. Precipitating factors
   E. Occurrence in relation to other events (e.g., menstrual cycle, coital activity, gastrointestinal activity, voiding, other pertinent functions)
   F. History of similar symptom
   G. Outcome of previous therapies
   H. Impact on the patient's quality of life, self-image, relationship with family, and daily activities
   I. Role of other stresses in the chief complaint
II. Menstrual history
   A. Age at menarche
   B. Date of onset of last menstrual period
   C. Timing of menstrual periods
   D. Duration and quantity (i.e., number of pads used per day) of flow
   E. Degree of discomfort
   F. Premenstrual symptoms
   G. Contraception (i.e., current and past methods)
III. Obstetric history
   A. Number of pregnancies
   B. Number of living children
   C. Number of abortions, spontaneous or induced
   D. History of previous pregnancies (i.e., duration of pregnancy, antepartum complications, duration of labor, type of delivery, anesthesia used, intrapartum complications, postpartum complications, hospital, physician)
   E. Perinatal status of fetuses (i.e., birth weights, early growth and development of children, including feeding habits, growth, overall well-being, current status)
   F. History of infertility (evaluation, diagnosis, treatment, outcome)
IV. Medical history
   A. Allergies
   B. Medications currently used
   C. Past and current medical problems
   D. Hospitalizations (reason, date, outcome)
   E. Vaccinations (type, date)
V. Surgical history
   A. Operative procedures (i.e., outcome, complications)
VI. Review of systems
   A. Pulmonary
   B. Cardiovascular
   C. Gastrointestinal
   D. Urinary
   E. Vascular
   F. Neurologic
   G. Endocrinologic
   H. Immunologic
VII. Breast symptoms
   A. Masses
   B. Galactorrhea
   C. Pain
   D. Family history
VIII. Social history
   A. Exercise
   B. Dietary habits (including calcium or folate supplementation)
   C. Drug use
   D. Alcohol use
   E. Smoking habits
   F. Marital status
   G. Number of years married
   H. Sexual history (partners, contraception, protection from STDs)
   I. Occupational history (i.e., exposure to environmental toxins, ionizing radiation, infectious agents)
   J. Emotional, physical, or sexual abuse
IX. Family history
   A. Significant medical and surgical disorders in family members

Chief Complaint

It is often effective to begin the history with an open-ended question concerning the symptoms that patients may have. This gives them the opportunity to describe their symptoms and concerns in their own words. Less information will be obtained if the interviewer asks only focused, closed-ended questions to which patients can answer only yes or no. Some clinicians find it helpful to have an outline of questions about the gynecologic history to obtain all the necessary information.

The following questions are typical of a gynecologic history:

- What were the circumstances at the time the problem began (i.e., time, place, activity, cycles)?

- What has been the sequence of events? (Having a calendar to refer to is often helpful.)
- Have you had this problem before? Can you describe the previous occurrence and what led to its disappearance?
- To what extent is the problem interfering with your daily life and the life of your family?
- Have you had previous evaluations or treatments? (Records from previous physicians may be helpful.)
- Why did you seek evaluation for the problem now?
- What questions do you want answered today? What do you expect and want from today's visit?

Menstrual History

The cycle interval is counted from the first day of menstrual flow of one cycle to the first day of menstrual flow of the next cycle. The range of normal is wide, and a recent change in the usual pattern may be a more reliable sign of a problem than the absolute interval. Although 28-day cycles are the median, only a small percentage of women have cycles of that length. The normal range for ovulatory cycles is between 21 and 35 days.

Estimating the amount of menstrual flow by history is difficult. The average blood loss is 30 milliliters (range, 10-80 ml). The need to frequently change saturated tampons or pads (i.e., more often than one per hour for 6 or more hours) and the passage of many or large blood clots are usually signs of excessive blood flow.

Dysmenorrhea is common. It usually begins just before or soon after the onset of bleeding and subsides by day 2 or 3 of flow. The discomfort is characteristically midline and often is associated with backache and, in primary dysmenorrhea, with systemic symptoms such as lightheadedness, diarrhea, nausea, and headache. Mittelschmerz, or midcycle unilateral pelvic pain at the time of ovulation, is usually mild and seldom lasts for more than 1 or 2 days.

It is important to ask whether or not there is bleeding between menstrual periods and whether this occurs after coitus. Intermenstrual bleeding is a characteristic sign of cervical cancer, although it also is present with benign lesions such as cervical polyps and fibroids or infection.

Finally, physicians should inquire about the presence of premenstrual syndrome (PMS). The symptoms experienced by women with PMS may be physical, emotional, and behavioral. The most common of the physical symptoms are fatigue, headache, abdominal bloating, breast tenderness and swelling, acne, joint pain, constipation, and recurring herpetic or yeast infections. Although these physical symptoms are often uncomfortable, most women with moderate to severe PMS complain most about their premenstrual emotional symptoms, especially depression, anxiety, hostility, irritability, rapid mood changes, altered libido, and sensitivity to rejection. Women with PMS may also experience changes in behavior, including physical or verbal abuse of others, suicide attempts, withdrawal, craving for or intolerance of alcohol, craving for sugar or chocolate, and binge eating.

Many women report that long-standing or severe PMS can cause psychological or social problems that may be as disruptive as the premenstrual symptoms themselves. Psychological reactions to PMS include guilt, shame, decreased self-esteem, unassertiveness, decreased self-confidence, a negative body image, and a sense of hopelessness. In addition, many women with long-standing PMS report that their recurrent emotional and behavioral symptoms have eroded their relationships with co-workers, friends, husbands, and children. Finally, PMS has been an unrecognized factor in poor work records or failed educational pursuits for many women.

Sexual History

Although there are many models for sexual histories, most are not appropriate for the non-sex therapist or in the setting of a brief office visit. A model for office practice has been developed, with two types of sexual histories: a screening history and a problem-oriented history. The screening history is brief and suited for inclusion in the comprehensive medical history that typically is part of a patient's first visit to her gynecologist. The problem-oriented history is more detailed and designed to investigate problems identified by the screening history.

The screening history is designed to determine whether or not major sexual difficulties exist that need in-depth evaluation and therapy, and whether the problem can be dealt with by the physician or should be referred elsewhere for more intensive evaluation. In an attempt to put patients at ease, physicians can begin the sexual history by prefacing questions with statements such as “Most people experience….” or “Because sexual problems can develop as part of other gynecologic problems….” If physicians can convey a willingness to help, patients are more likely to discuss problems. In addition, the screening history should begin with a discussion of topics that are unlikely to provoke anxiety. For example, questions about the occurrence of pain during intercourse are less likely to cause anxiety than questions about orgasmic function or noncoital sexual practices.

With these principles in mind, physicians can begin with a general question, such as “Are you having any sexual problems?” If the response is noncommittal, a more specific question, for example, “Are you satisfied with the frequency of sexual relations?” can be posed. Once a problem is identified, physicians can proceed to the problem-oriented sexual history and ask about the date of onset, severity, previous evaluation and treatment, the results of such treatment, conditions that diminish or exacerbate the problem, the patient's response to the problem, and the effect of the problem on the patient's relationship with her partner. To conclude the screening history, physicians should invite patients to discuss concerns that have not been covered by the screening history. Even if a patient denies having any problems, the screening history is of value because it demonstrates the physician's willingness to discuss sexual problems.

As suggested, the problem-oriented history is designed to differentiate organic from psychogenic sexual problems, determine the complexity of the problem, determine the need for referral of the patient to a more sophisticated sexual counselor, and provide information for the formulation of a treatment program if the physician elects to treat the patient. The problem-oriented sexual history should include the following topics:

- Onset of the sexual problem
- Course of the sexual problem
- Conditions that decrease or increase the severity of the sexual problem
- Previous evaluation of the sexual problem and the results of such evaluation
- Previous treatment of the sexual problem and the results of such treatment
- Severity of the sexual problem
- Patient's reaction to the sexual problem
- Impact of the problem on the patient's sexual relationship
- Patient's sexual attitudes and upbringing
- Patient's sexual practices
- Quality of patient's sexual or marital relationship

A rational treatment or referral plan can be formulated on the basis of discussion of these and related questions.

In addition to screening for sexual dysfunction, it is important to obtain a history of STDs. Physicians should tactfully question patients about past episodes of STDs, sexual practices, number of sexual partners, sociosexual background of sexual partners, use of barrier forms of contraception, use of intravenous drugs, previous blood transfusions, genital lesions, persistent vaginal discharge, and pelvic pain. The discussion of STDs provides an opportunity to discuss modes of prevention, including the practice of safe sex and the use of barrier methods of contraception when the sexual history of a partner is unknown.

Psychosocial History

Health care providers can play a vital role in identifying women who are victims of psychological, physical, or sexual abuse. Unfortunately, women who are abused are often hesitant to acknowledge it. Questions should include the following:

- Are you or have you ever been in a relationship in which you have been physically hurt or threatened by a partner?
- Have you ever been forced to have sex against your will?
- Has your partner ever destroyed things you care about?
- Are you or have you ever been in a relationship in which you were treated badly?

If the answer to any of these questions is yes, the physical examination may reveal signs of physical abuse. In addition, many abused women may report chronic pain, sleep or appetite disorders, and frequent vaginal and urinary infections. One may suspect an abusive relationship if the patient's partner is present at every office visit, insists on staying close to the patient, and answers all the questions directed to her.

Once abuse is recognized, the physician must acknowledge the problem and direct the woman to an appropriate community resource. Inquiry about the woman's safety should be made before she leaves the office. Some physicians obtain wallet-sized cards or brochures from local agencies that provide support and protection for

battered women, and place them in the rest rooms. This provides an option for those women who would not acknowledge abuse when asked by their health care providers.

Depression is another very common condition that may be detected during an annual gynecologic examination. The potential life-threatening nature of depression and the availability of effective antidepressant medications with few side effects make it even more important to diagnose depression. To diagnose depression, physicians can ask the following questions:

- Have you lost interest in the things you used to enjoy?
- Do you feel sad, “blue,” or “down in the dumps”?
- Do you have feelings of guilt or worthlessness?
- Do you have thoughts of death or suicide?
- Are you sleeping too much, or do you have difficulty falling asleep or staying asleep?
- Do you have a loss of energy and feel tired all the time?

An affirmative answer to one or more of these questions may mean the patient is depressed and a candidate for psychotherapy or drug therapy. More than 50% of depressed individuals will respond to antidepressant therapy.

Adolescent History

As the percentage of adolescents increases in practice, gynecologists find themselves dealing with problems unique to the 13- to 19-year-old age group. These include menstrual and breast disorders, pubertal development problems, and the challenges presented by sexually active adolescents. Almost 50% of high school students, male and female, had sexual intercourse and only 57% reported that they had used contraception the last time they had intercourse. The frequency of adolescent sexual activity and its consequences mean that gynecologists caring for adolescents will certainly encounter gynecologic problems such as STDs and pregnancy among their young patients. Gynecologists who provide such care to adolescents, particularly with respect to history taking, need to know their specific needs, with particular importance placed on confidentiality. The gynecologist must be prepared to handle multiple issues related to pubertal development, sexuality, self-esteem, and body image, and approach the adolescent patient in a somewhat different manner than that used for the adult female. This includes having the parent present with young women, 14 years of age or less, during history taking, and speaking to the adolescent first in the office setting when she is fully clothed. If the adolescent refuses to have the parent or mother present, the physician may ask the young woman's permission to speak to her mother or guardian with respect to important issues, especially those requiring treatment.

GYNECOLOGIC EXAMINATION

The pelvic examination is one of the most commonly performed medical procedures and is often considered aversive by women. Aspects of the pelvic examination, such as genital exposure, make it highly likely women will have feelings of anxiety, vulnerability, apprehension, or fear. It is important that the gynecologist observe a woman's behavior, which will communicate her feelings. Behavioral indications of patient anxiety are important, not only because anxiety can hinder communication, but because anxiety can lead to delays in performance of potentially lifesaving pelvic examinations and other preventive screening measures. A complete physical examination is most commonly performed at the first visit. In order to reduce anxiety, patients should be encouraged to give feedback to the physician during the examination, especially when the examination causes pain. Description of the examination, including which portions may include mild to moderate discomfort (such as the rectal examination), should be given to the patient beforehand. When the physician enters the room, the patient should be sitting up on the examination table with the examination gown completely covering her. During the physical examination another female participant, either nurse or medical assistant, must be present. This woman can assist the physician and also lend psychological support to the patient. The patient should be asked to lie down and place her feet in the stirrups, and the physician should be at the level of the patient's head, speaking to her when her position is changed. This dialog may include the physician asking the patient about her symptoms, location of any pain, or other pertinent questions. Studies evaluating anxiety in women with respect to pelvic examinations have found those who have had a less positive first experience have higher anxiety levels with their gynecologists. Patients also come in with other worries about baring themselves, body odor, and personal concerns which should not be unrecognized by the physician. Noting that these behaviors may take place, gynecologists can take necessary measures to reduce patient anxiety and prevent delays and avoidance of gynecologic examinations in the future.

Evaluation of General Appearance

A general impression should be recorded of patients' nutritional state, distribution and proportion of body fat, texture and condition of skin and hair, presence of facial or excessive body hair, acne, abnormal nevi (greater than 5 millimeters, asymmetric outline, variable pigmentation, and indistinct borders), and any specific physical features.

Examination of the Head and Neck

The patient's hair is examined for cleanliness, texture, and scalp health. The eye examination may include ophthalmoscopy to detect retinal aberrations. The patient's nose, throat, and teeth can also be checked. Finally, the anterior cervical, posterior cervical, and supraclavicular nodes, as well as the thyroid gland, should be palpated.

Examination of the Cardiopulmonary System

Hypertension is the most common chronic disease in women over 50. Therefore, every woman, especially those over 50, should have her blood pressure measured with her annual gynecologic examination.

Careful cardiac auscultation may be performed as part of the gynecologic examination, because many patients eventually undergo surgery or childbirth. Mitral valve prolapse (MVP), the most common cardiac condition diagnosed by auscultation in asymptomatic women, can be problematic during surgery or pregnancy. A prolapsing mitral valve is more common in young women than in men. In most cases, it is not associated with other cardiac defects and consists of a large valve with redundant leaves. Although most women with MVP are asymptomatic, others may experience anxiety, chest pain, palpitations, bacterial endocarditis or, rarely, sudden death.

Diagnosis of MVP is made by auscultation of a midsystolic nonejection click and a late systolic murmur. Because alterations in venous return influence the auscultatory findings, they may change in nature from examination to examination and may even disappear, only to reappear at a later examination. The diagnosis of MVP, which can be confirmed by 2-dimensional echocardiography, is important because of its association with bacterial endocarditis, von Willebrand disease, autoimmune connective tissue disorders, and hyperthyroidism. Women in whom this diagnosis has been made probably should have antibiotic prophylaxis at the time of delivery or during invasive diagnostic and surgical procedures. In addition, they may require antiarrhythmic or even anticoagulant therapy and should be followed or evaluated for the systemic conditions noted.

Breast Care

Examination of the Breasts The breast examination begins with a breast-oriented history. Patients are asked whether they have noted any lumps, pain, discharge, or other changes in their breasts. They should also be asked about breast surgery, date and results of the last mammogram, current and past hormone use, and family history of breast cancer. Axillary and supraclavicular nodes are then palpated. The breasts should be examined with patients both sitting or standing and lying supine. In the vertical position, the nipples and inframammary folds are evaluated for asymmetry. The examiner looks for elevation of one nipple, flattening of one breast, dimpling of the skin, or asymmetry by having patients raise both arms above the head and lean forward, and then contract the pectoral muscles with hands on hips. Then, with patients in the supine position with one arm above the head, all quadrants of each breast are felt with the flat part of the distal phalanges of the fingers. The subareolar area should also be palpated, because 15% of carcinomas occur under the areola. The axillary and supraclavicular areas should be palpated for enlarged or tender lymph nodes. The nipples and adjacent areolar tissue are then compressed in an effort to express fluid from the nipple. The examination of the breasts should conclude with a description of the examination results and a recommendation for follow-up physical or radiologic examinations.
Mammographic Examinations Gynecologists as primary care physicians have the responsibility for implementing widespread screening mammography. A diagnostic approach to the breast, including clinical breast examination, possible fine-needle aspiration, and mammography, may be implemented by the gynecologist and performed with findings of a breast mass or suspicious area. Ongoing discussion has addressed the value of screening mammography with respect to breast cancer mortality. A study reported that there was no reliable evidence that screening for breast cancer reduces mortality. A follow-up study from the same investigators showed that breast cancer mortality may be a misleading outcome measure and that screening may lead to more aggressive treatment. Additional studies have noted that mammograms can be lifesaving and that recommendations for gynecologists based on all available information are to urge all women to follow the advice of their physicians and obtain mammograms per guidelines.

Examination of the Chest

From the back, a curvature of the vertebral column can be assessed by observation and palpation. The chest can also be percussed and auscultated.

Examination of the Abdomen

Patients should be positioned supine, with arms against the body to relax the abdominal musculature. If necessary to obtain adequate relaxation, the knees can be elevated and flexed. In a methodical and consistent manner, all quadrants of the abdomen should be examined. Relaxation of the abdomen to evaluate a suspected mass can be assisted by having patients breathe deeply and then exhale. After all quadrants have been examined, the inguinal nodes should be palpated. Asking about abdominal scars may provide information that was not elicited during the history.

Bulging of the flanks suggests free abdominal fluid, but thin-walled ovarian cysts and irregularly shaped uterine leiomyomata may have a similar clinical picture. Although large ovarian cysts and leiomyomata most commonly cause protrusion of the anterior abdominal wall, there are many confusing exceptions. Palpation for a fluid wave through the lateral quadrants of the abdomen is also a useful procedure. Percussion for areas of flatness or tympany and for shifting dullness may aid in determining whether the distension is caused by intraperitoneal fluid or by intestinal gas. Auscultation is especially useful in differentiating among a large tumor, a distended bowel, or an advanced pregnancy as the cause of abdominal enlargement.

Examination of the Extremities

Examination of the lower extremities supplies important information regarding the cardiovascular system. Edema and varicosities should be noted. In a patient with congenital absence of the vagina, evidence of muscle atrophy in the extremities should be sought, because such patients may have nerve root compression secondary to congenital vertebral anomalies. The peripheral pulses and reflexes may also be evaluated at this time. Examination of the calves and ankles for melanomas or dysplastic nevi is advisable.

Pelvic Examination

The first examination of the female genitourinary system often takes place in the neonatal period. An examination is indicated at any age when abnormal bleeding or pelvic symptoms are present, there are questions about primary or secondary sexual development, or sexual activity is being initiated. For teenagers, the first pelvic examination should probably occur at 18 years of age or at the initiation of sexual activity, whichever comes first. Examinations usually are repeated at yearly intervals, at which time a Pap smear should be performed in addition to a pelvic examination and a screening for breast cancer and hypertension.

The pelvic examination provides physicians with an opportunity to dispel myths and misunderstandings and to educate with respect to pelvic anatomy, physical development, and sexual function. Patients often are reassured if the physician carries on a running dialogue, describing the findings, asking and answering questions, and demonstrating on occasion the physical findings with the aid of a hand-held mirror. To maximize the educational aspects of an examination, clinicians can (a) describe all procedures in advance, (b) maintain eye contact with patients during the examination, whenever possible, and (c) explain all findings clearly.

Patient Preparation The pelvic examination is performed with the patient lying on her back with both knees flexed. The buttocks are positioned at the edge of the examining table, and the feet are supported by stirrups. This position allows the necessary exposure of the pelvic organs. Traditionally, patients have been placed with the head and body in a horizontal position. This position does not allow maintaining eye contact and increases a patient's sense of vulnerability. The alternative, assuming the availability of an adjustable examination table, is to elevate the head of the table between 30 and 90 degrees. There are no apparent technical disadvantages to this alternative position, and many patients find it easier to relax, actually making the bimanual part of the examination more accurate. The patient should empty her bladder just before the examination.
Equipment The minimal equipment needed to perform a pelvic examination includes a good light source, a speculum of the correct size, a nonsterile glove, and a water-soluble lubricant. Additional supplies that should be available in the examination room include a variety of speculum sizes, materials to obtain cytologic samples, including fixative, various culture media, large cotton-tipped swabs, pH indicator paper, and a screening test for fecal occult blood. Specialized examinations require other specific equipment.
External Genitalia Examination The pelvic examination begins with inspection of the vulva. Physicians should note and record evidence of developmental abnormalities, as well as the general state of cleanliness, discharge, hair growth and distribution, and abnormalities of the skin, including tumors, ulcerations, scratch marks, rashes, and minor lacerations or bruises. Vulvar varicosities or hemorrhoids should be noted, also. A careful inspection of the skin folds, vulva, and pubic hair may reveal occult disease or infection. The vulva should be palpated for subcutaneous lesions. The labia are then spread, and the condition of the hymen and vulvovaginal skin and the size of the clitoris are noted. The examination should be performed in a systematic manner and include the labia majora, labia minora, vestibule, urethral opening, periurethral glands, Bartholin glands, perineum, anus, and perianal areas. With an index finger in the outer vagina and the thumb on the perineum, the labia and urethra are palpated for masses or tenderness. Patients are asked to contract the muscles of the vaginal opening to assess the tone of the levator muscles and the degree of perineal support, and then to strain to reveal the presence of a urethrocele, cystocele, rectocele, enterocele, or vaginal or cervical prolapse.
Vaginal Examination The vagina should first be inspected with the aid of a speculum. Specula come in various sizes, and an appropriate size should be selected. The largest size that is comfortable often provides the best visualization. Painless insertion of the speculum may be aided by several techniques. First, the muscles at the opening of the vagina may be relaxed by gentle downward pressure with one or two fingers. The speculum may be moistened with warm water before insertion, but other types of lubricants should be avoided if cultures or cytologic samples are to be collected. The speculum blades should be inserted obliquely, not vertically, through the introitus, immediately rotated to the horizontal plane, and then slowly opened after the vaginal apex is reached. The vaginal walls and cervix should be inspected for lesions. The vaginal discharge should be assessed for volume, color, consistency, and odor. The endocervical mucus should also be examined. Samples for cervical or vaginal cytologic examination and cultures, and direct microscopic examination of the vaginal or cervical discharge should be obtained as indicated. Before the speculum is removed, the cervix should be evaluated for ectropion, erosion, infection, discharge, lacerations, polyps, ulcerations, and tumors. As the speculum is removed, with the patient bearing down, the degree of vaginal wall relaxation and uterine prolapse can be assessed. With the speculum removed and the patient still bearing down, one can observe whether or not the patient exhibits stress incontinence.

Bimanual Examination

The technique for the bimanual examination is shown in Figure 26.2, Figure 26.3, Figure 26.4, Figure 26.5 and Figure 26.6. After the speculum has been withdrawn, the physician should gently insert the index and middle fingers along the posterior wall of the vagina. At the same time, the other hand is placed on the patient's abdomen in the midline. The first palpable structure is the cervix. Next is the uterine fundus. The bimanual technique can outline its position, size, shape, consistency, and degree of mobility. Uterine or cervical mobility can be assessed further by placing the fingers on one side of the uterus and moving them to the contralateral side. This can be done on both right and left sides to detect chronic or acute inflammatory changes and fixation. The other hand is then placed on one lower quadrant of the abdomen and slowly worked inferiorly and medially to meet the fingers of the hand examining the vagina. In this way, adnexal structures on that side can be appreciated. The degree of adherence of an adnexal structure to the uterus often can be ascertained. Enlargement, consistency, and position of ovaries and tubes can be noted. The ovary is a sensitive structure, and patients differ in tolerance to palpation. The contralateral side should be examined similarly. Finally, the vaginal walls and adjacent structures (bladder and rectum) are palpated. The glove of the hand used for vaginal examination is then replaced with a clean glove for the rectovaginal or rectal examination.

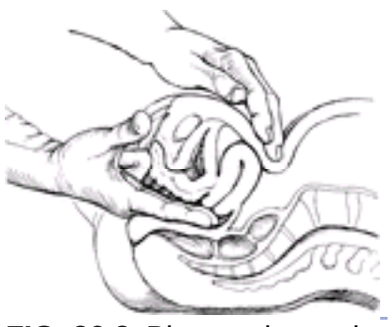

FIG. 26.2. Bimanual examination, first step. The fingers placed in the vagina feel the consistency and symmetry of the cervix and its axis in relation to the axis of the vagina. They then elevate the uterus toward the abdominal wall, so the total length of the uterus can be determined. (From Duncan AS. In: Bourne A, ed. *British gynaecological practice.* Philadelphia: FA Davis Co, 1955; drawn by G. McHugh, with permission.)

FIG. 26.3. Bimanual examination, second step. The fingers examining the vagina are moved into the anterior fornix to permit palpation of the uterine corpus. If the abdominal wall is thin and well relaxed, it is possible to define even minor irregularities in the contour or consistency of the uterus. Third step: with the fingers still in the anterior fornix and with the aid of the hand palpating the abdomen, the uterus is moved gently toward a retroverted position and then from side to side to determine its mobility and the presence or absence of pain on movement of the uterus. (From Duncan AS. In: Bourne A, ed. *British gynaecological practice.* Philadelphia: FA Davis Co, 1955; drawn by G. McHugh, with permission.)

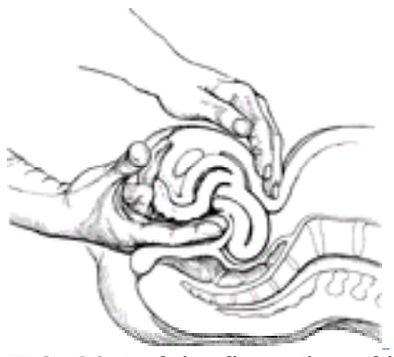

FIG. 26.4. If the fingertips of both hands come together when carrying out the second step of the bimanual examination, it can be concluded that the uterus is retroverted; the fingers in the vagina are then moved to the posterior fornix to outline symmetry, consistency, and mobility of the retroverted corpus. (From Duncan AS. In: Bourne A, ed. *British gynaecological practice.* Philadelphia: FA Davis Co, 1955; drawn by G. McHugh, with permission.)

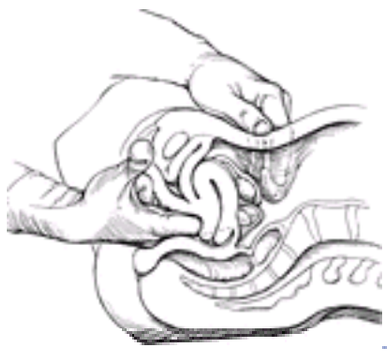

FIG. 26.5. Bimanual examination, fourth step. To outline the adnexa, the fingers examining the vagina are moved to the right fornix, and the examiner attempts to bring the fingers of both hands together at a point presumed to be superior to the fallopian tube and ovary. (From Duncan AS In: Bourne A, ed. *British gynaecological practice.* Philadelphia: FA Davis Co, 1955; drawn by G. McHugh, with permission.)

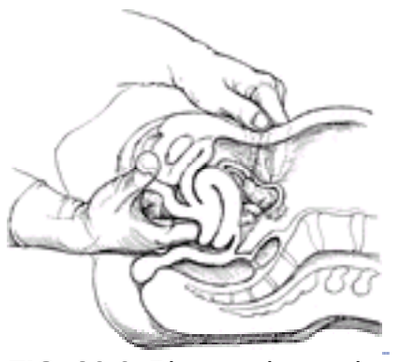

FIG. 26.6. Bimanual examination, fifth step. When the fingers of both hands are quite close together (it is desirable but not always possible to approximate these fingers), they are then moved gently toward the examiner, so the adnexa slip between the fingers as they can be outlined. (From Duncan AS. In: Bourne A, ed. *British gynaecological practice.* Philadelphia: FA Davis Co, 1955; drawn by G. McHugh, with permission.)

Rectovaginal Examination The rectal examination is uncomfortable, but it can be made less so if the physician gently places a finger into the anal opening and waits for the anal sphincter to relax before proceeding. The middle finger is inserted into the rectum and the index finger into the vagina. The tone and symmetry of the sphincter are determined. The parametrial tissue is then palpated between the index finger in the vagina and the middle finger in the rectum. Finally, the posterior uterine surface, adnexal areas, uterosacral ligaments, and pouch of Douglas, along with the anorectal area, are palpated. The rectovaginal examination enhances the evaluation of cul-de-sac or ovarian pathology. Particles of hard fecal material may interfere with an accurate examination.
Rectal Examination Additional information may be gathered from a separate rectal examination. Exerting pressure against the perineum allows introduction of the index finger. Hemorrhoids, polyps, and tumors of the rectum may be felt. The rectal examination can be assisted by placing one hand on the lower abdomen to make it a bimanual procedure. This examination is useful when a vaginal examination is impossible, such as in infants and children. The rectal wall is palpated throughout its circumference and as far as the finger permits. Almost one half of all rectosigmoid cancers can be detected by this palpation. The finger can also explore the surface of each pelvic wall, feeling for enlarged nodes or other abnormalities. Any fecal material can be tested for occult blood. Following the rectal examination, the patient is instructed to slide up on the table while the lower one third of the table is replaced. The examiner can answer any questions about the examination and then step out of the room while the patient dresses. Physicians should always wash their hands after examining a patient.
Recording the Findings Physical examination can be recorded on a preprinted form and should include at least the following elements:

I. Perineum
   A. Old lacerations
   B. Lacerations
II. External genitalia
   A. Stage of development
   B. Color
   C. Evidence of lesions
   D. Bartholin glands
III. Vestibule
   A. Skene glands
   B. Urethral orifice
   C. Hymenal ring
IV. Vagina
   A. Presence of leukorrhea

B. Color
C. Lesions
D. Tone
E. Rugae

V. Cervix
A. Shape
B. Consistency
C. Mobility
D. State of parity
E. Lesions

VI. Uterus
A. Position
B. Mobility
C. Size
D. Shape
E. Consistency

VII. Adnexa
A. Position and mobility of ovaries and tubes
B. Presence of masses or tenderness

VIII. Rectovaginal examination
A. Degree of confirmation of previous findings
B. Statement about additional pathology

IX. Rectal examination
A. Occult blood

Postexamination Discussion

Back in the consultation room, the findings, diagnoses, and plans for therapy are explained to the patient in terms she can understand. It may be helpful to have the patient paraphrase the information to make certain that she understands. This is especially relevant when surgery is contemplated, because the nuances of an operation and its results may be unclear to patients. At this time, the use of medications and the duration of their use are explained. The physician should explain carefully what the patient may expect if any special diagnostic or therapeutic procedures were performed (e.g., heavy leukorrhea after cryosurgery, bleeding after cervical biopsy). In some situations, patients may be instructed to abstain from sexual activity for a specific length of time. The importance of a follow-up examination should be stressed. Prescriptions for medications should be detailed adequately and restrictions on refills stated explicitly.

DIAGNOSTIC PROCEDURES

Pap Smear

The early diagnosis of cervical carcinoma is based on periodic cytologic screening of the cervix. Despite extensive debates regarding the optimal frequency and accuracy of the Pap smear, it has become the standard method of screening for cervical carcinoma. In addition to detecting early cervical cancer, the Pap smear also can be used to assess hormonal status and to assist in identifying sexually transmitted pathogens, such as herpes simplex, human papillomavirus (HPV), *Chlamydia trachomatis*, and *Trichomonas vaginalis*, as well as benign conditions. The presence of cancer of the cervix may indicate infection with HIV.

Pap smears should be obtained at periodic intervals in women when they reach the age of 18 or become sexually active, whichever comes first. They probably should be obtained yearly, especially in women who have had coitus with more than one sexual partner, began to have coitus as an adolescent, or have a history of an STD. A Pap smear should be performed annually in women who have had a hysterectomy for pelvic cancer or *in situ* disease, although it may not be necessary in women who have had a hysterectomy for benign disease.

To visualize the cervix, the largest speculum that is comfortable to the patient is used. The speculum is warmed and lubricated with warm water. The cervix is visualized, and a plastic or wooden spatula is used to scrape the squamocolumnar junction and any areas on the cervix or vagina that look suspicious (Fig. 26.7). In premenopausal women, the squamocolumnar junction is likely to be within the endocervical canal. The spatula is wiped on a clean glass slide, and the slide is sprayed immediately with a fixative (i.e., alcohol and ether) before the cells dry. A second specimen is taken from the endocervix with a cotton-tipped applicator or cytobrush that is placed into the endocervical canal and rotated 360 degrees 3 to 5 times. The cytobrush is more effective than a cotton swab in obtaining endocervical cells. The cells are then transferred to the slide, and the slide is again sprayed with fixative. The slide, previously labeled to identify its source, is then sent for cytologic evaluation.

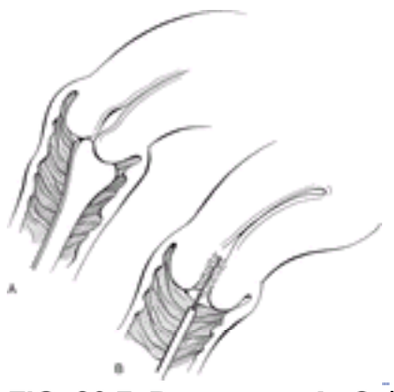

FIG. 26.7. Pap smear. **A:** Cells obtained from transformation zone using an Ayers spatula. **B:** Cells obtained from the cervix using a cytobrush.

Some well-publicized failures of Pap smears to detect cervical cancer led to an increased interest in technologic enhancements and automated assisted devices to reduce the rate of false-negative smear results. Studies evaluating automated preparation systems versus conventional cervical cytologic preparation have shown excellent cellular presentation and superior sensitivity for automated systems compared with conventional techniques. However, it is important to select carefully the laboratory used for processing, analyzing, and interpreting the specimens.

Thin-layer cytology for Pap smears has become widely accepted during the last decade, addressing some of the imperfections with traditional Pap smear screening. In traditional Pap smear screening there is a 5% to 10% false-negative result rate. Yearly testing decreases the possibility of a false-negative result for any particular woman. The thin-layer cytology, or “thin prep,” appears to decrease the false-negative rate by picking up more potentially precancerous changes. However, it is unclear as to whether decrease in false-negative rate translates to a reduction in the cervical cancer death rate.

With respect to office practice, thin-layer cytologic preparation is made by submerging the sample in a vial of liquid fixative and mixing the cells in the solution. This avoids difficulties with the fixative, piled up cells, and air drying common to smears on glass. The thin prep also appears to decrease the false-positive rate from inflammatory conditions. The atypical squamous cells of undetermined significance-to-squamous intraepithelial cell ratio was reduced by 54% in a thin-prep group.

Vaginitis

Although normal vaginal secretions are clear or white, homogenous, and odorless, with vaginitis there may be an abnormal discharge, vulvar irritation, dysuria, and vaginal odor. The majority of cases of vaginitis are due to bacterial vaginosis, vaginal candidiasis, trichomonas vaginalis, or atrophic vaginitis. Additionally, STDs such as gonorrhea and chlamydia may cause an abnormal vaginal discharge. Detailed history should include the description of the discharge, presence or absence of odor, duration of symptoms, sexual history, and history of infections.

Standard office procedures include preparation of a wet mount, with material from the swab or the speculum placed on each end of a plain microscope slide, and microscopic examination to assess for bacterial vaginosis. Patients with bacterial vaginosis complain of thin white, yellow, or gray vaginal discharge, commonly with a

musty or fishy odor. The pH of the vaginal fluid is usually 5.0 or 6.0. Clue cells on the microscope slide on saline wet mount are described as vaginal squamous epithelial cells that have bacteria adhering to the membrane, giving them a speckled appearance as the focus shifts. Treatment of symptomatic patients and pregnant patients is routinely recommended.

Trichomonas vaginalis may be diagnosed by a saline wet mount showing polymorphonuclear leukocytes and motile flagellating organisms. The female partner complains of copious frothy yellow to green vaginal discharge. The patient and sexual partner should be treated.

Atrophic vaginitis is seen often in postmenopausal women and may be associated with a blood-tinged discharge. Evidence of atrophy on the vulvar vaginal examination may be present. The saline wet mount shows numerous leukocytes with small round epithelial cells. Topical therapy usually is prescribed, although oral therapy with an antifungal agent is considered with resistant infections.

Patients who have vulvar itching and a thick white curdlike discharge usually have vaginal candidiasis. The diagnosis is confirmed by examining a slide treated with 10% potassium hydroxide, with a sample of the discharge showing filaments, hyphae, or spores.

Colposcopy

Colposcopy aids in examining the visible portion of the female reproductive tract (i.e., vulva, vagina, cervix). This technique complements cytologic evaluation and may localize the source of abnormal cells seen on cytologic examination.

Vulvar diseases amenable to colposcopic evaluation include HPV infections, herpes genitalis, and preinvasive cancers. The magnification afforded by the colposcope may aid in the selection of areas for biopsy. The application of 3% acetic acid for 3 to 5 minutes may also help define abnormal areas, which typically turn white and display sharp borders (i.e., acetowhite epithelium). The colposcope may aid in the recognition of clinically inapparent vaginal intraepithelial neoplasia or HPV infection. These lesions also are characterized by acetowhite epithelium.

Colposcopy is used most commonly for evaluating the cervix in a patient with abnormal Pap smear results. After it is visualized and excess mucus is gently removed with a dry cotton ball, the cervix is treated with 3% to 5% acetic acid. As noted, flat condylomata or dysplastic areas turn white or develop a vascular pattern with a mosaic appearance or punctuation. The squamocolumnar junction and transformation zone are then inspected thoroughly, and a biopsy of suspicious areas is performed. In addition, a nonpregnant patient with an abnormal Pap smear result should have an endocervical biopsy. Bleeding occurring as a result of the biopsy can be controlled easily with ferric subsulfate (Monsel solution).

Endometrial Sampling

Advances in devices used for endometrial sampling have simplified the evaluation of abnormal uterine bleeding. Diagnostic dilation and curettage procedures under general or regional anesthesia have been replaced in many situations by outpatient endometrial biopsies, resulting in a savings of money, time, and morbidity. Endometrial sampling is of greatest value in the evaluation of abnormal bleeding when diffuse rather than focal endometrial changes are suspected.

Before obtaining an endometrial sample for biopsy, the physician should have the patient's informed consent. The physician should then rule out intrauterine pregnancy, cervical or endometrial infection, and cervical stenosis.

The size and position of the uterus are determined by a pelvic examination or by ultrasonography, and a speculum is placed in the vagina. If the patient is sensitive to cervical manipulation, a paracervical block can be administered. When endometrial cancer is suspected, an endocervical biopsy sample can be obtained before endometrial sampling. The cervix and upper vagina are then cleansed with an antiseptic such as povidone-iodine.

If the uterus is not anteflexed or retroflexed, a biopsy sample often can be obtained without placing a tenaculum on the cervix. If the degree of flexion is marked, a tenaculum aids in straightening the uterus. It is necessary in some women to anesthetize the anterior cervix with lidocaine 1% (Xylocaine) to avoid discomfort when the tenaculum is applied.

The instrument used to collect the sample is inserted to the top of the fundus, and the length of the uterus noted (Fig. 26.8). It is not necessary to dilate the cervix with sounds before obtaining the biopsy sample in most situations. Several samples are then obtained from the endometrial cavity and submitted for histologic evaluation. If cervical stenosis is present, instruments as narrow as 2 to 3 millimeters in diameter can be used, or the cervical os dilated. There are several instruments available for sampling the endometrium. The most commonly used is the Unimar Pipelle Endometrial Suction Curette (Cooper Surgical, Shelton, CT). Others include the Novak Endometrial Suction Biopsy Curette (Miltex Instrument Company, Lake Success, NY) and Tis-U-Trap Uterine Suction Curette Set (Milex Products, Chicago, IL).

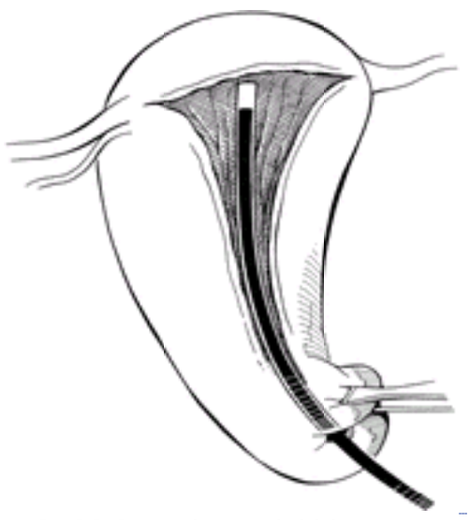

FIG. 26.8. Endometrial biopsy.

Patients may experience vasovagal syncope during the procedure and cramps or bleeding afterward. It is important to consider when sampling the endometrium that the device used can adjust to the shape and curvature of the uterus, which minimizes pressure on the uterine wall, reducing the likelihood of pain and cramping. Bleeding usually stops within 1 to 2 days after the biopsy.

Vulvar Biopsy

In the past, the toluidine blue test was used to direct vulvar biopsies. The vulva was washed with 1% acetic acid, dried, and then treated with toluidine blue dye. After 2 to 3 minutes, the dye was washed away with 1% acetic acid. Areas of possible vulvar intraepithelial neoplasia retained the dye and thus guided physicians to suspicious areas for biopsy. Because of the high rate of false-positive and false-negative results associated with this method, it has largely been replaced by colposcopy. Colposcopy has been shown to be a sensitive tool for diagnosing vulvar lesions such as HPV infections.

The only definitive way to exclude invasion is to perform a biopsy of, and to examine microscopically, suspicious areas of the vulva. Vulvar biopsy samples usually are simple to obtain in the office. The area under suspicion is cleansed with an antiseptic solution and then infiltrated with lidocaine 1% using a 25-gauge needle. Then, a 3- to 6-mm Keyes punch is used to obtain a sample (Fig. 26.9). Any bleeding that occurs can be controlled with silver nitrate or Monsel solution and gentle pressure. For larger areas, a single interrupted suture achieves hemostasis.

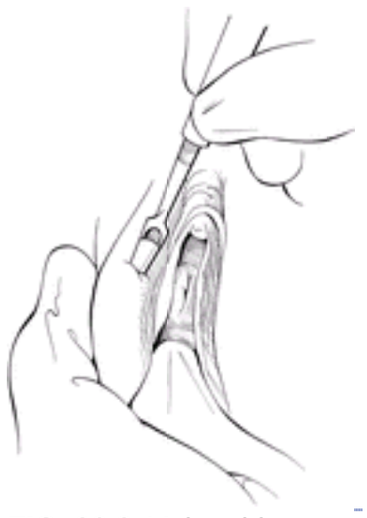

FIG. 26.9. Vulvar biopsy using Keyes punch.

Ovulation Detection and Prediction

The confirmation of ovulation is always an important part of the evaluation of patients with infertility or abnormal uterine bleeding. It also is useful in timing donor and homologous artificial insemination.

Methods used to detect ovulation reflect progesterone secretion by the ovary. The simplest among these is the determination of a biphasic temperature pattern by recording the basal body temperature (BBT). The BBT is that taken immediately on awakening and before activity. Persistent elevation in the BBT of 0.5°F to 1.0°F (0.2°C-0.4°C) in response to the secretion of progesterone reflects ovulation. However, ovulation has already occurred, and the BBT does not allow prediction of when it will occur. Measures of serum progesterone or the presence of secretory endometrium can also be used to confirm that ovulation has occurred. As with the BBT, these methods provide confirmation of ovulation but do not make it possible to predict the day of ovulation for the timing of coitus or insemination.

Serial ultrasonographic studies of follicular growth and disappearance and subsequent formation of a corpus luteum is another method of detecting and timing ovulation. The serial sonographic changes associated with ovulation include a preovulatory follicle of 20 millimeters or more, a change in the shape of the follicle, thickening of the follicular wall, disappearance of the follicle, and the appearance of fluid in the cul-de-sac. However, these changes can occur without actual ovulation, and ovulation can occur without these characteristic changes. Only direct observation of ovulation during laparoscopy, or pregnancy, provides definite evidence of actual ovulation.

The introduction of home test kits for detecting the midcycle surge of luteinizing hormone in urine has made it possible for patients to predict when ovulation will occur. A peak in urinary luteinizing hormone typically occurs between 8 a.m. and 3 p.m., and ovulation usually occurs 12 to 36 hours later. This makes it possible for infertile couples to time coitus or insemination more accurately than ever before. False-positive results may occur in women with polycystic ovary syndrome and in those taking ovulation-inducing drugs.

Transvaginal Ultrasonography

Although there is no substitute for a bimanual pelvic examination, transvaginal ultrasonography may enhance and extend the pelvic examination. Ultrasonographic examination cannot replace the physician's physical determination of the mobility and texture of tissues or the presence of tenderness, but it can provide objective confirmation of the size, shape, and location of pelvic organs. The introduction of lightweight, mobile machines with 5- and 7.5-MHz probes has made office-based ultrasonography a valuable diagnostic technique. Compared with other methods of imaging, ultrasonography is unsurpassed in safety and in providing inexpensive images.

Several advantages of ultrasonography available in the gynecology office include picture clarity, ease of operation, and dynamic use of the probe. The probe can be used during almost every pelvic examination to enhance the diagnostic abilities of the bimanual examination and will probably be present in every gynecologist's office within the next 3 to 5 years. The process of transvaginal sonography improves upon the bimanual pelvic examination by allowing the hand on the abdomen to move organs or structures. Structures may be moved or touched to attest for presence of pain, and fluid collections may be observed.

Office-based ultrasonography can be helpful in the following situations:

- Evaluating pelvic masses
- Monitoring follicular growth in response to ovulation-inducing drugs
- Diagnosing and sizing uterine leiomyomata
- Differentiating intrauterine from ectopic pregnancies
- Diagnosing pelvic abscesses
- Evaluating the endometrium in women with abnormal uterine bleeding

Another important area in which ultrasonographic evaluation is valuable is in the postmenopausal woman. In evaluating endometrial abnormalities, endometrial thickness of 5 millimeters is used to determine whether further evaluation is needed. Women whose endometrium measures less than or equal to 5 millimeters are considered to have normal results, and those women whose endometrium measures greater than 5 millimeters are subjected to endometrial biopsy in a screening study performed in a private office setting.

A suboptimal examination or confusion resulting from artifacts may have serious consequences, however. The ultrasonographic image is only as good and as useful as the clinical skills used to relate the sonographic findings to the situation under evaluation.

A variation of pelvic ultrasonography is sonohysterography, in which a clear fluid is infused into the uterus while a vaginal ultrasonographic examination is performed (Fig. 26.10). This technique is a useful adjunct and a less costly alternative to office hysteroscopy in women with abnormal uterine bleeding, Asherman syndrome, and infertility. Using it, one can detect reliably irregularities of the endometrium caused by adhesions or polyps but cannot distinguish hyperplasia from neoplasia.

FIG. 26.10. Sonohysterogram.

A pelvic examination and baseline vaginal ultrasonographic examination are performed to evaluate mobility, size, and position of the pelvic organs. A pregnancy test is done if there is any suspicion of pregnancy. The cervix is cleansed with povidone-iodine or another antiseptic solution and a 5.0- to 5.3-French catheter is introduced with a ring forceps into the cervix. H/S Catheter Set for Hysterosalpingography (Ackrad Laboratories, Crawford, NJ) is commonly used. The speculum is removed, and the ultrasonography probe reintroduced into the vagina. Sterile saline is then infused slowly from either a 30- to 60-milliliter syringe or a bag, while the uterus is scanned from cornu to cornu and from the external cervical os to the fundus. Not only can intrauterine lesions be seen, but tubal patency can be ascertained by observing the accumulation of fluid in the cul-de-sac.

Office Hysteroscopy

The development of small hysteroscopes that use carbon dioxide or saline as a distension medium has made it possible to determine in the office setting, often without

anesthesia, the cause of abnormal uterine bleeding, the size and shape of the uterine cavity, the presence of congenital anomalies of the uterus, the location of a misplaced intrauterine device, and the presence of intrauterine adhesions, polyps, or submucous myomata. Office hysteroscopy is of significant value in evaluating women with abnormal uterine bleeding who have ovulatory menstrual cycles. In such cases, focal rather than diffuse endometrial abnormalities may be present.

The procedure is safe, simple, and quick. It is performed early in the menstrual cycle to avoid an intrauterine pregnancy or a thick endometrium. Patients should give informed consent. The cervix is cleansed with an antiseptic solution, and the hysteroscope is inserted through the cervix (Fig. 26.11). Insertion of the hysteroscope is facilitated by the performance of a bimanual examination before the hysteroscopy to assess the size, shape, and flexion of the uterus. Flexible diagnostic hysteroscopes typically do not require use of a tenaculum on the anterior cervix. Larger flexible hysteroscopes designed for obtaining biopsies usually require dilation. Injection of a local anesthetic to the anterior cervix and paracervical areas and use of nonsteroidal antiinflammatory drugs reduce the discomfort associated with the procedure for most patients. The endocervical canal, endometrial cavity, and tubal ostia are evaluated systematically, and biopsy samples can be taken of endometrial pathology. Patients should be informed that after the procedure they may experience some uterine cramping or bleeding that should subside within 24 hours.

FIG. 26.11. Office hysteroscopy.

Office Microlaparoscopy

Microlaparoscopic procedures may be performed safely under local anesthesia with conscious sedation in the office under selected circumstances. Careful patient selection is critical for the safety of this procedure, which most often is performed for pelvic pain mapping. Improved instrumentation and refined conscious sedation techniques have contributed to the increased interest in this procedure. Pain mapping may identify subtle areas of disease that might have been overlooked if patients had received general anesthesia. Proper patient selection is critical with respect to patient safety, and it is important not to include patients for whom more extensive surgery may be necessary, extensive endometriosis is expected, or when medical problems or obesity are present. In addition, another major obstacle to office laparoscopy is lack of insurance coverage. As gynecologists become more skilled in microlaparoscopic surgery under local anesthesia with conscious sedation, the number of office laparoscopies may increase during the next decade.

Bone Mineral Density Testing

Osteoporosis is a major health threat in the United States, which is particularly prevalent in the postmenopausal woman. The gynecologist often is called upon to assess risk factors for osteoporosis in the menopausal population and in those women who are hypoestrogenic. Although the dual energy x-ray absorptiometry (DEXA) scan of the spine and hip is the gold standard for evaluation of osteopenia and osteoporosis, newer measures of bone strength, such as heel ultrasonography, have been introduced and used in a gynecology office setting. Gynecologists have used office-based heel ultrasonographic bone mineral density-measuring devices. Measurements of bone mineral density are determined as a T score in the heel, as with the spine and hip density measurements. This additional service in the gynecology office will help in screening women for osteoporosis, with appropriate referral for a spine and hip study. In addition, a combination of risk factor evaluation and the bone mineral density measurement in the office may increase the ability to predict the development of osteoporosis and fracture risk and improve evaluation and treatment decisions in the menopausal patient. The efficiency of routine bone density screening in the gynecology office has not been totally established.

SUMMARY POINTS

- An effective history and examination require that physicians understand why patients are seeking medical care.
- A thorough gynecologic history and examination should include an evaluation of personal health habits and psychosocial issues, including sexuality, abuse, emotional disorders, and drug, alcohol, or tobacco addiction.
- A thorough summary of the physician's findings and a discussion of their implications will reduce the patient's anxiety and improve compliance with medial therapies.
- Office hysteroscopy and endometrial biopsy are a valuable alternative to dilation and curettage.
- Transvaginal ultrasonography may enhance and extend the examination of the pelvis.
- Office microlaparoscopy may be useful in specific, selected circumstances for pain mapping in the patient with chronic pelvic pain.
- Office bone mineral density testing with a heel scanner may be useful in combining risk factor evaluation and the scan result with respect to evaluation and treatment decisions.
- The expertise and experience of gynecologists make them excellent agents for consolidating the health care of women, while providing the majority of care for a large female population. The office-based focus of current and future gynecologists is a significant component of their ongoing contribution to the health care of women.

ACKNOWLEDGMENT

The authors wish to thank Mrs. Alyce Soffer for her assistance in the preparation of this manuscript.

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Chapter 27

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Office Surgical Procedures

PREPARING THE FACILITY
PREPARING THE PATIENT
ANESTHESIA
Local Anesthesia
Paracervical Block
Conscious Sedation
PREVENTING COMPLICATIONS
THE PROCEDURES
Office Hysteroscopy
Microlaparoscopy
Office Dilation and Curettage (D&C) and Endometrial Sampling
Endometrial Ablation
Saline Infusion Sonography
Contraceptive Procedures

SUGGESTED READINGS
Anesthesia
Hysteroscopy
Microlaparoscopy
Dilation and Curettage
Endometrial Ablations
Saline Infusion Sonography
Intrauterine Devices
Norplant

As all medical specialties evolve, so has obstetrics and gynecology. Procedures that were once exclusively performed in the hospital setting are now exclusively performed in the office setting. Some office procedures (i.e., endometrial biopsy, transvaginal ultrasound/saline infusion sonography) have decreased the number of hospital surgical procedures a physician needs to perform to make a diagnosis. Additionally, medical therapies are now used that routinely replace surgical therapies (i.e., methotrexate for ectopic pregnancies). All these changes have resulted in shifting care from the hospital setting to the medical office. These changes in the specialty of obstetrics and gynecology coupled with the recent demands placed on the medical community for cost control has helped spark the trend in the development of more outpatient-oriented care and office surgical suites. Although the technology to perform minor gynecologic surgical procedures in an office setting has been available for years, most “simple” gynecologic procedures are still typically performed in the hospital setting. This chapter will discuss the preparation and briefly review a number of minor procedures which can be performed in an office surgical suite.

PREPARING THE FACILITY

Although many procedures can be performed in an office setting, the particular layout, room sizes, equipment availability, and staffing issues may make it difficult for the practitioner to perform certain office surgical procedures. The facility should, at a minimum, allow for easy access of wheelchairs and stretchers. Additionally, the basic medical supplies needed would include pulse oximeters, basic airway management equipment, electrocardiogram monitoring, intubation supplies, rooms equipped with call alarm buttons, intravenous line stands, a crash cart, and waste containers for sharps. An electronic table capable of placing patients in the Trendelenburg position, with cushioned knee stirrups, is preferred for procedures that last over 10 minutes or use anesthesia. It is important to keep in mind that in some states there are regulations for specific facility requirements when conscious sedation is used. Before developing an office surgical suite physicians should check with local regulatory committees so they will be able to meet any local standards and needs assessments.

PREPARING THE PATIENT

For procedures that are performed in the office setting, a clinician should prepare the patient the same way as they would for the similar in-hospital procedure. Important attention should be paid to the medical history and past medical history to make sure the patient is a good candidate for an in-office procedure and is of low anesthetic risk. Patients with multiple medical problems, cardiovascular disease, or neurologic disease may be better served in the hospital setting. Consents similar to what one would obtain for a day-surgery hospital procedure should be signed. It is important to remember that consent will be required not only for the surgical procedure but also for the anesthesia used. Basic preparatory instructions for the individual procedure should be given as well as postprocedure instructions in case discharge planning is needed. Fasting is recommended when conscious sedation is required, which is abstinence from food for 8 hours and clear liquids for 2 hours.

ANESTHESIA

Although some office procedures can be performed without anesthesia, some will require oral or intravenous sedation. The term *conscious sedation* implies a state in which patients can tolerate procedures with adequate cardiopulmonary function and respond to verbal commands. The American Society of Anesthesiologists (ASA) has published guidelines for sedation and analgesia performed by medical staff not trained in the practice of anesthesia. In the office setting nonanesthesia residency–trained physicians should limit patients to ASA classification I or II (Table 27.1). The clinician should avoid procedures on patients with significant cardiac, respiratory, or neurologic disease in the office setting.

Status	Description
I	Healthy patient
II	Mild systemic disease
III	Severe systemic disease, not incapacitating
IV	Severe systemic disease that is a constant threat to life. Moribund, not expected to live 24 h irrespective of operation

TABLE 27.1. *American Society of Anesthesiologists (ASA) patient classification*

Per hospital policy, anesthesia records should be maintained on the patient's ventilatory and oxygenation status. Hemodynamic variables should be recorded frequently and at a minimum it should be recorded:

- prior to the administration of anesthetic agents
- following the administration of sedation
- upon completion of the procedure
- upon recovery
- at the time of discharge.

A designated medical professional (nurse, physician's assistant, or physician) other than those performing the procedure should be present to monitor the patient's vital signs throughout the procedure. A staff member trained in advanced cardiac life support (ACLS) should be immediately available. The patient should have intravenous access. Naloxone and flumazenil should be available when opioids and benzodiazepines are used.

Anesthesia techniques will vary upon the physicians training and facility requirements. Most obstetrician-gynecologists performing office surgical procedures should be versed in conscious sedation, administration of local analgesia, and paracervical blocks. Ideally patients undergoing diagnostic and therapeutic procedures receive

moderate sedation. The definitions within the continuum of sedation are described in Table 27.2.

Minimal sedation: may be achieved with oral or intravenous medication. Cognitive function may be impaired but the patient responds normally to verbal commands. Ventilatory and cardiovascular functions are unimpaired.
Moderate sedation and analgesia: ordinarily referred to as conscious sedation. Medications are usually administered intravenously. Consciousness is depressed but the patient can respond to verbal commands. The patient is capable of maintaining a patent airway and spontaneous ventilation; cardiovascular function is well maintained.
Deep sedation: results in substantial depression in consciousness, the patient is not arousable, except by repeated painful stimuli.
General anesthesia: drug-induced loss of consciousness.

Duke JC. Education module for nonanesthesiologists providing sedation and analgesia for diagnostic and therapeutic procedures. Denver Health Hospital, Department of Anesthesiology, Denver, CO.

TABLE 27.2. *Explanations of various levels of anesthetic sedation*

Local Anesthesia

Local anesthesia can be a safe and effective means of providing analgesia for office procedures. Local anesthesia is defined as the elimination of sensations, especially pain in one part of the body using topical or regional injections of medications. Most obstetrician-gynecologists are educated in the use of local anesthetics during residency training. The secrets of success with local anesthetic use is injecting slowly, using a sufficient amount of medication and waiting for the medication to take effect. Several agents may be used and include benzocaine, mepivacaine, bupivacaine, and lidocaine. It is important to remember that local anesthetics have cardiac and central nervous system toxicity, particularly with intravasation into the venous system. Local anesthetics are frequently mixed with epinephrine. Symptoms of epinephrine overdose include tachycardia and hypertension, and one should watch for these signs when using local anesthetics containing epinephrine.

Paracervical Block

Most gynecologists should be proficient in performing a paracervical block. Paracervical blocks are useful not only for cervical biopsies, cervical conization, and loop electro-excisory procedures but also for office dilation and curettage (D&C) procedures and office hysteroscopy. In performing a paracervical block, in addition to the supplies needed for the local infiltration, it is useful to have available a needle extender or long spinal needles. The application of 1% benzocaine spray or lidocaine ointment prior to insertion of the needle may relieve some of the discomfort from inserting the needle. For the paracervical block, injecting 10 mL of anesthetic (usually 1% lidocaine) at the 4 and 8 o'clock positions and waiting 10 minutes gives excellent results. This is believed to limit sensation from the uterosacral nerve bundles from S2, S3, and S4. With this technique the only area of tenderness appears to be the fundus of the uterus and providing local anesthesia to this area is difficult as it is supplied by the tenth thoracic nerve (Fig. 27.1).

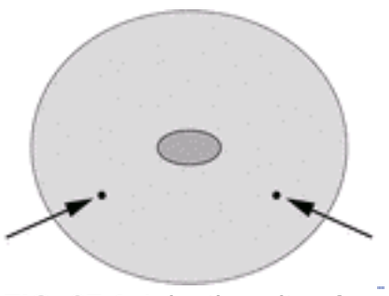

FIG. 27.1. Injection sites for paracervical block at 4 and 8 o'clock positions.

Conscious Sedation

Conscious sedation is defined as a minimally depressed level of consciousness whereby a patient can maintain their own airway independently and respond to verbal commands. The medications used for conscious sedation procedures include local anesthetics, sedatives, and anxiolytic and opioid analgesics. The ideal drugs to use in an office setting would have a quick onset and quick clearance rate. The medications used should have a predictable onset of action and minimal side effects. Anxiolytics and opioids are more commonly used by nonanesthesiologist practitioners for conscious sedation. The window of safety between effect and oversedation is narrow for sedatives and therefore limits their use in the outpatient setting for most physicians. It is important that the surgeon avoids turning a conscious sedation case into general anesthesia, especially in the office setting. There is an approximately a 0.2% mortality rate with conscious sedation, mostly due to oversedation and inadequate monitoring.

Diazepam (Valium) is the most popular of the anxiolytics used; however, midazolam (Versed) has also been used. Diazepam is popular because it can be given both intravenously and orally. The usual dose is 2.5 mg intravenously every 10 minutes to a maximum dose of 0.15 mg per kg or 10 mg. The drawback to diazepam is its long duration of action, which is why some physicians prefer midazolam. Midazolam can also be administered orally, intravenously, or intramuscularly. It has a short half-life. The usual recommended dose is 1 mg intravenously every 5 minutes to a maximum dose of 0.07 mg per kg or 5 mg in the office setting.

The opioids are medications that will decrease the patient's awareness of painful stimuli. These drugs can produce respiratory suppression and should be used cautiously. The preferred drug in this class for conscious sedation is fentanyl. Fentanyl has a quick onset of action and short half-life. In the office setting the standard dose is 25 to 50 µg every 5 minutes, to a maximum of 3 µg per kg, or 250 µg intravenously. Morphine and meperidine have also been used instead of fentanyl, however, they have a longer duration of action. It is important to note that morphine and meperidine appear to work better for patients with visceral discomfort.

Naloxone and flumazenil are two drugs that are essential to have available while providing conscious sedation using opioids and benzodiazepines. Naloxone (40 mg intravenously) is used to reverse the respiratory depression seen with opioids and flumazenil (0.2 mg intravenously) is a benzodiazepine antagonist (Table 27.3).

TABLE 27.3. *Agents approved for conscious sedation and dosing regimens for adults*

PREVENTING COMPLICATIONS

There are two basic groups of complications from surgical procedures:

1. Allergic reaction to the medications used.
2. Technical difficulty with the procedure.

Being prepared is the key to managing procedure complications. Careful history will help eliminate most allergic reactions, but a staff member trained in resuscitation and having agents like Benadryl (50 mg i.v.) and epinephrine may be lifesaving. It is imperative that the recommended limits for in-office sedation for the medication

being used are not exceeded. An approximately 0.2% mortality rate occurs with conscious sedation. Those deaths are mostly due to the lack of adequate monitoring of cardiac and respiratory functions during the procedure. Good judgment is the key to avoiding complications. It is much better to discontinue the office procedure if it appears more complex than originally planned. To help improve outcome after any surgical complication it is important to have an emergency plan available for these unforeseen surgical complications (i.e., local ambulance number, local emergency room number, crash cart, and staff trained in ACLS techniques).

THE PROCEDURES

Office Hysteroscopy

Setup, Equipment, and Preoperative Care Office hysteroscopy is a useful tool for the evaluation of abnormal uterine bleeding, infertility, and recurrent pregnancy loss. Typically an office hysteroscopy can be performed in a regular exam room without much modification. The most common medium used for distention with office hysteroscopy procedures is CO_2. CO_2 is readily available and uses a low-flow insufflator (100 mL/min). It is essential to note that a CO_2 insufflator for laparoscopy is a high-flow insufflator and should *never* be used for office hysteroscopy. Advantages of CO_2 is its low cost, low "mess," and overall performance and safety. It is important to remember however that CO_2 is not a good medium for evaluation of patients with abnormal bleeding while they are bleeding. These patients may be better served with a "liquid" distention medium including high-molecular-weight dextran, sorbitol, normal saline, or lactated Ringer solutions. Several hysteroscopy manufacturers have developed low-cost complete fluid systems for office hysteroscopy procedures that aid in making the procedure safe and simple. When starting to perform office hysteroscopy procedures it is important to make sure you have the correct equipment available. For office hysteroscopy there are two different kinds of hysteroscopes—rigid and flexible. Flexible hysteroscopes tend to be more expensive and have slightly poorer quality images when compared to rigid hysteroscopes. Most physicians prefer rigid hysteroscopes for office procedures. The standard office rigid hysteroscope is 4 mm in size, however, microhysteroscopes with 2.4 mm and 2.7 mm optics are available. The smaller size decreases the need for cervical dilation, which has the advantage of decreasing the pain and bleeding associated with the procedure. In addition to the sheath size for the hysteroscope physicians have a choice of telescope angle. Most physicians prefer to use a telescope at 0, 12, 15, or 30 degrees. Many hysteroscopy systems are available for operating room and office use. All systems have their particular advantages and disadvantages. Several systems should be tested in your office setting to determine which system is the best for you before purchasing a system. Look for a system from a company with reliable service that has the operating equipment you will need (graspers, forceps, scissors) and a telescope with the brightest, clearest image within your budget.
Surgical Technique After the patient has checked in and appropriate vital signs have been taken adequate analgesia should be given (see " Anesthesia" earlier in the chapter). An attempt to pass the hysteroscope without dilation should be made. However, the cervix may need to be dilated. Good techniques for cervical dilation include laminaria or misoprostol. Since these techniques require preplanning it is best at the preoperative appointment to assess the cervix to determine if dilation will be necessary. The problem with laminaria insertion is it requires a visit to the office the day prior to the procedure and many patients experience severe cervical/uterine cramping. Another option is the use of misoprostol 400 mg orally 4 to 6 hours prior to the procedure. The hysteroscope is usually inserted under direct visualization passing through the cervical canal into the endometrial cavity. To aid in visualization during the hysteroscopy, the cervix should be cleared of all blood using a sponge forceps prior to entering the cervical canal. Another way to keep the lens clean when using a liquid distention medium is to start the distention medium prior to entering the cervix. The running fluid at the tip of the hysteroscope upon entering the cervical canal aids in keeping the lens clean and in visualization at the start of the procedure. In addition, if the medium is cloudy upon entry, waiting 15 to 30 seconds to allow the continuous flow process to work will provide a clearer field of vision. In contrast, if CO_2 is used as the distention medium, do not start the CO_2 until after entrance into the cervical canal. This will avoid making blood-tinged bubbles within the cavity which will obstruct the view. Once the hysteroscope is passed through the cervical canal into the uterus a systemic overview of the cavity should be performed prior to performing any operative procedures. Inspect the fundus and locate both tubal ostia first then pull back to the level of the internal os and inspect the entire anterior then posterior wall of the uterus (Fig. 27.2).

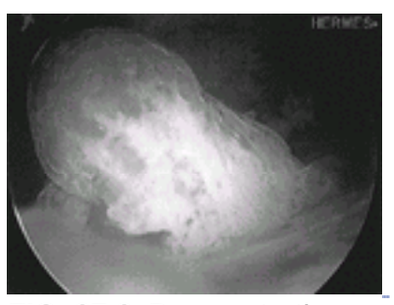

FIG. 27.2. Demonstrating a posterior wall intrauterine mass in an office hysteroscopy evaluation.

Postoperative Care Most patients will have light spotting or light bleeding for up to 5 days after their hysteroscopy procedure and should be advised of such. Intercourse and douching should be restricted for 24 hours. Tampons may be used for the postoperative bleeding that occurs. Patients should be advised that they could have minimal cramping which is best resolved with a nonsteroidal antiinflammatory drug (NSAID) or other analgesic. Patients should be instructed to call if they have heavy bleeding, severe pain unresolved by the NSAID, or fever greater than 100.5°F.

Microlaparoscopy

Setup, Equipment, and Preoperative Care Microlaparoscopy under local anesthesia has raised interest in the medical community due its cost-effectiveness in comparison to in-hospital procedures. Several different microlaparoscopy procedures can be performed in the office setting, however, the difficulty in performing office microlaparoscopy for most physicians is not obtaining the training or equipment needed to do these procedures but rather having adequate office facilities to accommodate a microlaparoscopy suite. In addition to adequate facility size, the following equipment should be available for the office procedure:

- "micro" laparoscope and microlaparoscope lens
- video camera
- video monitor
- trocar sheaths
- laparoscopic scissors, graspers, and bipolar coagulation
- a table capable of accommodating the Trendelenburg position
- resuscitation equipment
- intravenous line supplies

v sterile surgical gowns and drapes. Several "micro" laparoscopes are available for use. The refinements in fiberoptic technology have led to excellent quality 2-mm laparoscopes. Microlaparoscopes range from 25 to 27 mm in working length and have a 0-degree angle of view. There are 2-mm accessories available such as graspers, blunt probes, and biopsy forceps. While concerns remain over optical clarity with these "micro" laparoscopes, comparison of the accuracy of a 1.98-mm microlaparoscope with the standard 10-mm laparoscope (endometriosis scores and adhesions scores) yields no difference between the two. To avoid major complications, candidates for office laparoscopy should have no more than a minimal amount of prior abdominal surgery and no medical history suggestive of a significant risk of abdominal adhesions.
Surgical Technique It is important to realize that even experienced laparoscopic surgeons should perform office microlaparoscopy with an experienced microlaparoscopic surgeon prior to performing these procedures on their own. Even experienced laparoscopic surgeons will find the "micro" equipment more difficult to use at first until a feeling is established for the differences in depth perception and smaller field of view when compared to their full-size counterparts. Procedures best suited for the microlaparoscopic technique include infertility evaluations with chromopertubation, tubal ligation procedures, conscious pain mapping, and second-look procedures. The average length of an infertility evaluation procedure is 18 minutes. Some patients undergoing microlaparoscopy can have the procedure performed strictly under local anesthesia. However, this limits the length of the procedures and the amount of gas that can be used for insufflation. Most patients are better served with some conscious sedation as this often allows the procedure to last 30 to 45 minutes in contrast to only 15 minutes with local anesthetic alone. For the microlaparoscopy procedure, the patient is placed in dorsal lithotomy position on a table capable of performing Trendelenburg. A paracervical block should be give if a uterine manipulator is used such as the Cohen cannula. The patient is sterilely prepped and draped. If conscious sedation is used, this is given according to the guidelines described previously. Local anesthetic is then given in the area of the umbilicus. The use of a Verres needle/sheath combination system allows entry of the Verres needle without reintroduction of a trocar sheath for the procedure. The abdomen is insufflated and the pelvic organs visualized. Remember insufflation pressures will be higher in these patients because they do not have abdominal muscle relaxation. Pressures and gas flow should be titrated to patient comfort. Observation and chromopertubation are performed in a manner similar to that using the 10-mm laparoscope.
Postoperative Care Routine postoperative care for laparoscopic procedures should be followed for patients undergoing in office laparoscopic procedures. Patients should be stabilized prior to discharge and return for a postoperative incision check in 1 to 2 weeks. Patients should be advised to call if they experience heavy vaginal bleeding, pain that is not resolved by NSAIDs, or a fever greater than 100.5°F.

Office Dilation and Curettage (D&C) and Endometrial Sampling

Setup, Equipment, and Preoperative Care The vast majority of office endometrial samplings and D&C procedures can be performed with minimal office

modifications. Most of the equipment needed is readily available and disposable. In addition to the obvious cost savings for office D&C procedures, the office procedures are more time-efficient for the physician. Office D&C procedures may be performed for a variety of reasons but the most common indications include pregnancy termination and management of an incomplete abortion prior to 12 weeks gestation. It is very important to confirm pregnancy status and location by ultrasound prior to performing the procedure. The most common reasons for in-office endometrial sampling include evaluation for abnormal uterine bleeding, postmenopausal bleeding, recurrent pregnancy loss evaluation, and as part of an infertility workup.

Surgical Technique The most popular technique for office D&C uses the Karman cannula. The Karman cannula is a soft catheter and is an efficient suction device as it has two suction ports. The larger the bore of the catheter the more effective is the aspiration procedure. As the soft catheter works so well we find that there is a limited role for the sharp curettage technique. The soft catheter probably reduces the risk of uterine perforation when compared to the traditional sharp curette. In choosing the size of the cannula the diameter of the cannula should equal the size of the uterus using the standard sizing of the number of weeks of pregnancy. Therefore when performing a D&C for an incomplete abortion in a uterus measuring 8 weeks gestation, an 8-mm cannula should be used. Office procedures should be used only on those patients with a uterine size less than 12 weeks gestation. Prior to arrival at the office we usually pretreat the patient with Valium, 5 to 10 mg orally. After check in and routine vital signs are obtained, a bimanual exam is performed to determine the uterine size. A speculum is inserted to perform a paracervical block (see “ Anesthesia” earlier in the chapter for description of this technique). After adequate anesthesia is induced the catheter should be passed through the cervical os. Sometimes cervical dilation is needed and this may be accomplished with dilators, laminaria (or its synthetic counterpart), or misoprostol. Initially the chief purpose of uterine curettage was for endometrial sampling, however, the classic curettage has been essentially replaced with the office endometrial sampling. Endometrial sampling is a diagnostic screening test and the use of an in-office endometrial sampling procedure has essentially eliminated the need for many D&Cs performed in the operating room. During the past 50 years many different instruments have been developed for office endometrial biopsies. Most of the sampling devices used for this purpose have a 5-mm or less outer dimension and are made of plastic. Some of these devices require a syringe or suction pump, however, the most popular endometrial sampling device is the disposable hollow plastic tube with an aspiration port that has a solid plastic obturator (Pipelle).

Postoperative Care Most patients do well after an in-office endometrial curettage or sampling. The patients should be advised that they might have cramping and bleeding for 3 to 4 days after the procedure. Patients often respond well to NSAIDs for uterine cramping. They should be advised to call the office if they develop a fever, have vaginal discharge, or have bleeding past 4 days.

Endometrial Ablation

New technology now allows the physician to perform office endometrial ablation. Several types of endometrial ablation devices are on the market, some using water, balloons, or impedance-controlled bipolar radio frequency. In randomized studies 46% of patients were able to use the balloon technology in the office under local anesthesia (some with i.v. sedation) and 73% using the bipolar radio-frequency system were able to be performed in the office setting.

Novasure (bipolar radio frequency) technology can be performed as an outpatient or office-based procedure. The average treatment time is 90 seconds compared to 8 to 12 minutes for balloon technology. With the Novasure system, the Novasure introducer sheath is introduced through the cervical os (Fig. 27.3). The three-dimensional bipolar electrode expands from the introducer sheath and with the aid of CO_2 conforms and checks the integrity of the uterine cavity. The ablation is accomplished and the electrode is retracted into the sheath and removed. There is a 91% success rate (decrease in flow) and 41% amenorrhea rate (Table 27.4). The endometrial balloon (Thermachoice) is very easy to use (Fig. 27.4). The catheter is primed and tested. The catheter is then introduced into the uterus much like a sound. The balloon is filled and the Thermachoice heats the fluid. After a heating period, 8-minute treatment period, and cooling period the catheter is removed. Temperatures and uterine pressures are measured continuously. This helps confirm uterine integrity.

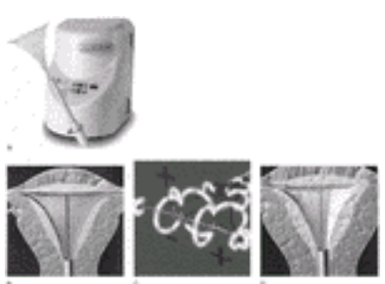

FIG. 27.3. Novasure endometrial ablation technology using a balloon system.

TABLE 27.4. *Endometrial ablation procedures*

FIG. 27.4. Thermachoice endometrial ablation technology using a balloon system. (Reprinted with permission from Gynecare, Somerville, NJ.)

Surgical Technique The surgical technique will depend upon the equipment used. Physicians who desire to use the ablation technology should be trained by those experienced in using the equipment. Contacting your local equipment sales representatives and surgeons to serve as experienced preceptors should be the easiest way to become proficient using ablation equipment. If these procedures are being performed in conjunction with hospital systems, there may be information on credentialed individuals in the medical staff office.

Postoperative Care Most patients will do well after discharge. Generally an NSAID or similar medication is prescribed to control postoperative pain. Patients should be advised to contact the office with excessive postoperative pain that is not relieved by the NSAIDs or if they experience excessive postprocedure bleeding. In order to insure that the patient is satisfied with the ablation results it is important to educate patients about the typical results seen with endometrial ablation. Most patients will not experience a decrease in the menstrual flow for approximately three menstrual cycles after the ablation. The percentage of decrease in flow and amenorrhea rates, which vary with the technology used, should be reviewed prior to the procedure. As many as 30% to 40% of women may need further intervention within 4 to 5 years; however, patient satisfaction remains high if the limitations are discussed preoperatively.

Saline Infusion Sonography

Since the development of high-resolution ultrasound, saline infusion sonography (SIS) has been gaining in popularity. Numerous studies have looked at the benefit of ultrasound in establishing the diagnosis in women with abnormal uterine bleeding. However, it is sometimes difficult to image the endometrial contents and rule out pathology on a reliable basis. The use of fluid instillation into the uterine cavity coupled with ultrasound has become a useful diagnostic tool. SIS is easily performed in the clinical setting and is remarkably well tolerated in most patients. The clinical use of SIS is not in its use to replace surgery but to identify those patients who need surgical intervention. Multiple indications for SIS are listed in Table 27.5.

TABLE 27.5. *Indications for saline infusion sonography*

Setup, Equipment, and Preoperative Care The minimum supplies required to perform SIS include a SIS catheter, instillation medium, a 20-cc syringe, povidone-iodine solution, scopettes, an open-sided speculum, and an ultrasound that preferably has transvaginal capabilities. The most widely used medium for instillation into the uterine cavity is saline; however other contrast media have been investigated, including Echovist and Albunex. These media do not appear to

perform better than normal saline and are more costly. SIS can be performed during any time of the cycle; however performing SIS during the follicular phase will avoid the disruption of an early pregnancy. In addition during the follicular phase there is a thinner endometrium, which may aid in better evaluation of the uterine lining. Instilling saline during menses may lead to poor uterine distention so avoiding the procedure during the menstrual cycle is preferred. There are several SIS catheters on the market (Fig. 27.5, Fig. 27.6 and Fig. 27.7). Alternatively, pediatric Foley catheters, insemination catheters, and pediatric feeding tubes, can be used. The choice of the catheter will depend on the patient and therefore several catheter types should be available to the physician performing the SIS. In particular, one should have a thin, stiff catheter available for nulliparous cervices and a balloon or cone type catheter for multiparous cervices. The balloon should be used in patients with multiparous cervices to occlude the os. This will limit the amount of medium leaking out of the uterus and improve uterine distention.

FIG. 27.5. Placement of the Goldstein catheter for saline infusion sonography using a cone to occlude the cervical os. (Reprinted with permission from Cook Ob/Gyn, Spencer, IN.)

FIG. 27.6. Saline infusion sonography catheter, balloon type.

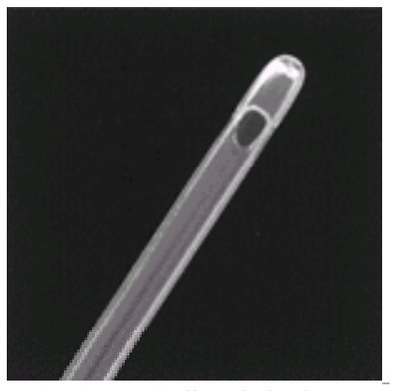

FIG. 27.7. Saline infusion sonography catheter, insemination type.

Technique After performing a bimanual exam or baseline ultrasound to determine uterine position, a speculum is inserted and the cervix is identified. The cervix may be cleansed with povidone-iodine or similar antiseptic solution. The catheter is primed with saline and then inserted through the cervical os. The exact placement will depend upon the catheter used. For a balloon-type catheter, the balloon should be positioned in the cervical canal or lower uterine segment and inflated. However the Goldstein SIS cone-type catheter is inserted to 7 cm, or near the uterine fundus, with the white acorn cone occluding the cervical os (see Fig. 27.5). A ring forceps may be needed to assist in placing the SIS catheter. Once the catheter is in place the speculum is removed with special care taken so that the catheter is not dislodged. The vaginal ultrasound probe is inserted into the vagina and the uterus is imaged as the saline is infused slowly. Usually about 5 to 10 cc of saline is used in order to get good distention. It is important to remember the seal will not be watertight. Although a watertight seal may produce better images, this will result in significantly more cramping with the procedure. When there is a large efflux of saline out the cervix, more saline may be needed to get good images. Visualization in both the longitudinal and transverse axis should be performed. The entire uterine cavity should be visualized from left to right broad ligaments longitudinally and from the cervix to the fundus in the coronal plane (Fig. 27.8). It is important to realize that full distention of the uterus is not necessary to get a good quality evaluation. Indications for SIS are summarized in Table 27.5.

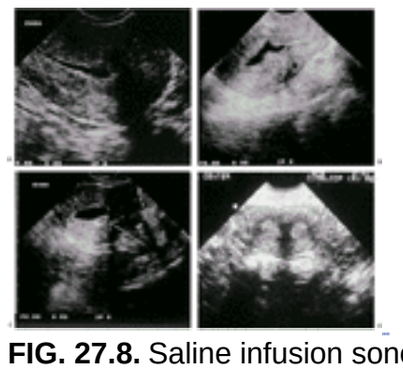

FIG. 27.8. Saline infusion sonography (SIS) evaluation of the uterine cavity. **A:** SIS demonstrating a normal uterine cavity. **B:** SIS demonstrating an intrauterine mass. **C:** SIS demonstrating a localized posterior wall thickening. **D:** Bicornuate or septate uterus visualized prior to instillation of saline.

Postoperative Care Most patients have minimal discomfort after a SIS procedure. Patients usually do well using NSAIDs or similar analgesics for pain control. Patients should be advised to call if they are experiencing heavy bleeding not associated with menses that continues for more than 4 days. Additionally patients should be evaluated if they have a fever greater than 100.5°F or vaginal discharge.

Contraceptive Procedures

As part of residency training most obstetrician-gynecologists will obtain the clinical training needed to perform insertion and removal of an intrauterine device (IUD) and the Norplant system.

Two IUDs are available in the United States: Mirena and Paragard. IUDs are generally recommended as a contraceptive method to women in a stable monogamous relationship who are not at risk for pelvic inflammatory disease, sexual transmitted diseases, or ectopic pregnancies. IUDs are contraindicated in the following situations:

- suspicion of pregnancy
- congenital uterine anomaly
- fibroid uterus which severely distorts the uterine cavity
- pelvic infections
- unresolved abnormal Pap smear
- untreated cervicitis or vaginitis
- genital bleeding of unknown etiology
- women with multiple sexual partners
- leukemia
- acquired immunodeficiency syndrome (AIDS)
- breast cancer
- ectopic pregnancy or history of ectopic pregnancy.

The Mirena IUD consists of a T-shaped polyethylene frame with a steroid reservoir around the vertical stem (Fig. 27.9). The reservoir consists of a cylinder made up of a mixture of levonorgestrel and silicone. There are 52 mg of levonorgestrel within the system which provides levonorgestrel at a rate of 20 µg per day initially. This level declines to half the 52-mg level at 5 years. Levonorgestrel is a progestogen, which is used in a variety of contraceptive products. There is a stable blood level of 150 to 200 pg/mL 3 weeks after insertion of the Mirena device. The T system is 32 mm in length and width. The T-shaped body also has barium embedded which makes it radiopaque. There is a monofilament string attached to the T-shaped body stem. Although the exact mechanism for contraception is not clearly identified it appears that the Mirena IUD has mostly local effects within the uterine cavity. Additionally, Mirena may have an effect on ovulation. In a 1-year study of the system only 45% of cycles were ovulatory; however, in a 4-year study 75% of cycles were noted to be ovulatory. Contraceptive effectiveness is quoted to be 0.2 pregnancies per 100 women and the cumulative 5-year pregnancy rate is 0.7 per 100 women. Half of the pregnancies that occur while using the Mirena IUD are ectopic gestations, at a rate of 1 ectopic pregnancy per 1,000 users per year. It is important to inform patients that the Mirena IUD can alter the menstrual bleeding pattern. During the first 3 to 6 months of use there may be an increase in vaginal spotting. Additionally, it has been noted that approximately 20% of users will amenorrheic after 1 year of use.

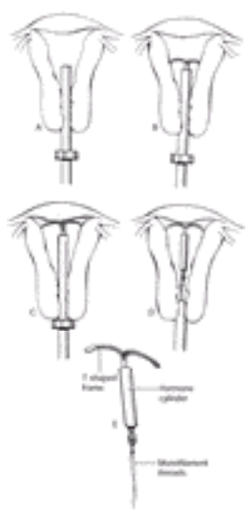

FIG. 27.9. The Mirena intrauterine device. **A:** Insertion of Mirena into uterine cavity. **B:** The arms of the Mirena are released. **C:** Mirena is positioned near the uterine fundus. **D:** Releasing the Mirena IUD and withdrawing the inserter. **E:** The Mirena IUD.

The Paragard IUD has a T-shaped polyethylene body. The vertical portion of the T is wound with 176 mg of copper wire along with a copper collar of 68.7 mg on each of the transverse arms. The exposed areas of copper are approximately 380 mm ^{2}. Paragard has a monofilament thread attached the bulb end of the base of the T-shaped device. The available data indicate that the copper is continuously released into the uterine cavity. The additional copper load to the body from a copper IUD may precipitate symptoms in patients with Wilson disease. The exact mechanism in which the copper provides contraception is unclear; however it is thought that there is interference with sperm transport, fertilization, and embryo implantation. The Paragard should be kept in place no longer than 10 years. Women who use the copper IUD should be advised that blood loss at the time of menses might increase. There is an approximately 35% increase in menstrual blood loss among copper IUD users.

If a woman becomes pregnant while an IUD is in place, the manufacturers recommend removing the IUD if the string is visible. Removal under these conditions is usually simple. It is important to confirm the location and viability of the pregnancy prior to removal of the IUD. Patients in whom the IUD cannot be removed or those who choose not to have the IUD removed should be informed that there is an increased risk of septic abortion and preterm labor/delivery.

IUD Insertion Technique An IUD should only be inserted, managed, and removed only by clinicians trained in IUD use. The Mirena and Paragard have different techniques for preparing the IUD insertion, so clinicians should refer to the package inserts for guidance. IUDs can be inserted at any time during the menstrual cycle. Traditionally physicians have preferred to insert an IUD at the time of menses to insure that the patient is not pregnant. However insertion at the time of menses increases the risk of expulsion of the IUD during the first 2 months of use. It is best to give patients an NSAID 1 hour prior to IUD insertion. After loading the IUD into its insertion device the uterus should be examined by bimanual examination and a speculum inserted into the vagina and the uterus sounded. With both IUDs there is an adjustable flange that should be set to the length to which the IUD should be inserted. A single tooth tenaculum is applied to the anterior lip of the cervix to aid in cervical and uterine straightening. Benzocaine spray or local infiltration of lidocaine may be used prior to tenaculum placement. The IUD must be inserted within 5 minutes of loading so that the arms will spring back open after insertion. The IUD is then passed through the cervical canal to the fundus. The plastic flange should be at the level of the internal os if the IUD is inserted correctly. Once correct placement is confirmed, the insertion device is used to release the arms of the IUD. The insertion device is then removed gently so as not to disturb the placement of the IUD. The monofilament thread should be cut approximately 2 cm from the external os. The risk of uterine perforation is 1 in 1,360 insertions. Insertion immediately in the postpartum period, particularly during lactation has been associated with an increased risk of uterine perforation. However there is no increased risk of perforation if the IUD is inserted immediately after expulsion of the placenta. It is our preference, however, to delay insertion of an IUD until the second postpartum month.
Postoperative Care After insertion of an IUD the patient should be taught how to palpate the strings monthly. Patients should be seen in 3 months to review bleeding pattern and concerns with the IUD. At that time, a speculum examination should be performed to rule out partial expulsion of the IUD. Removal of an IUD is generally easy. It is important to note the type of IUD prior to removal. The strings are grasped with a ring forceps and pulled outward through the vagina until the IUD is expelled. If the strings break off during removal or the strings are not visible, removal under ultrasound guidance is advisable. Under ultrasound guidance, while using packing forceps, the lower stem is located. Using gentle traction, it is removed through the internal then external os. If gentle force does not produce the IUD then the IUD may be embedded and, in such cases, hysteroscopic removal in the operating room may be needed. It is important to note that some IUDs that are used outside the U.S. do not have strings and are designed for permanent placement. These should not be removed in the office setting.
Norplant The Norplant contraceptive system consists of six Silastic capsules each filled with 36 mg of levonorgestrel powder. The capsules should be placed in the subcutaneous layer of the inner aspect of a woman's nondominant arm. Norplant capsules are designed for 5 years of use with a typical first year failure rate of 0.09% and a cumulative failure rate of 1.1% over 5 years. Discontinuation of use prior to 5 years appears to be the major problem with the Norplant system. The major reasons for discontinuation of use include bleeding abnormalities, weight change, headaches, and change in libido. Women with active venous thrombosis, unexplained vaginal bleeding, or history of stroke or breast cancer are not candidates for Norplant. Women using the drugs listed in Table 27.6 should not use Norplant as these drugs increase the metabolic clearance of levonorgestrel, which can decrease its efficacy. The most common side effects of the Norplant system include changes in the menstrual pattern, weight changes, and headaches.

Phenobarbital
Phenytoin
Carbamazepine
Rifampin

TABLE 27.6. *Drugs that decrease the effectiveness of the Norplant system*

Norplant Insertion Technique Both insertion and removal of the Norplant system require formal training to avoid complications. Norplant insertion should be scheduled during the first week after menses. Patients should be told to avoid intercourse during this time to avoid inadvertently becoming pregnant. Location for

placement of the Norplant capsules is the first decision that should be made. Ideally the capsules should not be noticeable. It is important to remember good placement of the capsules translates into easy removal. The location of the Norplant capsules to avoid detection should be on the inner aspect of the upper arm. Ideally the location should be above the level of the nipple and medial enough that it lies on the medial aspect of the arm. The capsules are traditionally fanned, and are placed approximately 15 degrees apart from each other. Once a location is chosen, the physician should use the Norplant template included in the kit and mark a dot for the incision site and a dot for the position of each of the distal tips. The Norplant kit contains all the necessary equipment needed for a standard simple insertion. Patients should be in the supine position when the capsules are inserted. The arm should be placed flat on the examining table with the palm upward and the elbow bent to 90 degrees (as if the patient is signaling to make a right-hand turn). Local anesthesia is given at the incision site, taking care not to use too much anesthesia which may distort the tissue planes. The needle should be advanced its full length just under the skin along the planned tract of each capsule. After adequate anesthesia is obtained, a 3-mm horizontal incision should be made at the incision site that has been chosen. The obturator should be loaded into the trocar provided in the kit. The trocar, with obturator in place, is introduced directly through the incision with the open end of the bevel facing the ceiling. The skin below the incision site should be held in place for traction. The trocar is then advanced until the level of the second line on the trocar is at the incision site. The obturator is removed and the Silastic capsule is introduced. The obturator in then replaced. The obturator is used to push the implant down the shaft of the trocar and into place. Once in place the obturator and trocar are removed gently and slowly. This procedure is performed a total of 6 times at 15-degree angles until all capsules are placed. After all 6 capsules are placed, the edges of the incision should be reapproximated with Steri-Strips.

Postoperative Care of Norplant Patients who have the Norplant inserted close to the time of ovulation should use barrier contraception for 1 week. Patients should be advised to check for signs of infection at the incision/insertion site, which occurs in less than 1% of Norplant insertions.

Norplant Removal The most important thing to remember is that good placement of the Norplant capsules leads to easy removal. One method of removal of the Norplant system is described here. As with other procedures many techniques have been developed to aid with the removal of the capsules. No particular procedure appears to have an advantage over another. It is recommended that removals be scheduled for a 20-minute appointment. Most Norplant removals take 15 minutes, however on rare occasions we have known them to take up to 45 minutes. Patients should be advised that removal is more painful than insertion. The incidence of difficult removal is quoted by the manufacturer to be about 13%. The area should be palpated and the location of the Norplant capsules identified. The following equipment is needed for removal:

- examining table
- sterile gloves
- sterile drapes
- antiseptic solution
- lidocaine or similar anesthetic
- needles and syringes
- scalpel
- marker
- straight and curved mosquito's or a similar clamp
- Steri-Strips, sterile gauze, and tape.

The location of each capsule is marked. If all capsules cannot be identified, localization by ultrasound or radiograph may be necessary. The area is then cleansed with Betadine and a local anesthesia is administered prior to making an incision where all the capsules converge. Additional anesthesia should then be given under the base of each capsule and behind each capsule for about a 1 cm of its length. In addition to providing anesthesia this will serve to raise the capsules. Injection of the anesthetic above the capsules may obscure their location and this should be avoided. Pressure is then applied to the distal end of the implant toward the incision to see if the tip can be “milked” into view. Most of the time, a fibrous sheath will be noted around the implant. This sheath should be nicked and the implant is then “milked out” through this nick and then through the incision on the arm. Unfortunately not all implants can be removed this easily; occasionally the incision will need to be probed and the capsule grabbed. Using a forceps to grab the fibrous tissue over the implant, it may be necessary to nick this tissue prior to removing the implant. Occasionally it is difficult to grab the implant with the forceps and manipulating the skin and implant to an area over the forceps may be easier than fishing for the capsule. Other techniques have been described for Norplant removal and are summarized in Table 27.7. After all the capsules are removed, a Steri-Strip should be applied and the incision dressed with sterile gauze.

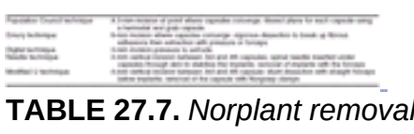

TABLE 27.7. *Norplant removal techniques*

SUMMARY POINTS

- Many gynecologic procedures can be performed in an office setting as they require minimal anesthesia and have minimal risk of complication.
- Performance of office procedures requires a clinician with sufficient training and experience and a facility with proper capabilities and appropriate staffing.
- The facility should allow for easy access, have an electronic table capable of comfortable patient positioning, and have available appropriate medical instrumentation required for local anesthesia and conscious sedation.
- Procedures that can be performed in the office include saline infusion sonography, intrauterine device placement, subcutaneous implant placement, dilation and curettage, hysteroscopy, endometrial ablation, and microlaparoscopy.

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Chapter 28

Frederick Larsen

Gynecologic Ultrasound

SONOGRAPHIC INSTRUMENTATION AND TECHNIQUE
Abnormal Uterine Bleeding
Pelvic Mass
Pelvic Pain
Ectopic Pregnancy
Infertility
SONOGRAPHICALLY GUIDED PROCEDURES
OTHER IMAGING MODALITIES
SUMMARY POINTS

SUGGESTED READINGS
Sonographic Instrumentation and Technique
Abnormal Uterine Bleeding
Pelvic Mass
Pelvic Pain
Ectopic Pregnancy
Infertility

Historically, assessment of abnormal physical findings in the gynecologic patient was limited to rudimentary plain film x-rays or exploratory surgery. Today, there are multiple diagnostic modalities including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) that can be used in the evaluation of gynecologic disorders. This chapter emphasizes the use of US for the initial evaluation of the most common gynecologic disorders for which imaging is indicated. The roles of MRI and CT are also briefly mentioned in this chapter as adjunctive tests in circumstances where sonography is nondiagnostic, or as a means to enhance diagnostic accuracy.

The use of gynecologic sonography has become widespread in gynecologists' offices and in emergency and radiology departments. Its accessibility and high patient acceptance make it applicable as an initial means for assessing many gynecologic disorders. Some practitioners have incorporated transvaginal sonography (TVS) in their routine pelvic assessment, even using it as a surrogate for a pelvic examination, particularly when the patient is obese. Others use it as a problem-solving tool only when a gynecologic disorder is suspected. Without commenting on the wisdom of following either pathway, it can be said that the US machine has become an extremely useful tool found in many, if not most, practitioners' offices. TVS is operator-dependent, and significant clinical experience with pathoanatomic correlation is required for effective use. For those who do not routinely perform pelvic sonograms as part of their practice, but rather order them, it is crucial that they have a working understanding of not only the lexicon of US but also at least a rudimentary ability to interpret the images that are collected.

In selected cases in which standard pelvic sonography is not diagnostic, however, MRI or CT may be used to better delineate anatomic abnormalities. Other advances in the use of pelvic US, such as saline infusion hysterosonography, have eliminated some of the indications for these more expensive examinations. These two imaging modalities are available only in diagnostic imaging departments and are more costly than TVS. However, their selective use may help improve the diagnostic evaluation, especially in disorders that may have only subtle sonographic findings such as adenomyosis. MRI and CT might be better suited for initial staging or workup of certain neoplasms because they can both better delineate retroperitoneal structures such as lymph nodes and images can be obtained in a variety of scan planes that may not be obtainable with US.

This chapter discusses and illustrates the common uses of these imaging modalities in evaluation of a variety of gynecologic disorders. The subsections are divided according to the most common indications for imaging evaluation of gynecologic disorders. Additional information can be found in several texts that provide more extensive coverage of this topic.

SONOGRAPHIC INSTRUMENTATION AND TECHNIQUE

A unique feature of US is that it allows orientation from an internal perspective rather than one based on external landmarks. In other words, the uterus, for example, can be viewed not just in cross-section but in its normal longitudinal orientation, much closer to the real anatomic orientation. US uses sound waves at various frequencies to allow imaging of internal organs or vessels. The sound waves emitted by the transducer are transmitted through the soft tissue and reflect off any perpendicular tissue/fluid interface and return (much like a sonar) to the transducer while a portion of the sound waves continue through until they encounter another perpendicular tissue/fluid interface and send back a reflected echo delayed in time. The US machine collates the information from the returning sound waves based on their return time and intensity and reconstructs a two-dimensional image. Both the origin of the signal, the transducer, and the receiver are contained in the same unit. Simplistically speaking, three-dimensional ultrasonography (3DUS) uses computer software to rapidly collate multiple two-dimensional images into a three-dimensional image.

The most commonly used probe or transducer configurations are those in which transducer elements are rotated (mechanical sector) and those that are made up of multiple send–receive sub-elements, in which the beam is formed by selective electronic activation (curvilinear or phased array). Other recent technologic advances allow newer US machines to make use of the physics principle known as the Doppler effect. This principle states that sound or light waves reflected by a moving object will undergo a change in frequency proportional to the relative velocity of that object, toward or away from the transducer. Detecting these frequency changes can help determine the blood flow through vessels coming to or from a structure being imaged.

US is particularly useful in defining the internal acoustic characteristics of a structure, thus distinguishing fluid-filled structures from solid structures. This makes US the imaging modality of choice in evaluating the ovary and any associated cysts or neoplasms. This imaging technique is not as well adapted to distinguish solid structures from other adjacent, or surrounding, solid structures. A perfect example of this is the ease at which an intrauterine gestational sac can be seen while a comparably sized intracavitary uterine polyp or fibroid can be quite difficult to distinguish from the adjacent endometrium or myometrium.

Diagnostic sonography of the pelvic organs can be performed using the transabdominal sonography (TAS) approach in which the uterus and adnexa are imaged through a distended urinary bladder or transvaginal sonography (TVS), in which the probe is inserted into the vagina for imaging of the uterus and ovaries. In general, the lower the frequency emitted by the US transducer, the further the penetration and the deeper the window of visibility. Therefore, TAS ordinarily uses lower frequency sound waves (3.5–5.0 MHz) to allow for the deeper penetration required to visualize underlying structures beneath a layer of subcutaneous and adipose tissue through the bladder. A TAS is useful in fully assessing the uterus if markedly enlarged or severely anteverted. Due to problems visualizing the pelvic organs through intervening tissues such as small and large bowel as well as the anterior abdominal wall, the transabdominal approach is best performed with a fully distended urinary bladder enabling a better global depiction of the uterus and adnexa (Fig. 28.1). Despite this, TAS is limited by body habitus and intervening bowel or fat that tend to increase artifact and scatter the incident US beam. In general, TAS is best used for large masses such as fibroid uteri that extend out of the pelvis above the urinary bladder. Occasionally, the ovaries of some women can be better imaged transabdominally than with a transvaginal probe, in particular those that are high in the pelvis, are adjacent to an enlarged uterus, and are very anteriorly located.

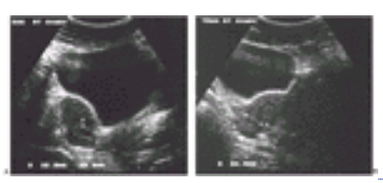

FIG. 28.1. Transabdominal sonography. **A:** Parasagittal image through right adnexal region showing right ovary (between *cursors*) and normal uterus. **B:** Parasagittal image in the transverse plane showing the transverse dimension of the right ovary (between *cursors*).

TVS uses higher frequency sound (5–8 MHz) which allows higher image resolution at the sacrifice of not being able to penetrate and “see” clearly objects more distant than 10 cm. The higher frequency sound waves used in TVS give much better definition because of the closer proximity of the transducer to the structures being imaged, although there is limited penetration. TVS is also an optimal modality with which to image obese women who have a large amount of adipose tissue in the anterior abdominal wall because the US transducer is positioned immediately adjacent to the uterus and ovaries. For most applications a tightly curved transducer probe that has high line density affords the most detailed image (Fig. 28.2). It becomes increasingly difficult to see the fundal region of the uterus as the uterus leaves the pelvis, as in the case of the large fibroid uterus. By contrast, the transvaginal component of an examination of the uterus and associated fibroids can typically better establish the relationship or proximity of the fibroids to the endometrial cavity than can TAS alone. Visual clarity with TVS is usually superior when imaging ovarian abnormalities as compared to TAS and can also be helpful as a means of distinguishing between ovarian and uterine masses. In addition, TVS with Doppler sonography affords assessment of flow of vessels adjacent to and within the uterus and ovaries.

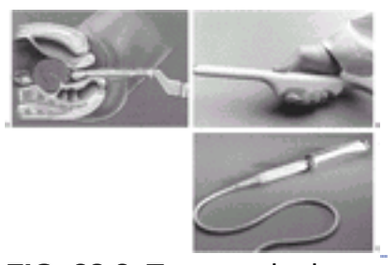

FIG. 28.2. Transvaginal sonography. **A:** Diagram showing transvaginal probe adjacent to cervix in a retroflexed uterus. (Drawing by Paul Gross, MS.) **B:** Picture of tightly curved curvilinear array transvaginal transducer probe. **C:** Flat-faced transvaginal probe with needle guide attached to the shaft.

To perform TVS, the patient is placed in the lithotomy position. After the probe is wiped with a disinfectant, it should be covered by a latex sheath before insertion into the vagina. Nonlatex vinyl covers are also available for those women allergic to latex. For optimal patient comfort, the probe should be inserted into the vagina while the operator's finger gently depresses the posterior introitus. The orientation on the screen for TVS is by convention displayed with the apex of the image at the top of the monitor. A US examination must be thorough and reproducible; for this reason, most would suggest performing each US following the same order and same routine. A complete pelvic US examination begins with images of the uterus as the central pelvic landmark in both long and short axis. The probe can be withdrawn into the midvagina and directed anteriorly to provide short-axis views of a uterus that is anteflexed. The retroflexed uterus is easily imaged without major manipulation of the probe because it is in the anatomic plane of the vagina, though some vaginal probes angle the US beam superiorly making this somewhat more difficult or uncomfortable for the patient. The operator can then orient the probe into the adnexal regions using the internal iliac artery and vein as landmarks for elineation of the ovarian fossa. The normal ovary can usually be found within close proximity to the internal iliac artery and vein but there is substantial variation in the location of the ovaries, particularly in women who have undergone hysterectomy or who have enlarged ovaries. Typically, enlarged ovaries or ovaries with cysts are relatively easy to identify while the normal postmenopausal ovary might be more difficult to visualize. The operator can use one hand to mildly compress the abdominal wall and evaluate the mobility of these organs. If there are no adhesions, the uterus and ovaries should move smoothly away from each other as the probe is advanced. This has been termed the “sliding organ sign” and, if absent, may suggest the presence of agglutinating pelvic adhesions.

Transvaginal color Doppler sonography (TV-CDS) combines the anatomic information provided by TVS with flow information provided by CDS. This probe and attached equipment are more expensive than the standard TVS scanner and do not improve acoustic visualization; rather, they allow detection of flow within blood vessels. However, TV-CDS can provide additional information that is useful in evaluating some patients with pelvic masses (Fig. 28.3). The TV-CDS involves assessment of flow within the uterus and adnexal structures. The flow to or within a structure can be quantified by analysis of the waveform using either resistive index, which is maximum systolic velocity–minimum systolic velocity, divided by maximum systolic velocity. Alternatively, the pulsatility index, which is maximum systolic velocity–maximum diastolic velocity, divided by the mean velocity, can be used. These parameters are unitless values and angle-independent parameters of relative impedance to forward flow. One must obtain signals between 30 and 60 degrees of the angle of the vessel in order to provide optimal waveforms. Waveforms reflect the change in frequency over time, which is related to flow velocity (i.e., the Doppler effect). Standard, frequency-based color Doppler is encoded with red colors indicating flow toward the transducers or blue colors indicating flow away from the transducers. A new type of processing known as *amplitude* or *power Doppler* allows determination of overall blood flow. It is more sensitive than frequency-based measurements but is degraded by motion.

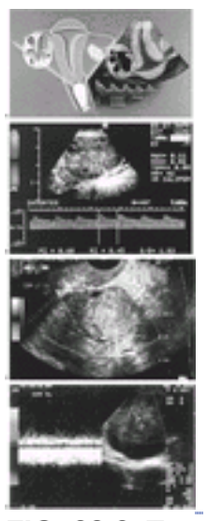

FIG. 28.3. Transvaginal color Doppler sonography (TV-CDS). **A:** Diagram showing the components of a TV-CDS, which include real-time imaging and display of vessels, with subsequent selection of sample volume for Doppler analysis by evaluation of the Doppler waveform. (Drawing by Paul Gross, MS.) **B:** TV-CDS showing low-impedance flow (resistive index = 0.45; pulsatile index = 0.60) within the wall of a corpus luteum. See color figure 28.3.

The technique of TV-CDS is highly operator-dependent but can provide important information as to the character of the blood flow in the uterus and adnexal structures. Depending on the clinical indication, the examination should include evaluation of arterial and venous blood flow to and within the uterus and ovaries. There is a range of sensitivity to flow between scanners from different manufacturers and there is no minimal clinical standard.

Documentation of US studies performed, particularly in an office setting, represents a major issue. Hard copy images should be included as part of the patient's medical record. In the past, hard copy images or videotaping of the study were the only ways to objectively document what was found. More recently, many have begun digitalizing the images and storing them on optical or compact disk devices. This method of documentation and storage of US images has the advantage of being readily available for review without loss of image quality over time. When digital storage of images is used, there should always be safeguards in place to avoid loss or destruction of the information saved, a standard no different than what we should adhere to with hard copy images. US is, to some extent, subjective and attempts to document results of a US are incomplete without a narrative description of the overall impression by the operator.

While becoming more widely available and used in obstetric practice, the clinical value of 3DUS in gynecology over the standard technique has yet to be proven. It has been shown to be efficient and accurate in detecting müllerian abnormalities (Fig. 28.4) and shows promise in some urogynecologic applications. Some investigators have shown 3DUS volumetric measurements of embryonic pole and gestational sacs to be predictive of pregnancy outcome, while others have shown that 3DUS may enhance sensitivity in the diagnosis of ovarian neoplasms. It appears likely that 3DUS will be more frequently used in the future as its role is further clarified and accepted or proven to be of benefit in specific clinical circumstances.

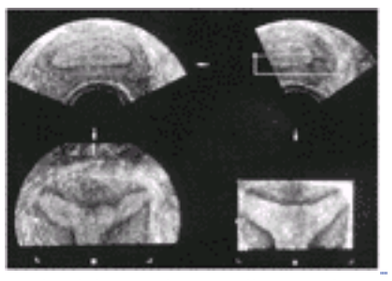

FIG. 28.4. Three-dimensional ultrasound examination of a septate uterus. **Upper left:** Transverse view of the uterus at the plane indicated. **Upper right:** Uterus in the longitudinal plane. **Lower left:** Coronal section. **Lower right:** Composite three-dimensional rendering that can be manipulated with computer software in a variety of ways, enhancing diagnostic accuracy.

Abnormal Uterine Bleeding

TVS has an important role in the evaluation of women of reproductive age presenting with unexplained uterine bleeding. TVS can help distinguish dysfunctional uterine bleeding (i.e., hormonally related) from mechanical or anatomic sources of abnormal bleeding (i.e., uterine leiomyomas, polyps, retained IUD, etc.). Because of the proximity of the transvaginal probe to the uterus, the endometrial and myometrial architecture can be accurately depicted in detail in most patients. However, high resolution delineation of the uterus requires proper imaging technique. For example, because the endometrium is not a precise geometric shape, operator error can account for over- or underestimation of its thickness. Thus, it is of utmost importance to orient the scan of the endometrium for measurement purposes in its greatest long-axis plane and maximal thickness in the fundal region, which optimizes its bi-layer measurement (Fig. 28.5). Saline infusion sonohysterography (SIS) has become an important and effective adjunct to standard TVS and replaced more costly procedures such as pelvic MRI. The endometrial cavity is a potential space where the opposing anterior and posterior uterine walls are normally in contact with, but not adherent to, each other. A fibroid or polyp within the endometrial cavity is often difficult to visualize on standard TVS because its US characteristics are similar to the contacting endometrium or myometrium. SIS uses saline as an acoustic contrast medium that distends the endometrial cavity and that enables visualization of any structures within the space in greater detail than with TVS alone where both uterine walls are in contact (Fig. 28.6). With saline infused into the cavity, the walls of the uterus separate and polyps or intracavitary fibroids that might otherwise have been missed are readily visualized. SIS also has been shown to be useful in evaluating müllerian abnormalities such as distinguishing uterine septa from a bicornuate uterus.

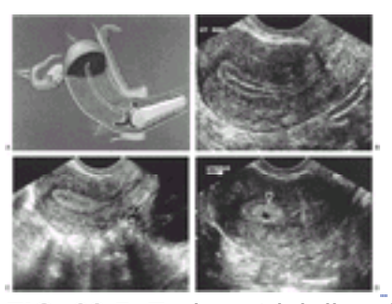

FIG. 28.5. Endometrial disorders. **A:** Diagram showing proximity of the endometrium of an anteflexed uterus to the transvaginal probe. The field of view depicting the long axis of the uterus and endometrium is shown. (Drawing by Paul Gross, MS.) See color figure 28.5A. **B:** Transvaginal sonogram showing multilayered endometrium typical of follicular phase endometrium. **C:** Typical secretory phase endometrium demonstrating increased thickness (between cursors) and homogeneous echogenicity. **D:** Echogenic mass (*arrowhead*) within endometrium containing punctate cystic area representing an endometrial polyp.

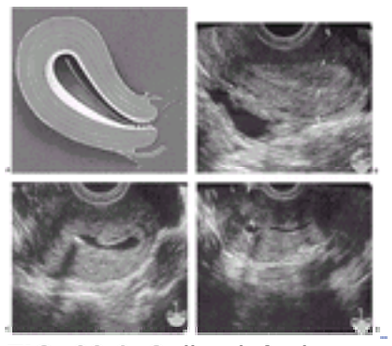

FIG. 28.6. Saline infusion sonohysterography (SIS). **A:** Diagram showing intrauterine catheter used for distension of lumen with saline for detailed evaluation of the endometrium from the inside. (Diagram by Paul Gross, MS.) See color figure 28.6A. **B:** Standard transvaginal ultrasonography showing a secretory phase endometrial stripe. **C:** Same uterus evaluated with SIS revealing an anterior endometrial polyp not seen with standard sonography. **D:** SIS revealing intrauterine synechiae with saline having filled above and below the adhesion. On standard sonography the endometrial stripe appeared normal, with a 6-mm thickness.

Clinically, it is important to remember that the differential diagnosis of premenopausal women presenting with bleeding is different from bleeding seen in postmenopausal women. In general, premenopausal bleeding is usually associated with anovulation or some mechanical factor such as intracavitary fibroids or endometrial polyps, whereas a variety of pathologies including atrophic endometritis, hyperplasia, and endometrial carcinoma are most common in the postmenopausal woman.

In women of childbearing age, the endometrial thickness varies according to the stage of the menstrual cycle. During menses, the normal endometrium is 3- to 5-mm thick with a mildly echogenic texture. Real-time examination of the endometrium while a patient is menstruating will often allow visualization of myometrial contractions associated with an efflux of solvent. As the endometrium proliferates in the periovulatory period, a multilayered texture can be seen with thicknesses ranging from 5 to 8 mm. The outer echogenic layer represents the basalis, whereas the inner layer is the enlarging functionalis. In the secretory phase, the endometrium becomes diffusely echogenic and enlarges up to 12 to 14 mm in thickness.

No specific US findings confirm anovulation as the cause of abnormal bleeding. In essence, all other potential anatomic or pathologic sources of bleeding must be excluded before arriving at the diagnosis of dysfunctional or anovulatory uterine bleeding. There are several US findings that are suggestive of an intracavitary abnormality that might be the source of abnormal bleeding such as a thickened endometrium, an endometrial stripe that is distorted, or an acoustic appearance that is not uniform or is heterogenous.

Uterine fibroids are clonal expansions that disrupt the normal arrangement of the myometrial bundles and are typically hypoechoic or of mixed echogenicity when compared to normal myometrium. Some fibroids contain calcifications that appear as areas of high acoustic reflection similar to that seen in bone. The pedicle of a subserosal fibroid can often be demonstrated during scanning and palpation of the mass relative to actual uterine body. The effect of submucosal fibroids on the endometrium can be assessed by visualizing the endometrial stripe in the area immediately adjacent to the fibroid. Submucosal fibroids typically displace and thin the overlying endometrium, something best visualized with SIS. Occasionally, fibroids may be present as solid masses in the adnexal regions, representing either interligamentary or pedunculated tumors. Endometritis usually produces a thickened endometrium sometimes surrounding intraluminal fluid but neither of these findings is pathognomonic. Intraluminal fluid may be seen in postmenopausal women and is usually a benign finding as long as the single-layer thickness of the endometrium is less than 4 mm. Intracavitary fluid collections due to a hematometra or pyometra may also be seen in the presence of cervical stenosis, particularly in the setting of secondary amenorrhea.

One of the more valuable roles of TVS is evaluating unexplained bleeding in the postmenopausal woman. Typically, an endometrial stripe thickness of less than 3 mm is observed in postmenopausal women not on hormone replacement therapy (HRT) and 2- to 3-mm thicker in those on HRT. In patients with a thickened or highly echogenic endometrium, TVS can suggest the presence of abnormal histology such as hyperplasia or endometrial polyps, but it is not histologically specific. That is to say, there is no endometrial stripe thickness above which carcinoma or hyperplasia is always found and conversely no thickness below which cancer is never encountered. Many studies have been published assessing whether there is an optimal cutoff below which one can safely presume a low likelihood of pathology and avoid invasive diagnostic procedures to assess endometrial histology. Earlier meta-analyses concluded that using 5 mm as the cutoff, irrespective of whether the patient was on HRT, resulted in a sensitivity of 92% in identifying any endometrial pathology and 96% for detecting carcinoma. An endometrial thickness of less than 5 mm was associated with a significantly reduced risk of an underlying carcinoma. More recent literature suggests that this 5-mm cutoff is not as reliable. For this reason,

especially in the face of continued bleeding or in a high-risk patient, tissue sampling should always be considered.

Pelvic Mass

Sonography provides a means to evaluate the size, location, and internal acoustic characteristics of pelvic masses (Fig. 28.7). Larger masses (over 10 cm) may best be delineated using TAS. TVS provides important information about the location of the pelvic mass relative to the ovary and uterus and provides higher resolution for better delineation of the internal architectural characteristics compared with TAS. CDS can assess vascular integrity in cases of possible torsion or detect neovascularity, helpful in predicting whether a mass is benign or malignant. This is less frequently performed in an office setting due to the expense of a US unit with CDS capability and the high level of training required to perform CDS. A general outline of diagnostic considerations according to location and internal acoustic characteristics is shown in Table 28.1.

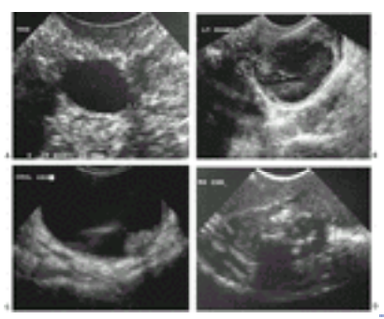

FIG. 28.7. Pelvic masses. **A:** Transvaginal sonogram of a smooth-walled cyst (between cursors) exhibiting the sonographic features consistent with a functional or physiologic cyst. **B:** Hemorrhagic corpus luteum with organized hemorrhage containing thin fibrin strands and internal echoes within the mass. **C:** Papillary excrescence arising from the wall of a mostly cystic ovarian mass. This morphologic feature is highly suggestive of cancer. **D:** Mass containing several echogenic foci and solid areas indicative of a dermoid cyst.

TABLE 28.1. *Differential diagnoses of pelvic masses by TAS and TVS*

Any woman of childbearing age can have a physiologic or functional “cyst” present when undergoing TVS. Most of these functional “cysts” demonstrate fluid free of internal echoes and smooth walls. The cysts have no internal septations and are typically less than 5 cm in size. In the follicular phase, there may be multiple unilocular cysts less than 2 cm in size that represent the pool of available developing follicles from which a dominant follicle is selected. Following ovulation, this dominant follicle becomes a corpus luteum, which is also typically a smooth-walled unilocular “cyst” but with more internal echoes. Labeling these physiologic structures “cysts” is the source of a great deal of unnecessary concern for women that can be best avoided by using terms such as “follicle” instead of “cyst” or by emphasizing the fact that these are completely normal findings in women of reproductive age. In the absence of abnormal or suspicious US findings or in the absence of symptoms such as continuing pelvic pain, repeat sonography of physiologic or functional-appearing cysts found on US is unnecessary.

Up to 15% of asymptomatic postmenopausal woman have been shown to have simple ovarian cysts with acoustic characteristics associated with benign histology. Indeed, one of the pitfalls of the readily available office US may be that incidental masses might be found in this age group, prompting unnecessary surgery. It has been shown that the risk of malignancy in unilocular cysts with a mean diameter less than 5 cm is very low in both premenopausal and postmenopausal women. Conservative management should therefore be the method of choice for women with such cysts identified by TVS. Larger “unilocular” simple cysts have been shown to have higher rates of actually having small papillations or internal growths that were undetectable by TVS and higher rates of malignancy, and thus warrant surgical excision

In the premenopausal woman, it is important to differentiate functional cystic masses that may spontaneously regress from ovarian neoplasms that will persist or continue to enlarge. Hemorrhagic corpus luteum cysts typically exhibit thin fibrin strands of echogenic material within a mostly hypoechoic mass contained by a somewhat thickened and irregular wall. On the other hand, the presence of a papillary excrescence or irregular and thickened internal septations is more indicative of ovarian neoplasms. The morphologic findings of early ovarian cancers can be subtle, but persistent internal septations with irregularity suggesting papillations, especially with any increase in peritoneal fluid, suggests the possibility of malignancy and warrants surgical intervention.

Although the sonographic appearance of masses are typically nonspecific and cannot give a precise diagnosis, there are a few patterns that demonstrate relatively high specificity. One of these is the “ground glass” appearance of an ovarian endometrioma, the other is the echogenic focus seen within benign cystic teratomas. With the improved resolution of modern US scanners, it is not uncommon to see small teratomas that appear as heterogenous echogenic regions within a normal ovary. If a dermoid cyst is found in one ovary, it is important to evaluate the contralateral ovary carefully because approximately 15% of patients have bilateral dermoid cysts.

The TV-CDS provides an adjunctive evaluation of patients with pelvic masses to help lessen the potential of the mass being malignant (Table 28.2). For best results, the TV-CDS findings need to be correlated with morphologic and clinical findings. Although the technique has some limitations, it is helpful in preoperative assessment of women with pelvic masses. Depending on the patient population studied, diagnostic accuracies in the 80% to 90% range have been reported. There is some overlap of impedance values between some functional and neoplastic ovarian cysts. Even so, in the proper clinical setting, TV-CDS improves the confidence in distinguishing benign from malignant lesions over that possible with TVS alone. Malignant lesions tend to have abnormally low-impedance flow, a sign of decreased vascular impedance seen in neovascularity of tumor vessels (see Fig. 28.3) with clusters of vessels in morphologically abnormal areas. The TV-CDS test has better sensitivity in the postmenopausal age group because the prevalence of ovarian cancer is higher at this age and because benign masses, which may also demonstrate low-impedance flow (pelvic inflammatory disease, endometriosis, or hemorrhagic corpora lutea), are far more prevalent in the premenopausal age group.

TABLE 28.2. *Sonographic features of benign and malignant pelvic masses*

To date, no single screening test or combination of surveillance modalities has been shown in a well-conducted clinical trial or even through substantial indirect evidence to reduce ovarian cancer mortality. The major limiting factor in screening for ovarian cancer is its low prevalence. Methods that have been extensively investigated for ovarian cancer screening have included serum tumor markers, primarily serum CA125, and TVS. For women with a known germline mutation (*BRCA1* or *BRCA2*) or with a family history suggestive of a significant possibility of a genetic predisposition to a heightened ovarian cancer risk, an effective screening strategy remains to be developed. Given the high risk in this population, most experts advocate multimodality screening with serum CA125 levels and TVS in patients who elect to delay or decline prophylactic oophorectomy.

Pelvic Pain

TVS plays an important role in evaluating patients with acute pelvic pain (Fig. 28.8). Demonstrably normal-appearing ovaries with no free intraperitoneal fluid on TVS virtually eliminate a primary ovarian source for acute pain. The uterus can be evaluated sonographically and pathologic causes of pelvic pain such as uterine fibroids, with or without degeneration, can be ruled out. TVS is relatively poor at identifying peritoneal endometriosis that is more commonly seen in the setting of chronic pain but is excellent at detecting ovarian endometriomas which can rupture and cause an acute exacerbation. If present, TVS can detect ovarian enlargement with a high degree of sensitivity. Care must be exercised, however, as presence of an enlarged ovary does not necessarily correlate with presence of symptoms. Tuboovarian

abscesses can easily be visualized by TVS and the diagnosis considered in the presence of pelvic pain, fever, and complex adnexal masses.

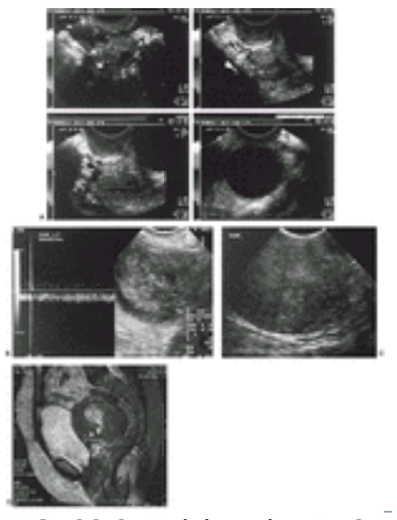

FIG. 28.8. Pelvic pain. **A:** Composite transvaginal sonogram showing enlarged left ovary (*top right* and *bottom left*) without flow and associated with a paraovarian cyst in left adnexa (*lower right*). The right ovary (*top left*) was normal, showing intraparenchymal flow. The left adnexa was found to be twisted three times and was surgically untwisted with good result. See color figure 28.8A. **B:** Doppler sonogram of enlarged left ovary containing venous flow. This finding suggests potential viability of this partial ovarian torsion. **C:** Irregular echogenic area within myometrium suggestive of adenomyosis. **D:** Sagittal T2-weighted magnetic resonance image confirming the presence of adenomyosis in the fundal region.

Ovarian torsion, a surgical emergency, must be eliminated as a cause of acute pelvic pain when a tender mass is noted on pelvic examination. TVS can confirm the presence of a complex adnexal mass and allow assessment of its size and internal acoustic characteristics. CDS provides additional useful information by determining whether there is normal blood flow to the ovary. Because venous flow is the first function affected by torsion, CDS is helpful in determining its presence or absence in an enlarged, edematous ovary. The absence of venous flow suggests the possibility of torsion in a properly performed CDS examination. It is important to examine flow in the contralateral ovary to confirm that the absence of flow is a real finding and not an artifact produced by improper color priority settings on the US machine. The CDS findings in ovarian torsion will also depend on the degree of vascular compromise and chronicity of this disorder. Intermittent ovarian torsion cannot be eliminated as a potential cause of pain even with demonstrable blood flow on CDS, though it will confirm the presence of a pelvic mass without which torsion is unlikely. CDS can also be used to confirm the reestablishment of flow after surgical detorsion. Isolated torsion of a paraovarian cyst is an infrequent event but is manifested on US by a cystic structure separate from, but adjacent to, the ovary that has absent or reversed diastolic flow.

One of the most common causes of acute pelvic pain is a hemorrhagic ovarian cyst. Blood within the hemorrhagic cyst can have several sonographic appearances. Fresh or acute bleeding within an ovarian cyst can appear echolucent. Organized clot has a more heterogenous and echogenic appearance. The hemorrhagic component typically demonstrates no flow, whereas the surrounding normal ovary has both arterial and venous flow. Free peritoneal fluid from a ruptured hemorrhagic cyst can also be observed and is certainly not rare as a cause of acute pelvic symptoms as blood is irritating to the peritoneal lining. Other ovarian neoplasms, such as endometriomas and benign cystic teratomas, can also rupture leading to peritoneal irritation accompanied by acute pelvic pain.

Often, pelvic pain originates in the uterus. Degenerating fibroids may cause severe midline pelvic pain most often seen during pregnancy. TAS or TVS can confirm the presence of fibroids though there is no specific US appearance of a fibroid with degeneration. However, the presence of fibroids on US does not necessarily mean that they are the cause of the pain as asymptomatic fibroids are quite prevalent in the general population. Adenomyosis is a cause of acute pelvic pain and may produce subtle findings that can be seen on TVS which include irregular echogenic areas in the subendometrial myometrium. Rarely, actual cystic spaces within the myometrium are seen. It can be difficult to distinguish adenomyosis or an adenomyoma from an intramural leiomyoma. The vascularity associated with adenomyosis is usually diffuse compared to that of a fibroid, but it can mimic the vascularity surrounding fibroids in appearance. Contrast-enhanced MRI has been most often used to detect the presence of adenomyosis.

When evaluating acute pelvic pain, one must also consider nongynecologic causes of pain such as appendicitis and renal calculi. An understanding of pathologic findings possible in these settings is important. On TAS, an inflamed appendix will appear as a noncompressible fusiform structure in the right lower quadrant that has a thickened (over 6 mm) wall. When ruptured, fluid may be seen surrounding the abnormal appendix. US can also detect hydronephrosis suggestive of ureteral obstruction that may accompany ureterolithiasis. In the hands of skilled operators, TAS may be able to localize renal calculi in the distal ureter in some patients; these will appear as a highly echogenic focus within the ureter. If a ureteral jet is clearly seen within the urinary bladder on CDS, ureteral patency can be confirmed and complete ureteral obstruction ruled out.

Ectopic Pregnancy

Prior to the advent of sensitive ß-human chorionic gonadotropin (ß-HCG) assays and US, the diagnosis of ectopic pregnancy was most often made after the tube had ruptured and the patient became hemodynamically unstable with an acute abdomen, necessitating immediate laparotomy. With TVS and sensitive ß-HCG assays, ectopic gestations are often diagnosed prior to the onset of symptoms, making a ruptured ectopic pregnancy much less common and providing an opportunity for medical management with methotrexate. TVS provides an accurate means for detection of ectopic pregnancy (Fig. 28.9). An ectopic pregnancy will often not be observed on TVS, but its presence may be presumed based on the absence of an intrauterine gestation in the face of a quantitative ß-HCG measurement above a “discriminatory zone,” generally (depending on the assay) around 2,000 mIU/mL. In identifying or evaluating an intrauterine fluid collection, care must also be taken to distinguish a true gestational sac from a collection of blood termed a “pseudosac.” Classically, a “double ring” sign within the uterine cavity is consistent with an intrauterine pregnancy (IUP) but the presence of either a yolk sac or fetal pole within the intrauterine fluid collection is diagnostic. There are certain clinical settings in which this discriminatory zone may be less reliable such as after a recent spontaneous abortion or where there is a multiple gestation. In the absence of assisted reproductive technologies (ARTs) (controlled ovarian hyperstimulation [COH] or in vitro fertilization), finding an IUP effectively eliminates the risk of ectopic pregnancy. In patients who have undergone controlled ovarian hyperstimulation or in vitro fertilization, heterotopic pregnancy rates are as high as 1 in 100.

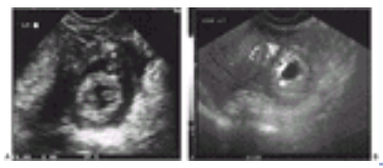

FIG. 28.9. Ectopic pregnancy. **A:** Unruptured ectopic pregnancy appearing as a “tubal ring” in left adnexa. **B:** Transvaginal color Doppler sonogram showing vascularity of “tubal ring” of an unruptured ectopic pregnancy. See color figure 28.9.

On TVS, ectopic pregnancy should be suspected in the presence of a cystic circular structure in the adnexa separate from the ovary in women in whom an IUP cannot be detected. The “tubal ring” is an indication of an unruptured ectopic pregnancy when not associated with surrounding fluid. One should be able to differentiate a corpus luteum or hemorrhagic ovarian cyst from an ectopic gestation in that the corpus luteum can be delineated to be within the contour of the ovary. Another finding associated with ectopic pregnancy is the presence of intraperitoneal fluid; indeed, this is one of the more sensitive findings in patients who will require surgical intervention. The presence of intraperitoneal fluid combined with an extraovarian adnexal mass in a pregnant patient without an intrauterine gestation should be viewed as a surgical emergency. Careful examination of the uterus with TVS can also help identify cornual and cervical ectopic pregnancies as well as aid in the diagnosis of abdominal pregnancy.

CDS may provide an additional means for delineation of ectopic pregnancies based on blood flow. The CDS provides a vascular “road map” separating the ovary from other adnexal structures. The vascularity of ectopic pregnancies varies from hypovascular to hypervascular depending on the viability of the ectopic gestation. The “tubal ring” of an ectopic pregnancy will most often have increased vascularity with blood flow present circumferentially, or nearly so. If present, this “ring of fire” is highly suggestive of ectopic pregnancy. While there are no specific or unique waveforms that arise from ectopic pregnancies, a waveform showing reversed diastolic

flow can be seen in ectopic pregnancies with necrotic trophoblastic tissue.

Infertility

TVS can provide important information in the evaluation of the infertile patient (Fig. 28.10) and is indispensable in the management of COH induced by parenteral gonadotropins necessary for modern ARTs such as in vitro fertilization. During COH, TVS is used in the serial assessment of follicular maturity as well as for the evaluation of the thickness and texture of endometrium. The number of follicles and their size can be determined, with mature preovulatory follicles measuring between 18 and 20 mm. In the periovulatory period, the endometrial thickness is typically 7 to 11 mm and a trilaminar appearance of the endometrial stripe has been associated with higher rates of implantation. Prior to the widespread use of TVS for oocyte retrieval, egg collection from mature follicles was accomplished by laparoscopy under general anesthesia. Today, oocyte retrieval is routinely accomplished by a TVS-guided, multi-follicle aspiration. In addition, TVS or TAS is used to monitor the transfer of embryos to the uterus at the completion of an in vitro fertilization cycle.

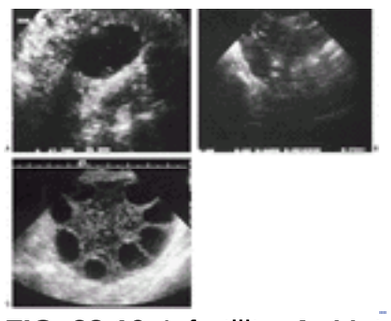

FIG. 28.10. Infertility. **A:** Mature follicle (between cursors) containing a small protrusion from the posterior wall representing the cumulus oophorus. **B:** Image taken during follicular aspiration showing echogenic needle tip within deflating mature follicle. **C:** Classic appearance of ovary seen in women with polycystic ovarian syndrome (“string of pearls”).

More recently, various investigators have used TVS in conjunction with uterine cannulation as a screening tool for assessing the endometrial cavity and tubal patency. Using various contrast media (including saline, as in SIS), the endometrial cavity can be evaluated for the presence of fibroids or polyps that may result in subfertility as well as for müllerian abnormalities such as a uterine septum often associated with recurrent miscarriage. In conjunction with SIS, the escape of saline out the fimbriated end of the tube is readily apparent in women with patent fallopian tubes as the cul-de-sac fills rapidly with fluid. The presence of cul-de-sac fluid during or after SIS confirms that at least one fallopian tube is patent. Attempts have been made to use CDS to assess in real time the efflux of echogenic contrast from each fallopian tube, with varying degrees of success.

SONOGRAPHICALLY GUIDED PROCEDURES

US can be very useful in assisting in difficult gynecologic procedures, particularly those involving the uterus. In cases in which dilation of the uterine cervix has been unsuccessful or more difficult than usual, simultaneous TVS or TAS can decrease the risk of uterine perforation and creation of a false tract. If perforation of the uterus is suspected, the path that the dilator or curette has followed, and its tip, can be readily visualized using sonography, as long as the instrument has not been moved once perforation is suspected. Traditionally, the internal US transducer was placed in the rectum or the abdominal transducer used to assist in directing the dilator as it traversed the cervix or confirmed the correct path to take. With the smaller transducers found on most vaginal US probes today, the transducer can usually be placed next to the cervix through an open speculum, particularly in patients whose cervix is flush with the vagina as in postmenopausal patients, or in those who have undergone cervical conization. Once the dilator is through the internal cervical os, TVS or TAS can localize the dilator or curette within the uterine cavity. Real-time monitoring of the procedure can virtually eliminate the risk of uterine perforation. US can also be helpful in monitoring a curettage being performed for the surgical management of either an incomplete miscarriage or early pregnancy termination. A US done at the end of the procedure can decrease the likelihood of the patient needing a second procedure at a later date by identifying those with an inadequate curettage. TAS monitoring of a mid-trimester abortion is critical to ensure complete evacuation of the uterine cavity and to decrease the likelihood of significant uterine or other organ injury. TAS can also be used to ensure correct placement of a uterine tandem being used for local radiation treatment of cervical or uterine cancer.

TVS can provide real-time delineation of the location of a needle relative to an area of interest within the ovary or adjacent structures (Fig. 28.11). For this purpose, a needle guide with an internal opening can be attached to the shaft of the vaginal transducer, which confines the course of the needle to a prescribed path in the exact plane of the two-dimensional scan. The most common use of this technique is transvaginal oocyte retrieval during an in vitro fertilization cycle, which is accomplished by aspirating individual follicles under direct US guidance. Cystic ovarian or adnexal masses may also be drained in this manner. Ovarian or adnexal masses that are amenable to transvaginal drainage include endometriomas (at the start of a controlled ovarian hyperstimulation cycle or when needed for the short-term relief of acute pain), symptomatic yet relatively small simple ovarian cysts (where there is no concern for malignancy), or hydrosalpinges (at the time of transvaginal oocyte retrieval for an in vitro fertilization cycle, particularly for those in whom surgical intervention is relatively contraindicated). Likewise, tuboovarian abscesses may be drained using the TVS-guided approach. In the case of endometriomas or hydrosalpinges, it is unlikely that transvaginal drainage will be curative, as they typically reaccumulate over time. If a cyst is drained and subsequently reaccumulates, only surgical excision will be curative.

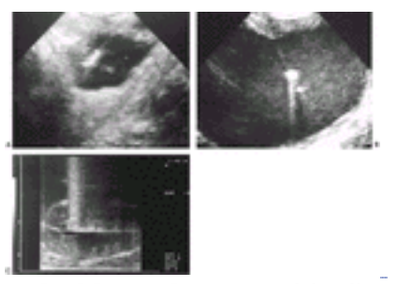

FIG. 28.11. Sonographically guided procedures. **A:** Guided aspiration of complex mass representing tuboovarian abscess. The needle tip is echogenic and within the abscess cavity. The patient defervesced after the procedure. **B:** Guided aspiration of large endometrioma. Note the classic “ground glass” appearance. The needle tip is easily seen within the mass. **C:** Transrectal sonography guidance for dilation and curettage in a patient with cervical stenosis. The curette is clearly within the lumen of the uterus.

OTHER IMAGING MODALITIES

MRI is an excellent, albeit expensive modality for secondary evaluation of a variety of pelvic disorders. These include adenomyosis, endometriosis, and certain pelvic masses such as benign cystic teratomas. The MRI provides global depiction of pelvic structures in selectable imaging planes, and it can identify lymphadenopathy associated with tumors. MRI can be particularly helpful in certain cases where it is not altogether clear if a pelvic mass originates from the ovary or from the uterus on physical examination or on US. MRI is also useful in clarifying müllerian abnormalities such as the bicornuate or septate uterus, although SIS appears to be equally effective. Enhanced MRI can also be helpful in assessing the extent of myometrial invasion in patients with endometrial cancer.

CT scanning is particularly helpful in the evaluation of the bony pelvis and has improved resolution and reduced scan times compared with MRI. Either MRI or CT may be used to delineate intraabdominal abscesses, though CT is often more readily available and less expensive. The presence of a rim-enhancing mass is diagnostic of an abscess.

SUMMARY POINTS

- Transabdominal and transvaginal scanning are both useful in establishing the source of abnormal uterine bleeding, characterizing pelvic masses found on physical examination, evaluating acute pelvic pain, diagnosing ectopic pregnancies, and assessing and treating infertility.
- Advances in technology such as higher transducer frequencies for improved resolution, rapid computerized assembly of two-dimensional images to yield virtual three-dimensional images, and smaller equipment have fostered wider clinical applications and made office use routine.
- US guidance during gynecologic surgical procedures has proved very useful in making difficult intrauterine procedures safer and diagnosing and treating selective pelvic masses by needle aspiration. It is the single most important advance in collecting oocytes for in vitro fertilization.
- Saline infusion sonohysterography has improved the diagnostic capability of TVS in circumstances of abnormal uterine bleeding.
- Pelvic US is the initial diagnostic modality of choice in most circumstances, whereas secondary tests such as CDS, MRI, and CT scanning provide a means to further enhance diagnostic specificity in difficult or nondiagnostic US studies.

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Chapter 29

Ann J. Davis

Pediatric and Adolescent Gynecology

EXAMINATION
Examination of the Prepubertal Child
Examination of the Newborn
Vulvovaginitis
Labial Agglutination
Lichen Sclerosus et Atrophicus and Other Chronic Skin Conditions
Vaginal Bleeding
Sexual Abuse
Precocious Puberty
ADOLESCENT GYNECOLOGY
Normal and Abnormal Puberty
First Gynecologic Visit
Abnormal Bleeding
Differential Diagnosis of Menstrual Disorders in Adolescents
Primary Amenorrhea
Dysmenorrhea
Pelvic Masses
Unintended Pregnancy
Contraceptive Patterns in Adolescents
Sexually Transmitted Diseases
SUMMARY POINTS

SUGGESTED READINGS
Pediatric Gynecologic Examination and Problems
Pediatric Sexual Abuse
Pelvic Masses and Endometriosis
Puberty and Menstrual Disorders

Pediatric and adolescent gynecology is frequently viewed as a single focused aspect of gynecology. In fact, these two areas are reasonably distinct, with a logical division being at the onset of puberty and the activation of the hypothalamic–pituitary–ovarian (HPO) axis. Prepubertal girls differ from postpubertal girls in anatomy, etiologies of similar symptoms, and the spectrum of likely and common syndromes. Both groups however require specific communication skills. Psychosocial and developmental milestones and characteristics help guide the obstetrician and gynecologist in how to communicate with each age group in an effective manner. Involvement of the family or adult caretaker is also critical in achieving the goals of providing excellence in gynecologic care. This chapter will discuss topics in both of these age groups, with an emphasis on the differences in children and teens as compared to mature reproductive women.

EXAMINATION

Examination of the Prepubertal Child

The genital examination of the prepubertal child should be approached quite differently from the gynecologic examination of an adolescent or adult. However, the complete exam may include all of the same elements as the examination of the more mature reproductive female: examination of the external genitalia, examination of the vagina and palpation of the uterus and adnexal structures.

Examination of External Genitalia It is often helpful to examine a toddler on her mother's lap while the mother elevates or abducts the child's hips for the so-called “frog leg position.” It is important to place the child on a towel or chuck pad in case urination occurs. An older child can sit straddling her mother's lap fully clothed while mother places her legs in the stirrups. Children between the ages of 4 and 6, and sometimes as young as 3, can position themselves in classic lithotomy with use of the stirrups. Clinicians can use their hands to provide lateral and downward traction on the area of the labia majora (Fig. 29.1). This will allow full visualization of the hymen and vaginal orifice.

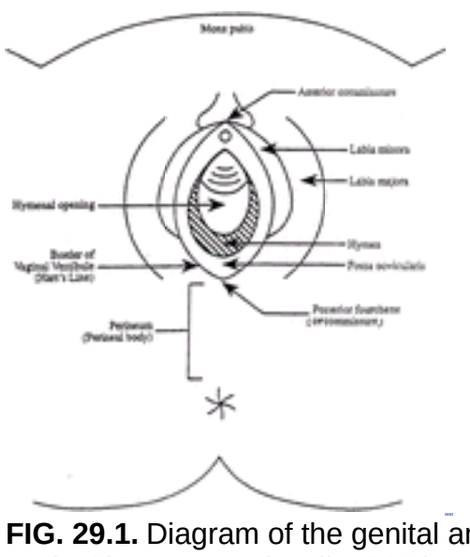

FIG. 29.1. Diagram of the genital anatomy of a prepubertal girl. This drawing shows a crescentic hymen. (From Pokorny SF. *Pediatric and adolescent gynecology.* New York: Chapman and Hall, 1996.)

Care should be taken to inform the child of the necessary steps of the exam. Continuously conversing with the child during the exam will allow her to relax.
Visualization of the Vagina Various positions have been described to visualize the vagina. In the very young infant or toddler a Valsalva maneuver can be helpful in the exam; the child can be asked to pretend she is blowing up a balloon or blowing out her birthday candles. This will often allow visualization of the distal 1 to 2 cm of the vagina. The knee–chest position is very helpful in the older child and can often be used in children 3 years of age and older. The child places her buttocks in the air with knees placed apart and allows her abdomen to sag. The examining physician and one assistant provide lateral and upward traction on the labia and buttocks. An otoscope can also be used as a magnification instrument and light source to shine into the vagina allowing visualization to the level of the cervix even without inserting the instrument. A vaginal speculum is neither appropriate nor indicated in the examination of the prepubertal child in the office (Fig. 29.2).

FIG. 29.2. The knee–chest position can be used to examine the vagina of a prepubertal child: the otoscope is used for a light source and magnification and *not* inserted into the vagina.

Examination of the Uterus and Adnexa Examination of the uterus and adnexa requires a rectal examination and should be reserved for the pediatric gynecology patient in which information regarding the uterus or adnexa is necessary in the evaluation. Rectal bimanual examination should not be done routinely in every child

requiring gynecologic examination. In prepubertal children the adnexa should not be palpable. In children, the ovaries lie at the level of the pelvic brim and drop into the pelvis with the onset of puberty. If an adnexa is palpable there is, by definition, an adnexal enlargement that will require swift and careful evaluation of a possible ovarian neoplasm. In the normal prepubertal child the uterus should be easily palpable on rectal examination. Prior to puberty two-thirds of the uterine volume is cervical in contrast to the one-third proportion in adults. The cervix, therefore, is a relatively easy structure to palpate on rectal examination in prepubertal children.

Examination of the Newborn

The obstetrician/gynecologist should be encouraged to observe the normal genitalia of the female infants that he or she delivers. Under the influence of maternal estrogens, the labia are generous in size, and the hymen is prominent and fimbriated or redundant in appearance. The female infant will sometimes experience an estrogen-withdrawal spotting episode within several days after birth. Mothers should be informed of this normal phenomenon in an effort to preclude maternal anxiety and even unnecessary visits to the pediatric emergency department (ED). In a series of pediatric patients seen in the ED of Cleveland's Children's Hospital for vaginal bleeding, the vast majority of those under the age of 2 were seen for this reason. These ED visits are completely avoidable through parental education.

Observation of the genitalia of female infants at birth allows the detection of various developmental and congenital abnormalities, some of which may be life threatening. If ambiguous genitalia are observed the obstetrician must use excellent communication skills in the delivery room to help set the stage for the evaluation of the infant and help decrease parental anxiety. The parents should be informed that the baby's genitals are not fully developed and a simple examination of the external genitalia cannot determine the actual sex. The parents should be told that they definitely have either a girl or a boy; but because development is not complete, data will have to be collected before they are told what sex the baby is and what treatment is required. Guesses must be avoided. It is critical to wait until all the information allows that the initial sex assignment given to the parents is the final and correct assignment.

The problem of ambiguous genitalia represents a social and potential medical emergency that is best handled by a team of specialists, which may include urologists, neonatologists, endocrinologists, and pediatric gynecologists. The differential diagnosis of ambiguous genitalia includes chromosomal abnormalities, enzyme deficiencies (such as 21-hydroxylase deficiency which is a form of congenital adrenal hyperplasia), and prenatal masculinization of a female fetus resulting from maternal androgen-secreting ovarian tumors or, rarely, drug exposures. The etiology of these problems, as well as intersex disorders that may be discovered in an older child can be complex.

The possibility of congenital adrenal hyperplasia (CAH) is especially critical to exclude. With the salt-wasting form of this disease, death can occur in the neonatal period so electrolytes should be immediately obtained. The presence of gonads in the labial scrotal folds in the infant with ambiguous genitalia eliminates the diagnosis of CAH.

One additional benefit of an observation of the genitalia of female infants at the time of birth is that some genital anomalies such as an imperforate hymen, vaginal agenesis, or other hymeneal anomalies (i.e., bands) may be diagnosed. Hymeneal abnormalities occur in less than 1% of newborn females and include imperforate hymens, cribriform hymens, and septate hymens. Normal hymeneal variations include hymeneal bumps, ridges, or bands. If there is any doubt about hymeneal patency, a rectal thermometer or small plastic catheter may be used to gently test for the vaginal space. Obstructive lesions include imperforate hymen, vaginal agenesis, or vaginal septa. The timing of repair of an imperforate hymen remains controversial. Some experts recommend repair at puberty after full estrogenization. Others repair imperforate hymens after the neonatal interval when convenient for the family. This approach may avoid anxiety during the critical preadolescent years of psychosexual identity if the girl perceives there is something wrong with her genitalia which is awaiting repair. In some cases a mucocolpos develops behind the imperforate hymen. This may be seen in the newborn in which the mucus production is under the direction of maternal estrogens, or at the time of breast budding in which endogenous estrogens orchestrate stimulation of mucus production. Rarely the mucocolpos may cause urinary obstruction that would necessitate urgent hymenectomy. Care must also be taken to delineate the exact anatomic nature of the obstruction and the clinician performing a hymenectomy should be comfortable that the obstruction is at the level of the hymen. Opening a thin imperforate hymen is a relatively easy surgical procedure, whereas the correction of other types of obstructive lesions such as vaginal septae requires careful planning, experience, and a high degree of skill.

Vulvovaginitis

Vulvovaginitis is the most common cause of vulvar symptoms in the prepubertal age group and the most common gynecologic complaint in prepubertal children. In children the primary site of infection is often the vulva; in contrast to mature reproductive women in which the vagina is usually the primary site of infection. Vulvovaginits in prepubertal children may be caused by specific pathogens including *Streptococcus pneumoniae, Neisseria gonorrhoeae, Chlamydia trachomatis, Shigella, Haemophilus influenzae*, and pinworms. More commonly however, the vulvovaginitis is nonspecific with no pathogenic organism responsible.

Cultures of the vagina in children with nonspecific vulvovaginitis will often reveal normal rectal flora such as *Escherichia coli*. Overgrowth of enteric bacteria can cause a primary vulvitis and a secondary vaginitis. In prepubertal children the normal flora may invade and irritate the vulvar area. This invasion in prepubertal children is due to several circumstances. First, the labia minora are thin and unestrogenized. Second, there is no anatomic barrier between the vaginal orifice and the anus since the labia majora are undeveloped and, prior to somatic growth, the anal and vaginal orifices are almost abutting one another. The unestrogenized vulva and vestibule normally appear mildly erythematous and may appear to be infected even when they are not if examined by clinicians unaccustomed to routinely examining prepubertal children. Smegma around and beneath the prepuce resembles patches of candidal vulvitis to the inexperienced examiner. The prepubertal vagina is alkaline in contrast to the acidity of the mature reproductive woman's vagina. At puberty, bacilli in the completely estrogenized vagina begin to produce larger amounts of lactic acid.

Presentation It is often difficult for a young child to describe vulvar sensations, but she may describe pruritis, pain, or a burning sensation. Parents sometimes note that the child cries during urination, scratches herself, touches herself frequently, or squirms when sitting in an effort to rub the sore vulva. Often, the child's pediatrician will have evaluated the child for a urinary tract infection (UTI) and pinworms. Vulvovaginal complaints of any sort in a young child should prompt the consideration of possible sexual abuse.
Diagnosis Most cases of vulvovaginitis are nonspecific. Specific pathogenic organisms should also be considered. When the initial presentation is compatible with nonspecific vulvovaginitis, some clinicians recommend proceeding with therapy without performing diagnostic tests. In cases where treatment was unsuccessful it is important to perform diagnostic testing for specific pathogenic organisms. This may include cultures of the vagina to rule out *S. pneumoniae, N. gonorrhoeae, C. trachomatis, Shigella*, and *H. influenzae.* Both *N. gonorrhoeae* and *C. trachomatis* cause a vaginitis rather than cervicitis in children so a vaginal culture is appropriate to exclude these pathogens. Use of DNA technology to diagnosis sexually transmitted diseases (STDs) in children is currently not recommended as a first-line diagnostic strategy by the Centers for Disease Control and Prevention (CDC). Use of indirect tests for STDs (such as enzyme-linked immunosorbent assay-based technology) is inappropriate in prepubertal children given the high possibility of false-positive results. Several methods of obtaining vaginal cultures from the vagina of children are applicable. One is insertion of a Dacron-tipped swab into the vagina moistened with nonbacteriostatic saline. Avoiding touching the hymen helps avoid any unnecessary discomfort to the child. Another method for obtaining cultures consists of placement of a catheter through which nonbacteriostatic saline can be injected, aspirated, and sent for culture.
Therapy The first step in treatment of prepubertal vulvovaginitis involves attention to vulvar hygiene and toileting. Proper wiping will decrease rectal flora in the vulvovaginal areas. In addition avoidance of vulvar irritants such as shampoo and deodorant soaps decreases the vulvar abrasion and irritation making it more difficult for the rectal flora to invade the vulvar epithelium. Sitz baths are very helpful in relieving symptomatology. Scrubbing the vulvar area should be avoided since this will only abrade the epithelium. Soaking the vulva clean is the preferable hygienic approach. A short course of broad-spectrum antibiotics can eliminate the overgrowth of enteric bacteria; however, unless the child changes her hygienic practices the nonspecific vulvovaginitis is likely to recur when colonization recurs.
Fungal Infections and Vulvovaginitis Fungal infections as a cause of vulvovaginitis are uncommon in prepubertal children. The prepubertal vagina is very alkaline and will not support fungal growth, which requires a more acidic environment. Exceptions to this rule may occur in immunosuppressed children such as organ recipients, children with human immunodeficiency virus (HIV), or children receiving high-dose steroids. Diaper rash, which may present with erythema, excoriations, and satellite lesions primarily outside the vulvovaginal area, is usually fungal related.

Labial Agglutination

Labial agglutination is another common presenting complaint in prepubertal children between 3 months and 6 years of age. These are the years of a nadir in circulating estrogens. The abraded unestrogenized labia minora agglutinate and form a telltale line at the point of the agglutination that is visible on genital examination. These girls sometimes complain of genital discomfort and dripping of urine. Urine can be trapped in the “pouch” behind the agglutination. Despite the fact that the urethra may not be visible on genital examination urinary obstruction is typically not a feature of this pediatric gynecologic problem.

Labial adhesions are extremely common, and usually asymptomatic. Some small degree of adhesions is seen in many 3- to 4-year old girls. Most experts agree that treatment should be reserved for symptomatic adhesions. The treatment consists of a short course of externally applied estrogen cream for several weeks. The area of agglutination will become thin and may spontaneously separate or can easily be separated in the office with the use of topical lidocaine jelly or anesthetic creams. It is critical that the estrogen be applied to the telltale line of adhesion and not lateral to the adhesion line. If pigmentation is seen lateral to the line of adhesion after estrogen application this indicates improper application of the estrogen cream. Manual separation of thick adhesions should not be done in the office, as it is very painful.

Attention must be given to the prevention of subsequent adhesions, as they clearly have a risk of recurring. One option is to recommend the use of a topical emollient,

such as vitamins A and D ointment to prevent reagglutination in a tapering-like manner after initial separation has occurred. Resolution of labial agglutination occurs at the onset of signs of endogenous estrogen production (breast budding).

Lichen Sclerosus et Atrophicus and Other Chronic Skin Conditions

Chronic skin conditions such as lichen sclerosus, seborrhea dermatitis, and atopic dermatitis may occur in young children. Lichen sclerosus et atrophicus (LSA) is a skin dystrophy usually seen in prepubertal girls or postmenopausal women. The appearance of LSA is consistent in both these age groups: a cigarette paper type of appearance in a figure-of-eight distribution around the vulva and anus, ending at the labia majora. Breaks in the integument with small blood blisters and abrasion are common, with inexperienced clinicians misinterpreting the condition as trauma possibly secondary to sexual abuse. LSA is particularly likely to occur in irritated vulvar areas in susceptible children. Appropriate first-line treatment in children is to prevent genital irritation and trauma. This may include avoidance of straddle activities, use of gel bike seats, and so forth. The extremely potent steroid (clobetasol) has been used in adults with success and is being used by experts in children despite a paucity of studies in this age group and the fact that clobetasol is not labeled for pediatric use. When this condition begins in childhood, it may regress with puberty, although this is not invariable.

Vaginal Bleeding

Vaginal bleeding in a prepubertal child warrants a careful investigation. The differential diagnosis of vaginal bleeding hinges on the absence or presence of other signs of pubertal development. In young children with breast development an evaluation for precocious puberty is warranted. Most children with genital bleeding will not have concomitant signs of pubertal development and local causes of the bleeding are probably present. The differential diagnosis in a child with genital bleeding without pubertal development is extensive and includes vulvar irritation/vulvovaginitis, *Shigella* vaginitis, breakdown of labial adhesions, urethral prolapse, malignant tumors of the vagina, foreign objects in the vagina, LSA, and sexual abuse.

Evaluation should include genital cultures, careful genital examination, and vaginal visualization. In cases that the vagina cannot be visualized in the office, or bleeding continues despite a negative exam, an examination under anesthesia is indicated. The exam should rule out foreign objects and rare malignant vaginal tumors (sarcoma botryroides and endodermal vaginal sinus tumors) primarily seen in girls less than 6 years of age.

Sexual Abuse

The possibility of sexual abuse should be considered in children presenting with a variety of presenting complaints including, but not limited to, vulvar vaginal symptoms, vaginal discharge, and genital bleeding. Sensitive but direct questioning of the parent or caretaker and the child by herself should be a part of any evaluation. The parent should be asked about any significant changes in behavior (such as the recent onset of nightmares, difficulties in school, changes in personality) that may accompany sexual abuse. Questioning the child who is verbal can be a useful “teachable moment” in which the physician explains the concept of the genital area as a “private zone,” and the idea that touching in this area should be reported to a parent. One concrete way to explain the “private zone” concept to a young child is to describe this as the areas that are covered by two-piece bathing suits. If the history is suspect or the injuries or physical findings are inconsistent with the reported history, a report must be made to the appropriate social service agency.

The possibility of sexual abuse must also be assessed in children presenting with genital bleeding. However it should be noted that the vast majority of children who have been sexually abused will have normal exams and not present with bleeding symptomatology. Furthermore, hymeneal size is not an accurate way to determine if a child has been abused. The genital examination in abused children usually does not differ from the exam in nonabused children. The child's history is of primary importance in the prosecution of sexual abuse. If forensic evidence is found, the source in the majority of cases is clothing and linens, which should always be collected in cases of recent assault.

Acute trauma and bleeding may result from a straddle injury or from sexual assault. Unintended trauma most commonly results in injury to the anterior vulva or laterally to the labia. Straddle injuries may result in the formation of a large vulvar hematoma, which may require evaluation. Penetrating injuries with transection of the hymen are most commonly the result of sexual assault. Any bleeding laceration of the vulva requires a careful examination to assure that there are no vaginal lacerations and to completely repair the injury. This may require an examination under anesthesia or the use of conscious sedation in the ED.

Precocious Puberty

Precocious puberty should be considered in children presenting with vaginal bleeding with or without other signs of pubertal development or in children presenting with early breast development or adrenarche. The definition of what is early development is changing. Data from a large study involving pediatric office practices indicate that African-American girls have an earlier onset of pubertal development than do Caucasian girls. Precocious puberty has traditionally been defined as pubertal development occurring before age 8. Data from pediatric office practices reveal that 27% of African-American girls and 7% of Caucasian girls had signs of breast budding or pubic hair development at age 7. Thus, the definition for precocious puberty should be reassessed in light of these data. Some experts recommend that precocious puberty be defined as breast budding prior to age 6 in African-American girls and prior to age 7 in Caucasian girls. Others argue that when other neurologic/behavior changes in African-American girls after age 6 or Caucasian girls after age 7 are associated with menarche, evaluation is warranted since these may be hallmarks of serious central nervous system (CNS) lesions. Most gynecologists will refer girls with possible precocious development to specialists for a thorough evaluation because of the rarity of the condition. The causes of precocious puberty include ovarian neoplasm, CNS lesions and tumors, McCune-Albright syndrome, and idiopathic precocious puberty.

ADOLESCENT GYNECOLOGY

Normal and Abnormal Puberty

The average age of menarche in the United States is 12.8 years (Fig. 29.3). Menstrual cycles in the first 2 years after menarche are frequently anovulatory, although the cycle length is typically regular within a range of about 22 to 45 days. Mean duration of bleeding is generally less than 7 days. The patient's estimate of quantity of menstrual flow is typically unreliable, and adolescents may have less basis for comparison than older women. Measurement of hemoglobin/hematocrit provides objective evidence of heavy bleeding.

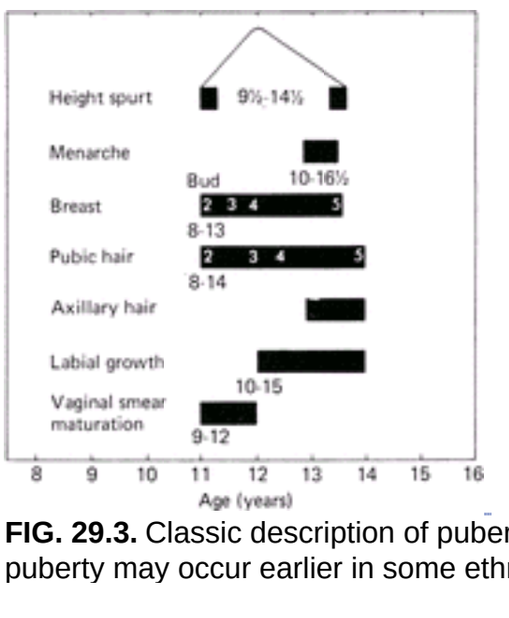

FIG. 29.3. Classic description of puberty. Numbers under each event represent the normal range of ages within which the event may occur. Newer data indicates that puberty may occur earlier in some ethnic groups. (From Tanner JM. *Growth at adolescence*, second ed. Oxford: Blackwell Scientific, 1962.)

First Gynecologic Visit

The American College of Obstetricians and Gynecologists (ACOG) Guidelines for Women's Healthcare indicates that the adolescent's first visit to an obstetrician/gynecologist should take place sometime between the ages of 13 and 15. This is in recognition of the role that obstetrician/gynecologists can potentially

play in providing preventive guidance, screening, and preventive services to adolescents. Obstetrician/gynecologists are uniquely suited to provide these services in that the consequences of adolescent risk-taking behaviors include unintended pregnancies, STDs, ectopic pregnancies, pelvic inflammatory disease (PID), and infertility—all conditions with which the gynecologist is familiar. This initial visit is an ideal opportunity to discuss normal adolescent development and concerns related to adolescents with a girl and her parents. In at least two surveys, adolescents have indicated their desire to discuss health issues such as STDs, contraception, and sexual abuse. These surveys have also indicated that these issues were infrequently addressed by clinicians.

At this visit, issues of confidentiality should be discussed with the adolescent and her parents. Numerous studies have concluded that without assurances of confidentiality, many teens will not divulge their health concerns, particularly those that relate to sex, substance use, and other risk-taking behaviors. However confidentiality does not mean secrecy. Involvement of the parent or guardian should be strongly encouraged and developed. Facilitating a discussion regarding risk behaviors between the parent/guardian and the adolescent (with the adolescent's approval) is an ideal approach.

The initial visit does not necessarily need to include a pelvic examination. The ACOG guidelines state that the provision of additional services beyond guidance and screening should be based on information obtained at this visit. If the adolescent has had intercourse, a pelvic exam, Pap test, and screening for STDs are appropriate.

When a pelvic exam is required careful attention to education and gentle technique at the first exam is particularly critical. Adolescents are less apprehensive if the clinicians describes sensations (i.e., “this will cause a pressure sensation that is not painful but may be a bit uncomfortable”) rather than only describing the purpose of the exam (i.e., “I am now putting the speculum in your vagina”). It is more important that this exam not be traumatic than that it confirm uterine or ovarian dimensions. The exam should be tailored to the needed information. If an adolescent has not been sexually active but is experiencing severe dysmenorrhea, the bimanual and rectovaginal components of the exam are more important than a speculum examination of the cervix. If a speculum exam is deemed appropriate and necessary, as with an adolescent who has had intercourse and thus requires a Pap smear and cervical cultures, an appropriately sized speculum is indicated. The Huffman or “virginal” speculum is quite narrow and can be used with a narrow or rigid hymen. However, visualization of the cervix with the Huffman speculum often requires manipulation that may be more uncomfortable than that required with the more frequently used Pederson speculum. The Pederson speculum should be the most frequently used speculum for adolescents and can be used comfortably for almost all teens. The Graves speculum, which is commonly used for adults, may be necessary for some obese or parous adolescents or when cervical procedures (colposcopy and biopsy) are indicated. Adolescents should be informed about the need for an examination; the amount of information that is provided before the exam should be tailored to the adolescent's wishes. The adolescent should be offered the opportunity to have a parent or friend accompany her during the exam. The exam itself should be performed slowly and gently with forewarning of each successive step of the exam. Pap smears are indicated for adolescents who have been sexually active, and routine screening for STDs is also recommended by the CDC.

The Guidelines for Adolescent Preventive Services (GAPS) is a set of recommendations arrived at by a panel of experts from a number of different disciplines. They are based on the rationale that:

1. The primary health threats to adolescents are behavioral rather than biomedical.
2. An increasing number of adolescents are involved in behaviors with the potential for serious consequences.
3. Adolescents are engaging in these behaviors at earlier ages.

The comorbidities that adolescents experience are related to the risk-taking behaviors of unsafe sexual practices, substance use/abuse, and violence. The GAPS report concludes that many adolescents are engaged in multiple health risks simultaneously, and most adolescents engage in some type of behavior that is a threat to their health and well-being. The multiplicity of risk factors points out the futility of trying to deal with only one specific issue. For example alcohol and drug abuse is related to irresponsible sexuality decisions and motor vehicle accidents. The ACOG guidelines were developed in an effort to screen for and detect the risk-taking behaviors that result in significant morbidities for adolescents and to provide early or preventive interventions and services.

Abnormal Bleeding

Menstrual irregularity is one of the most common presenting problems in the adolescent years. After menarche most adolescents will have an interval of anovulatory cycles. The duration of anovulation varies with the age of menarche. The earlier menarche occurs the sooner ovulatory cycles will occur. If a teen is less than 12 years of age at menarche approximately half of her cycles will be ovulatory within one year, in contrast to the teen who is 12 to 13 at menarche in whom it will be 3 years before half of the cycles are ovulatory.

During this anovulatory interval, menstrual cycles will generally be somewhere between 22 to 45 days apart with great cycle-to-cycle variation. This pattern is due to an intact HPO feedback system creating estrogen withdrawal bleeds. As estrogen climbs, follicle-stimulating hormone (FSH) levels decline, lessening follicular stimulation with a corresponding drop in estrogen. At the estrogen nadir, an estrogen withdrawal bleed is initiated. As puberty proceeds, HPO maturity progresses and levels of estrogen production become high enough to induce a luteinizing hormone (LH) surge with resulting ovulation. Cycles consistently outside the 22- to 45-day range, even in the year after menarche, are often signs of true pathology.

Differential Diagnosis of Menstrual Disorders in Adolescents

The differential diagnosis of menstrual disorders in the adolescent is very extensive and specific diseases are covered in other chapters of this text. However a basic approach is the division of the disorders into two distinct groups: those due to aberrations involving the HPO axis and those unrelated to the HPO axis (Table 29.1).

1. Aberrations in the HPO axis
a. Hypothalamic menstrual disorders
Associations
i. Stress
ii. Dietary practices
iii. Exercise
iv. Body fat
b. Endocrinopathies
i. Prolactinoma
ii. Thyroid disease
iii. Hyperandrogenic anovulation (PCOS)
iv. Congenital adrenal hyperplasia
v. Cushing syndrome
2. Normal HPO axis
a. Pregnancy
b. Bleeding disorders
c. Anatomical bleeding (cervicitis, polyp, endometritis, fibroid, congenital anomaly)

HPO, hypothalamic–pituitary–ovarian; PCOS, polycystic ovary syndrome.

TABLE 29.1. *Menstrual irregularity in the adolescent*

Examples of disorders unrelated to aberrations in the HPO axis include cervical bleeding (from cervicitis), endometritis, polyps, uterine fibroids, bleeding disorders, and abnormal bleeding related to congenital anomalies of the reproductive tract. It is most important to exclude pregnancy.

Every adolescent with a menstrual disorder should be assumed to be pregnant until proven otherwise by pregnancy testing. The potential medical consequences of missing a pregnancy-related complication dictate that a pregnancy test be performed in *all* cases of abnormal bleeding in an adolescent. The adolescent should be questioned privately without her parents about a history of sexual intercourse, whether voluntary or involuntary. In one study in which pregnancies were diagnosed in a pediatric ED, 10% had denied sexual activity. The clinician's skills will certainly be tested in the situation of an unexpected diagnosis of pregnancy. The adolescent should be strongly encouraged to tell her parent(s) or a responsible adult. Counseling about pregnancy options should take place immediately. The clinician must be aware of any relevant state laws that mandate parental notification or consent when an adolescent chooses abortion.

Bleeding from cervicitis is another important consideration. Cervicitis due to *C. trachomatis* can cause abnormal bleeding patterns. Bleeding disorders also deserve careful consideration including idiopathic thrombocytopenic purpura (ITP) and von Willebrand disease. These clotting disorders should be considered in all teens with heavy bleeding but are particularly likely to present with menorrhagia at menarche. In one series approximately half of all girls presenting with menorrhagia at menarche had a bleeding disorder.

Most menstrual irregularity in adolescents is related to aberrations in the HPO axis. These aberrations can be divided into two general groups: hypothalamic menstrual abnormalities and the endocrinopathies (see Table 29.1).

A variety of factors such as stress, body weight, exercise, and diet are related to hypothalamic menstrual disorders. The factors affect neurotransmitter patterns which in turn impact a pulsatile release of gonadotropin-releasing hormone (GnRH).

The endocrinopathies include thyroid disease, hyperprolactinemia, adult-onset CAH, and hyperandrogenic anovulation sometimes referred to as polycystic ovarian syndrome. Other rarer diagnoses include Cushing syndrome and steroid-producing ovarian tumors. All of these disorders are covered in detail in other chapters.

In teens, the hypothalamic disorders are the most common cause of menstrual cycling abnormalities. The diagnosis of a hypothalamic menstrual disorder is a diagnosis of exclusion. Historical questioning will often point toward hypothalamic causes. All teens with menstrual disorders should be specifically questioned about stress, dietary practices, their current, past, and desired body weight, and exercise practices. The physical exam should always include height, weight, temperature, and vital signs. The exam should also include consideration of physical signs of eating disorders. For example, the presence of bradycardia or carotene pigmentation may be critical findings leading to the diagnosis of a serious eating disorder.

The psychiatric definition of anorexia nervosa includes amenorrhea as one criterion. Amenorrhea may even precede severe weight loss. Anorexia nervosa should be managed by a skilled clinician familiar with the medical effects of the disorder, and psychological counseling is always indicated. When the adolescent is in counseling, the approach to the amenorrhea may become a wait-and-watch approach. There is evidence that the bone loss associated with anorexia nervosa may not be rapidly or completely reversible with the use of estrogen supplementation. In one study, approximately 50% of women with bulimia had menstrual abnormalities. Thus, eating disorders should always be considered as a possible cause when adolescents present with menstrual irregularities.

An individual with menorrhagia and signs of hirsutism should be evaluated with hormonal testing for disorders of androgen excess. For individuals without ovarian or adrenal androgen-producing tumors, oral contraceptives usually provide menstrual management and a decrease in acne and hirsutism.

Acute adolescent menorrhagia should initially be managed similarly to acute menorrhagia occurring in older women with hormonal therapy. Curettage is very rarely necessary. Various hormonal protocols have been published for severe menorrhagia including tapering regimens of combination oral contraceptives and intravenous estrogens. Well-controlled studies have not adequately compared these approaches but there is some evidence that there is no additional benefit to intravenous over oral therapy. Some clinicians are adamant that in patients with unopposed estrogens, such as those with polycystic ovary syndrome, the most critical aspect of the hormonal therapy is the progestin. The long-term approach to the patient with menorrhagia is dictated by the diagnosis; a patient with hyperandrogenic anovulation will require different ongoing therapy than the patient with a bleeding diathesis.

Primary Amenorrhea

Primary amenorrhea is defined as the absence of menses by age 15 or 16. The young woman who shows no signs of breast development by age 12 should be evaluated for delayed puberty, as should the young woman with breast development but no menses by age 15 or 16. In one large series from a tertiary referral center, ovarian failure was the most common cause of delayed sexual development. Congenital absence of the uterus and vagina and a physiologic delay of puberty were also frequently diagnosed etiologies. Other etiologies were diverse and numerically less frequent. Only 14% of all patients presenting with abnormalities of pubertal development had subsequent normal reproductive potential. All of these patients were in the physiologic delay category. Thus, the authors concluded that pubertal aberrancy should not be considered a benign entity because it is associated with significant morbidity, mortality, and compromise of reproductive potential.

Pregnancy must always be considered as a possible etiology of amenorrhea, whether it is secondary or primary amenorrhea. Just as with excessive or abnormal bleeding, the consequences of missing the diagnosis of pregnancy are serious, and a pregnancy test should always be performed to confirm the history.

Müllerian agenesis, obstructing vaginal septa and an imperfect hymen are associated with primary amenorrhea and thus are most frequently diagnosed during adolescence. Treatment options may include both surgical and nonsurgical management but should also focus attention on the psychological ramifications of this diagnosis.

Dysmenorrhea

Primary dysmenorrhea, beginning with the onset of ovulatory menstrual cycles, is common, occurring in up to 90% of adolescents. The use of nonsteroidal antiinflammatory drugs (NSAIDs) is usually helpful in relieving the prostaglandin-mediated symptoms, and many adolescents with dysmenorrhea have already tried over-the-counter (OTC) medications, although not always in appropriately therapeutic doses. Adolescents may be unaware that these drugs are more effective in relieving dysmenorrhea than other OTC analgesics. Severe dysmenorrhea and premenstrual molimina can affect the performance of adolescent activities (particularly school attendance, but also athletic endeavors) and these girls can benefit from the use of oral contraceptives. Parents may need to be informed of the potential noncontraceptive benefits of these medications, the rare risk of serious complications, and the fact that oral contraceptive use does not accelerate the initiation of sexual activity in this age group.

Adolescents who have persistent dysmenorrhea in spite of the use of NSAIDs and oral contraceptives should be evaluated for other causes of pelvic pain, such as irritable bowel syndrome and endometriosis. At one time, it was thought that endometriosis did not occur in adolescents. However, when teenagers with severe dysmenorrhea undergo laparoscopy, endometriosis can be found in a significant percentage. The percentage of adolescents with chronic pain who have endometriosis is not well established. In reported series of adolescents undergoing laparoscopy for chronic pain (generally defined as pain unresponsive to oral contraceptives and NSAIDs) up to 75% with this complaint have endometriosis. However, the percentage of teenagers with endometriosis found at laparoscopy depends on the indications for the surgical procedure and the criteria for diagnosis. Traditionally, visual confirmation was deemed sufficient; however, when strict criteria are used for diagnosis, endometriosis is not always confirmed. Endometriosis in adolescents is most frequently minimal or mild and may be atypical, with clear, white, or red lesions rather than the classic “powder-burn” lesion seen most frequently in older women. It has been suggested that there is an age-related change in the appearance and color of endometriotic lesions. There is good evidence supporting a familial occurrence of endometriosis; the evidence is most consistent with a polygenic/multifactorial etiology. An asymptomatic individual with a first-degree relative with endometriosis has a 7% risk of developing the disease.

Pelvic Masses

Pelvic masses in adolescents may be detected as a result of symptoms (pain, pressure, urinary symptoms) or signs (the presence of a pelvic or abdominal mass on examination). Pelvic masses in adolescents are most likely to be ovarian rather than uterine, although pregnancy should always be considered a possibility and ruled out.

Fewer than 5% of ovarian malignancies occur in children and adolescents. Ovarian tumors account for only 1% of all tumors in these age groups. Germ cell tumors make up one half to two thirds of ovarian neoplasms in individuals younger than 20. A review of studies conducted from 1940 until 1975 concluded that 35% of the neoplasms occurring during childhood and adolescence were malignant. In girls younger than 9 years of age, approximately 80% of ovarian neoplasms were found to be malignant. Germ cell tumors make up approximately 60% of ovarian neoplasms in girls, compared with only 20% in adults. Because neoplastic tumors are rare, these studies come from tertiary care centers and may not be representative of the true prevalence of these lesions. Some reports include only neoplastic masses, whereas others include nonneoplastic masses. One community survey of ovarian masses revealed that the frequency of malignancy was much lower; only 10% of masses were neoplastic, and only 6% of all masses were malignant. Another series reported that nonneoplastic masses in individuals younger than 20 constituted two thirds of the total; even in girls younger than 10, 60% of the masses were nonneoplastic, and two thirds of the neoplastic masses were benign.

The mature cystic teratoma (commonly referred to as a “dermoid”) is the most frequent neoplastic tumor of children and adolescents, accounting for more than one-half of ovarian neoplasms in women younger than 20. Ovarian cystectomy with careful palpation of the contralateral ovary is the best approach in order to maximize future reproductive potential in young women. Bivalving the contralateral ovary is not necessary as most contralateral tumors will be palpable.

Functional follicular cysts can occur at any age and have been reported in female fetuses, newborns, prepubertal children, adolescents, and mature reproductive women. Unilocular cysts will usually resolve spontaneously, and surgical therapy should be reserved for symptomatic masses, masses that do not resolve, suspected torsion, or masses that include a solid or multiloculated appearance on ultrasound. Attention to the long-term effects of ovarian function and future fertility dictate a conservative approach to ovarian masses in young girls; preservation of ovarian tissues with oophorocystectomy is a priority for benign tumors. Functional cysts in prepubertal girls may rarely be associated with sexual precocity, particularly when recurrent.

Unintended Pregnancy

The teen pregnancy rate in the United States is significantly higher than those seen in all other industrialized countries. However, a real decline in the U.S. teen pregnancy rate was seen in the 1990s. In 1990 the teen pregnancy rate was 117 pregnancies per 1,000 teen girls; this decreased to 97 pregnancies per 1,000 teen girls in 1996. Approximately 80% of this decline can be attributed to greater use of contraception and 20% to delay of coitus/interval abstinence.

The 1995 National Survey of Family Growth reported that more than 50% of adolescents have had intercourse. Although most of the youngest teens have *not* had intercourse, the percentage of young teens who have had intercourse has been increasing. Some of the adolescents in this survey reported the experience of

involuntary intercourse, and the younger the age at initiation of intercourse the more likely the experience was involuntary. Seventy-four percent of those who reported first intercourse at age 13 or younger reported that they had experienced involuntary intercourse.

At least 75% of adolescent pregnancies are unintended. Most (approximately 80%) adolescents use a method of contraception but do not always use the method consistently, correctly, and continuously. Developmental factors contribute to an adolescent's risk for unintended pregnancy. During early and mid-adolescence, concrete thinking is developmentally normal, and the “personal fable” and magical thinking mitigate against the reality that pregnancy could happen to the individual. Middle adolescents enjoy showing off their new “adult” bodies, frequently seek peer group approval, and feel invulnerable. However, they also have increased mobility and independence coupled with less adult supervision and protection. These factors frequently lead to risk-taking behaviors and experimentation with driving, substance use, and sexual activity. These teens may be unable to anticipate or prevent the consequences of these activities because of inexperience in abstract thinking. While they are developing the ability to perceive causal relationships and future consequences, this ability is variably applied, particularly in stressful situations such as an intimate or sexual relationship. There may be discordance among an individual adolescent's physical, social, sexual, and cognitive development. Thus, adolescents may not be developmentally equipped to use contraceptives effectively. Postponing sexual intercourse therefore is the preferred form of sexual behavior for most adolescents until they are developmentally capable of responsible sexual behavior.

Various approaches to promotion of abstinence have been studied. Curriculum-based approaches have been divided into two groups: abstinence-only and abstinence plus or sometimes labeled “comprehensive sex education.” Abstinence-only education is common given the 1996 federal law that gave states $85 million dollars in funding solely for this approach. Interestingly, in an analysis of published or known U.S. or Canadian studies with an experimental or quasi-experimental design, no programs that were abstinence-only based demonstrated a delay in sexual activity or increased contraceptive use in sexuality active teens. In contrast there have been some abstinence-plus curricula with positive results in delay of sexuality and increasing contraceptive use. It should be noted however that there are only a handful of studies on abstinence-only programs. Fortunately, a well-designed evaluation of the Title V abstinence-only programs will be available in the near future and help resolve the issue of whether abstinence- only education is effective. Given the lack of available evidence, ACOG issued a committee opinion noting the limitation of the abstinence-only approach in 1998.

Contraceptive Patterns in Adolescents

Approximately one third of adolescents wait a year after initiating intercourse before seeking medical contraceptive services, and another one third have not sought medical care. In spite of these figures, however, an increasing percentage of adolescents are using contraception at first intercourse. In 1982, 52% used no method of contraception at the time of first intercourse; in 1988, 35% reported using no method; and in 1995, 23% did not use any method of contraception at first intercourse. Birth control pills and condoms are the most popular methods of contraception among adolescents.

Adolescents generally have higher failure rates of various methods of contraception during typical use, primarily because of problems with compliance—defined for contraception as the use of a method in both a consistent and ongoing manner. Failure rates among adolescents using oral contraceptive pills can be as high as 15% to 18%; as many as 50% or more of adolescents have discontinued the method by the end of 1 year. Missed pills are frequently a problem for women of all ages but are particularly frequent among the youngest adolescents. In one study, only one-fourth of adolescents 14 or younger took their oral contraceptive pill every day. For many adolescents, the longer-term methods of contraception—depot medroxyprogesterone acetate, contraceptive patches, or contraceptive rings—may more appropriate methods, given the problems of compliance.

Sexually Transmitted Diseases

Biologic factors that impact an adolescent's risk of STD acquisition or complications include the active cervical metaplasia and ectopy, which may increase the risk of *Chlamydia* or human papilloma virus (HPV) acquisition. Aspects of adolescent development also affect the risks for STDs. The feeling of invulnerability may result in decreased use of condoms or denial of symptoms. In addition, the clinical presentation of STDs may be affected by both an excessive attention to hygiene (e.g., douching) or excessive neglect of perineal hygiene. When infection is suspected, the adolescent typically reacts with embarrassment and fear, which results in delays in seeking treatment. Once an STD is diagnosed, adolescents may fail to complete therapy, especially if symptoms decrease; they also frequently fail to keep follow-up appointments and have difficulty informing their partners of the STD acquisition.

Behavioral factors placing adolescents at increased risk include the fact that they may be more likely to have multiple sexual partners rather than single, long-term relationships; adolescents may have either concurrent partners or engage in serial monogamy. Almost half of all sexually active women between ages 15 and 19 have had two or more partners during the previous year. Teens may be more likely to engage in unprotected intercourse and may select partners at higher risk for STDs.

Adolescents have the highest rates of gonorrhea and HPV of any age group. Routine screening for *Chlamydia* is recommended by the CDC for all sexually active adolescents, regardless of other risk factors. Routine screening for *N. gonorrhoeae* should at least be done in all high-risk teens (previous STDs, multiplicity of partners), and teens living in areas where prevalence levels warrant routine screening, such as the southern United States. In many areas of the U.S. it is cost-effective to screen for both these STDS in the sexually active teen population. On careful examination the definition of high-risk teens often is the majority of sexually active teens.

Chlamydia screening has been shown in a randomized clinical trial to be associated with a lower risk of PID among those screened when compared to those individuals who were not screened. When control rates of sexual activity are applied (approximately 50% for adolescents between the ages of 15 and 19), adolescents have the highest rates of PID.

Clinicians should be aware that in the United States, all adolescents can legally consent to be screened and treated for STDs and have the right to these services without parental consent or knowledge. Barriers to STD prevention in adolescents and young adults include financial constraints, lack of transportation, discomfort with facilities and services designed for adults, and concerns about confidentiality.

Hepatitis B is the only completely preventable STD. The Advisory Committee on Immunization Practices now recommends the hepatitis B vaccination series at age 11 to 12. However, a cohort of adolescents currently exists who did not receive the vaccine at this age. Based on this finding, the American Academy of Pediatrics and ACOG both recommend that all adolescents receive the vaccine at the time of their next visit to their health care provider.

Treatment of STDs among adolescents is identical to treatment in adults. The difference in STD presentation in adolescents compared with adults relates to the developmental and risk-profile differences noted previously, which place adolescents at increased risk. In addition, problems of compliance with medication are common; single-dose therapies may thus be more appropriate for teens with uncomplicated gonorrhea or *Chlamydia* cervicitis.

SUMMARY POINTS

- This chapter has outlined and summarized the basic aspects of pediatric and adolescent gynecology, highlighting the differences from the manner in which conditions are evaluated and managed in adults. Psychosocial and behavioral factors greatly influence the health of adolescents. Preventive guidance and screening may be able to prevent or minimize these health problems.
- The gynecologic care of children and adolescents requires attention to a set of pathologic entities and treatments as well as psychosocial issues that are different from those of adults.
- A non-specific vaginitis is the most common cause of vulvovaginal symptoms in prepubertal children; sexual abuse must always be considered as a possible etiology.
- Most prepubertal children who have been sexually molested will have normal genital examinations.
- Most health threats in adolescents are related to risk-taking behaviors such as early sexual activity, alcohol, and other substance abuse.
- Menstrual irregularity in adolescents can be divided into two groups: Those due to an aberration of the hypothalamic–pituitary–ovarian (HPO) axis and those with a normal HPO axis. The aberrations are usually due to either the hypothalamic menstrual disorders or endocrinopathies. The most common cause of menstrual irregularity in teens with a normal HPO axis is pregnancy.
- Contraceptive compliance is difficult for adolescents and is the major factor that leads to higher failure rates during typical use for this age group than for older individuals.
- Adolescents with dysmenorrhea unresponsive to nonsteroidal antiinflammatory drugs and oral contraceptives may have pelvic endometriosis.

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Chapter 30

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Contraception

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SUMMARY POINTS

SUGGESTED READINGS

> Reproductive rights embrace certain human rights that are already recognized in national laws, international human rights documents, and other relevant consensus documents. These rights rest on the recognition of the basic right of all couples and individuals to decide freely and responsibly the number and spacing and timing of their children and to have the information and means to do so, and the right to attain the highest standard of sexual and reproductive health.
>
> —Beijing Platform for Action, 1995

All women have a basic human right to determine whether and when they will become pregnant. Sexually active women and men have a wide variety of contraceptive choices for implementing this right, ranging from temporary to permanent methods. Most women have the potential to become pregnant over at least three decades and most men are fertile for an even longer period. Thus, a series of contraceptive decisions may be necessary over a reproductive lifetime. Since 2000, the range of contraceptive choices in the United States has increased, with the approval of four new contraceptive methods: An estrogen–progestogen injectable, a vaginal ring, a contraceptive patch, and a progestogen-releasing intrauterine device (IUD). This chapter focuses on information to help women and men make the contraceptive choices that best address their needs and circumstances.

CONTRACEPTIVE USE IN THE UNITED STATES AND AROUND THE WORLD

Data from the U.S. National Survey of Family Growth indicate that, in 1995, 65% of women between the ages of 15 and 44 used some method of contraception. Among women who used contraception, permanent methods were the most popular; 28% had undergone tubal sterilization and 11% had partners who had undergone vasectomy. Oral contraceptives were the most popular temporary method, but the proportion of pill users decreased from 31% in 1988 to 27% of contraceptive users in 1995, while the proportion of condom users increased from 15% in 1988 to 20% in 1995. Only 3%, 1%, and 1%, respectively, used the injectable depot medroxyprogesterone acetate, levonorgestrel implants, and IUDs. Despite this level of reported contraceptive use, 49% of pregnancies concluding in 1994 were unintended; 54% of those ended in abortion.

Globally, according to the Demographic and Health Surveys, tubal sterilization is the most common method of contraception (in 1997, 20% of couples in which the woman was of reproductive age and who used a contraceptive method, used tubal sterilization), followed by IUDs (15%), oral contraceptives (8%), and condoms (5%).

CHOOSING A METHOD OF CONTRACEPTION

Although sterilization is the most widely used method of contraception in the United States and in much of the rest of the world, it is appropriate only for women and couples who have made a decision to permanently prevent pregnancy. The initial contraceptive choices for most women and men are temporary. Factors that influence the appropriateness of any contraceptive choice include the relative safety and effectiveness of the method for the individual, the frequency and acceptability of side effects, the willingness and ability to use the method consistently and correctly, cost, and the role of religious or cultural beliefs in method acceptability. Other factors include the frequency of coitus, the length of time pregnancy is to be delayed, the impact on lactation and on the breast-fed infant, and any potential impact of the method on future fecundity. In addition, many women are at risk for sexually transmitted infections, including human immunodeficiency virus (HIV) infection, and the need for dual protection against pregnancy and sexually transmitted infections is an issue of great importance for them. Sexually active women at risk for sexually transmitted infections are best advised to consistently and correctly use condoms for both pregnancy and disease prevention, or to use another method of contraception for pregnancy prevention together with condoms for disease prevention.

The need for such dual protection produces special challenges, as there is some evidence that the use of a highly effective method of contraception other than condoms may affect a person's willingness or ability to use condoms for disease prevention.

CONTRACEPTIVE EFFECTIVENESS

Contraceptive effectiveness is measured as reduction in the probability of conception with use of a contraceptive method over a defined period; it cannot be measured directly, largely because studies cannot determine the proportion of women who would have become pregnant during that time had they not been using contraception. By contrast, contraceptive failure rates can be directly determined and are the most clinically useful measures of effectiveness.

Widely used estimates of contraceptive failure rates are shown in Table 30.1. These rates are provided in two categories: “typical use” and “perfect use.” The former is similar to “use effectiveness” and is characteristic of a typical couple starting to use a method (some use the method properly and others do not); the latter is similar to “method effectiveness,” which is the result of consistent and correct use of the method. For some methods, the typical and perfect use rates are substantially different, which indicates that the user's willingness and ability to use these methods consistently and correctly are more important than they are for those methods that have similar typical and perfect use rates. For example, according to Trussell and colleagues (see Table 30.1), although women who take a combined oral contraceptive pill each day should have a near-zero probability of pregnancy, among typical couples in which the woman initiates use of oral contraceptives, 8% experience an unintended pregnancy during the first year if they do not discontinue pill use for any other reason. By contrast, the typical and perfect use failure rates are virtually the

same for IUD users and for users of levonorgestrel implants. Published estimates of contraceptive failure rates apply to groups and may vary substantially among individuals within those groups, particularly among those who use methods with major differences in estimates between typical and perfect use. Most failure rates address the risk of pregnancy within 12 months of starting to use the method. The risk of pregnancy for some methods, particularly those that depend on proper use, is likely to decline over time.

TABLE 30.1. *Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year in the United States*

ORAL CONTRACEPTION

Combined Oral Contraceptives

Combined oral contraceptives (COCs), containing both estrogen and progestogen, have been available in the United States since 1960, have been used by millions of women worldwide, and have been extensively studied. Formulations for oral contraceptives have changed over time from higher to lower doses of steroid hormones. Today, most COCs prescribed in the United States contain =35 µg of ethinyl estradiol. The progestogen component of COCs varies and may include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, and the progestogens of “third generation pills”: desogestrel, norgestimate, and gestodene (gestodene is not available in the United States). Monophasic pills have constant doses of estrogen and progestogen, whereas multiphasic pills vary the doses throughout the cycle.

The primary mechanism of COCs is inhibition of ovulation by suppressing follicle-stimulating hormone and luteinizing hormone. In addition, the progestogen thickens and decreases the amount of cervical mucus, which impedes the ascent of sperm into the upper genital tract. COCs may also act by affecting the endometrium and tubal transport. Although COCs are highly effective in preventing pregnancy when used consistently and correctly, 29% of COC users reported missing one or more pills in the last 3 months in the 1995 National Survey of Family Growth. COCs are substantially less effective when used inconsistently (i.e., as seen with many typical users) (see Table 30.1).

Metabolic Effects The estrogen and progestogen components of COCs produce metabolic changes, but for most healthy women, the changes associated with the available low-dose COCs have little or no clinical significance. Estrogens generally produce changes in lipid metabolism that are considered beneficial, including slightly increasing levels of high-density lipoprotein (HDL) and decreasing low-density lipoprotein (LDL). Depending on their level of androgenicity, progestogens can counteract these effects, decreasing HDL and increasing LDL. Therefore, the net effect depends on the doses of both estrogen and progestogen as well as the type of progestogen; however, most changes are within the normal range and not clinically relevant. Although some studies of older formulations of high-dose COCs reported progestogen-associated elevated glucose and insulin levels and higher rates of relative peripheral insulin resistance, clinical studies of low-dose COCs have not found clinically significant effects on glucose metabolism. A large, cross-sectional study of U.S. women found no elevation in hemoglobin A_1C, fasting glucose, insulin, and C-peptide levels among current COC users compared with those who never used COCs. Large, prospective studies have not found increased risks of diabetes mellitus among COC users with either high-dose or low-dose pills.

Cardiovascular Diseases Epidemiologic research confirms that the overall risk of serious cardiovascular complications attributable to COC use is extremely low for the vast majority of users of modern ethinyl estradiol preparations (=35 µg). However, individual user characteristics and the type of COC modify the risk. Cardiovascular complications associated with COC use occur while the pill is being used; once pills are discontinued, risk levels return to baseline.

Hypertension COC use may slightly increase blood pressure among normotensive women, but studies suggest this increase is reversible when COC use is discontinued. Among women with mild hypertension, COC use has also been associated with increased blood pressure. In a cross-sectional study of 94 women with mild hypertension, COC users had significantly increased daytime and nighttime ambulatory systolic blood pressure values (mean 8.3 mm Hg increase for daytime and mean 6.1 mm Hg increase for nighttime). No significant differences in diastolic blood pressure values were found.

Venous Thromboembolism The incidence rate of venous thromboembolism in healthy nonpregnant Caucasian women is estimated to be 5 per 100,000 woman-years. When such women use COCs, the incidence increases to between 15 and 30 per 100,000 woman-years, or three to six times higher than non-COC users, depending on personal characteristics and the type of pill. By comparison, the risk of thrombosis associated with pregnancy is about 60 per 100,000 pregnant women. The case fatality rate of venous thromboembolism is 1 to 2 per 100 and the risk of death from thromboembolism attributable to COC use is extremely low at 1 to 5 per million per year of use. The most important risk factor for thromboembolism is family history of the disease, which is often related to genetic thrombophilia. The most common genetic cause of thrombophilia is resistance to activated protein C (factor V Leiden), which occurs in about 5% of Caucasians but is rare in non-Caucasians. The presence of factor V Leiden substantially increases the risk of COC-associated venous thrombosis; screening for the condition before starting pill use has been considered. However, cost–benefit considerations lead most authorities to recommend against screening before starting COCs unless women have a family history of thrombosis. The third-generation low-dose pills with the progestogens desogestrel or gestodene have been associated with a nearly two-fold increased risk of thrombosis relative to “second- generation” pills, which contain levonorgestrel or norethindrone. Low-dose pills containing cyproterone acetate appear to have risks similar to desogestrel and gestodene pills. Although these elevated risks are noteworthy, they are nonetheless low in absolute terms—an estimated increased risk of 4 deaths per 1 million woman-years of use.

Arterial Diseases Older age, smoking, diabetes, and hypertension are major risk factors for stroke and myocardial infarction. For women with these risk factors, COC use increases their already elevated baseline risk; thus, women with multiple major risk factors for cardiovascular disease generally should not use COCs.

Stroke The annual incidence rates of hemorrhagic and ischemic stroke in healthy, nonsmoking women between 20 and 24 years of age are estimated to be 2 and 0.5 per 100,000, respectively. In women between 40 and 44 years of age, these annual rates are 5 and 1 per 100,000, respectively. Nonsmoking women less than 35 years old with normal blood pressure who use COCs have no extra risk of hemorrhagic stroke and only a marginally increased risk of ischemic stroke. Among such women 35 years or older, the risk of hemorrhagic or ischemic stroke is increased 1.5- to 2-fold during use of COCs. Smoking and hypertension increase the COC-associated risk of hemorrhagic and ischemic stroke. Use of COCs by women with classic migraine further elevates their moderately increased risk of ischemic stroke.

Myocardial Infarction In healthy, nonsmoking women of reproductive age with normal blood pressure, the risk of myocardial infarction is extremely low and the use of COCs causes little, if any, increase in risk. On the other hand, among women who smoke, have hypertension, or have hyperlipidemia, their baseline elevated risk for myocardial infarction is substantially increased by COC use. Myocardial infarction is rare in women under 35 years old, even if they have risk factors; for women 30 to 34 years old who use COCs and smoke, the risk is estimated to be 2 per 100,000 woman-years. By contrast, women 40 to 44 years old who use COCs and smoke have an estimated risk of 25 per 100,000 woman-years. Some studies suggest that women who take pills containing the progestogens desogestrel or gestodene may have an even lower risk of myocardial infarction than that associated with the very low risk of pills containing levonorgestrel or norethindrone, but findings are inconsistent.

Malignant Neoplasia COCs clearly reduce the risk of some cancers and may increase the risk of some others. Most data are based on COCs with higher doses of estrogens and progestogens than in the currently available pills; studies suggest that lower-dose preparations are likely to have similar effects on cancer risk.

Breast Cancer A pooled analysis of 54 studies found a small increased risk of breast cancer diagnosis (relative risk = 1.24) while COCs were being used and recently after use. The excess risk was among women with localized disease, and there was a corresponding decrease in metastatic disease. These findings argue that women who use COCs are:

- simply more likely to have existing breast cancers diagnosed because they are more likely to have clinical exams or mammograms
- more likely to have late-stage promotion of tumors that subsequently are more likely to remain localized to the breast.

The observation that the duration of COC use had no effect on breast cancer risk argues for the former explanation. The excess risk of breast cancer disappears 10

years after cessation of pill use. Thus, women who use the pill from age 15 to age 35 years have the same breast cancer risk at age 50 as comparable women who never took COCs. Because the incidence of breast cancer is low at ages when COC use is most common, any effect would affect a relatively small number of women. For example, among women who stop using COCs at 25 years of age, the cumulative risk from ages 25 through 34 years is estimated to be 1 excess cancer diagnosed per 10,000 women. In women who stop COC use at age 40, when incidence rates are higher, an estimated 19 excess cancers will be diagnosed from ages 40 through 49 years. As noted, even these excess cancers may represent only an earlier detection of existing disease; at worst, they represent a small absolute excess occurrence of localized disease.

Cervical Cancer Several studies in the past suggested that using COCs for 5 years or longer increased the risk of cervical cancer 1.3- to 1.8-fold, but the causality of the association was uncertain. More recent data indicate that COC use may not be associated with cervical cancer in women without persistent genital human papilloma virus (HPV) infection or in women with HPV infection who use COCs for fewer than 5 years. However, in women with persistent HPV infection who have used COCs for 5 or more years, the risk for cancer of the cervix may well increase up to 2-fold. Available data suggest that the increased risk decreases over time after stopping pill use. Questions remain about whether the risk is related to pill use per se, to other characteristics of pill users, such as sexual behavior, or to circumstances associated with pill use, such as cytologic screening. Regardless, where screening services are available, COC users should avail themselves of these services as advised for other women.

Ovarian Cancer Use of COCs reduces the risk of epithelial ovarian cancer, the most common cancer of the ovary. Risk reduction is related to the duration of use. Using COCs for 5 years or longer confers at least a 50% reduced risk that persists for up to 15 years after cessation of use.

Endometrial Cancer COC use reduces the risk of cancer of the endometrium. As with ovarian cancer, risk reduction is related to the duration of use; after about 5 years of use, the risk of endometrial cancer is at least 50% lower than in women who never used COCs. Risk reduction persists for 15 to 20 years after stopping pill use.

Liver Cancer Primary cancer of the liver is rare in populations where hepatitis B or C is not endemic. Some studies in the 1980s pointed to a substantially increased risk of primary liver cancer after long-term use of COCs. Subsequent studies suggest that, among women free of hepatitis B or C, long-term use (>6 years) of mostly less than 50 µg ethinyl estradiol pills may be associated with a modest increased risk of primary liver cancer. In populations where chronic hepatitis is common, pill use has not been associated with primary liver cancer. Liver cancer is rare and usually fatal within 1 year of diagnosis; thus, the fact that there has been no increase in liver cancer deaths in the United States in the four decades that COCs have been in widespread use argues against a substantial risk.

Other Cancers Some studies have found a lower incidence of cancer of the colon among women who have used COCs, but it is unclear whether the association is causal. Previous claims of increased risk of tumors of the pituitary and the skin in users of COCs have not been confirmed.

Medical Eligibility Criteria for COC Use

Most women can safely use COCs. There are some conditions, however, under which COCs should not be used. These conditions include the following:

- breast-feeding and less than 6 weeks postpartum
- age =35 years and smoking =15 cigarettes per day
- multiple risk factors for arterial cardiovascular disease (e.g., older age, smoking, diabetes, hypertension)
- elevated blood pressure of =160 mm Hg systolic or =100 mm Hg diastolic
- current or history of deep vein thrombosis or pulmonary embolism
- major surgery with prolonged immobilization
- current or history of ischemic heart disease
- stroke
- complicated valvular heart disease
- migraine with focal neurologic symptoms (migraine with aura)
- migraine without focal neurologic symptoms and age =35 years
- current breast cancer
- diabetes with nephropathy, retinopathy, neuropathy, vascular disease, or diabetes of more than 20 years duration
- severe cirrhosis
- liver tumors.

In addition, there are several other conditions for which women generally should not use combined oral contraceptives (Table 30.2).

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TABLE 30.2. *WHO medical eligibility criteria for contraceptive use*

Noncontraceptive Benefits of COC Use

In addition to protecting against pregnancy, including ectopic pregnancy, and the noted protection against endometrial and ovarian cancers, COC use provides other health benefits including preventing and treating menstrual abnormalities (including bleeding problems and pain); reduced risk of symptomatic pelvic inflammatory disease (PID) relative to use of no contraception (although there is no protection against lower genital tract infection and HIV infection); reduced risk of benign breast cysts; reduced risk of iron deficiency anemia; and treatment of acne. There is also some, albeit inconsistent, evidence that COCs may protect against osteoporosis and uterine fibroids. The protection against ovarian cysts, seen with higher dose COCs, is reduced in low-dose monophasic COCs and may not be present for triphasic COCs.

Return to Fertility After Discontinuing COCs

Women who discontinue COCs have no overall reduction in fertility. There may be a very short delay in time to conception compared with women not using COCs. This delay in time to conception is temporary, and by 3 to 12 months after discontinuation there are no differences in fertility rates.

Side Effects

Nausea and breakthrough bleeding are common side effects of COC use, although they often diminish or disappear after the first 3 months of use. Breakthrough bleeding may be due to the specific pill formulation, but it also may be caused by missed pills. If breakthrough bleeding lasts beyond the first 3 months of use, other gynecologic causes have been ruled out, and the bleeding is a problem for the woman, it may be beneficial to switch to a different COC formulation. Other approaches to managing breakthrough bleeding include adding oral estrogen along with the current COCs (1.25 mg conjugated equine estrogen or its equivalent, daily for 1 week at the time the breakthrough bleeding occurs), doubling up on active pills for 2 or 3 days until the breakthrough bleeding stops, doubling up on active pills through the end of the cycle, or using active pills in a continuous regimen. Nonsteroidal antiinflammatory drugs (NSAIDs) may also help alleviate breakthrough bleeding. Other common side effects associated with COCs are breast tenderness and headaches. Weight changes are often reported but most recent studies suggest that little, if any, weight gain can be directly attributed to COC use.

Progestogen-only Oral Contraceptive Pills

Progestogen-only pills are an appropriate alternative for women who desire an oral contraceptive but who are not candidates for COCs. They are commonly used by women who are breast-feeding after 6 weeks postpartum. Progestogen-only oral contraceptives act on the cervical mucus and may act on the endometrium to prevent pregnancy, but do not consistently inhibit ovulation. Progestogen-only pills are estimated to be as effective as COCs when taken consistently (see Table 30.1), but they are less forgiving of inconsistent use. The most common side effects associated with progestogen-only pill use are changes in vaginal bleeding patterns.

PROGESTOGEN-ONLY AND ESTROGEN–PROGESTOGEN INJECTABLES

Progestogen-only Injectables

Progestogen-only injectables first became available to women in the United States with approval of the U.S. Food and Drug Administration (FDA) in 1992. The injectable, containing 150 mg of depot medroxyprogesterone acetate, inhibits ovulation, produces an atrophic endometrium, and alters cervical mucus to decrease sperm penetration. Intramuscular injections are administered every 3 months (within a window of 2 weeks on either side). Most women who want to use a progestogen-only injectable can safely do so. Women with current breast cancer should not use this method. Several other conditions for which women generally should not use progestogen-only injectables are listed in Table 30.2.

The most common side effects experienced by progestogen-only injectable users are changes in vaginal bleeding patterns. During the first few months of use, many women experience irregular and prolonged bleeding. However, as use continues, bleeding becomes less frequent and up to half the women become amenorrheic by 1 year of use. Some women also report weight gain during the first several years of use; studies suggest a mean weight gain of 3 to 5 lbs per year.

Because of the highly effective suppression of ovulation leading to amenorrhea in many women, there is also a significant delay in return to fertility after discontinuation of progestogen-only injectables. The median time to pregnancy is 6 to 9 months after the last injection. Progestogen-only injectables are the only temporary contraceptives with a substantial delay in return to fertility.

Concern has been raised that progestogen-only injectable use may adversely affect bone mineral density. This question may be particularly important for adolescents, who have not yet reached peak bone mass. A meta-analysis of 12 studies concluded that women who were currently using depot medroxyprogesterone acetate had a lower average bone mineral density than non-users, with some suggestion that women with longer duration of use had greater reductions in bone mineral density. No differences in bone mineral density were found between past users and those who had never been users. One study has found that premenopausal women who discontinue progestogen-only injectables can regain much of their lost bone mass. However, whether adolescents who are still developing peak bone mass can regain bone density to normal levels has not been studied. Likewise, whether perimenopausal use will precipitate the decline in bone mass associated with menopause is unclear.

Estrogen–Progestogen Injectables

In 2001, the FDA approved the first combined estrogen-progestogen injectable for use in the United States. This injectable is administered intramuscularly on a monthly basis and contains 25 mg depot medroxyprogesterone acetate and 5 mg estradiol cypionate. Combined injectables appear to be similar to combined oral contraceptives in their mechanism of action, eligibility criteria, side effects, and safety profile. Vaginal bleeding patterns are more stable with combined injectables than with progestogen-only injectables, and most women experience a monthly withdrawal bleed. Return to fertility is not as delayed as it is with progestogen-only injectables.

LEVONORGESTREL IMPLANTS

Currently, the levonorgestrel implants in use in the United States consist of six capsules containing 36 mg of levonorgestrel for release over 5 years, with potential for effectiveness up to 7 years. A similar system, composed of two rods with 75 mg of levonorgestrel for release over 5 years, has been approved by the FDA but is not yet marketed in the United States. Both systems are inserted subcutaneously in the woman's upper inner arm, under local anesthesia. Although complications with insertions and particularly with removals have been reported, complication rates are related to the training and experience of the provider; studies show significantly fewer complications and faster removal times for the two-rod system than for the six capsules. A woman should have ready access to implant removal on request.

Levonorgestrel implants prevent pregnancy by disrupting normal ovulation in most women, including changes that range from insufficient luteal function to inhibition of ovulation. In addition, the cervical mucus becomes viscous and scanty, which inhibits sperm penetration.

Both systems are highly effective long-term methods, with little action needed by the contraceptive user. However, among the small number of women who become pregnant during use, the proportion of pregnancies that are ectopic is higher than among women who use no contraception.

Most women can safely use levonorgestrel implants. However, women with current breast cancer should not use them. Other conditions for which women generally should not use levonorgestrel implants are listed in Table 30.2.

An international cohort study of over 16,000 women followed for up to 5 years confirmed the safety of levonorgestrel implant use. This study found no significant excess risk of adverse effects for levonorgestrel users compared with controls (IUD users and women with tubal sterilization), other than small excess risks of gallbladder disease and hypertension.

Most levonorgestrel implant users experience changes in vaginal bleeding patterns, including prolonged or irregular bleeding. Although these changes are most pronounced in the first months of use and tend to diminish over time, they persist for many women. As bleeding changes are among the most common reasons for discontinuation of implants, women should be counseled about these bleeding changes before initiating implant use. Other reported side effects include weight gain, headaches, acne, and mood changes. Some women also experience persistent ovarian follicles because of the incomplete suppression of ovulation. These follicles generally disappear within 1 to 2 months and, thus, most do not require surgery.

CONTRACEPTIVE PATCH

In 2001, the FDA approved the first transdermal contraceptive patch. The patch is designed to release 20 µg ethinyl estradiol and 150 µg norelgestromin, the active metabolite of norgestimate, daily for 1 week. The patch acts similarly to oral contraceptive pills in that the user applies the patch weekly for 3 weeks, followed by a patch-free week to allow for menstrual bleeding. The patch is also similar to oral contraceptive pills in effectiveness, side effects, and incidence of breakthrough bleeding. It may be less effective among women who weigh 90 kg or more. In a study that compared the patch with an oral contraceptive, patch users experienced higher rates of breakthrough bleeding or spotting and reported more breast discomfort in the first 2 months of use, but not thereafter. Dysmenorrhea and headaches were infrequent reasons for discontinuation but were more frequent among patch users than among COC users. In clinical trials, patch users have demonstrated high compliance with method use, significantly better than COC users in one study. Over time, the patch may prove to be more effective than oral contraceptives with typical use because of increased compliance.

VAGINAL RING

Most steroid hormones are absorbed efficiently through the vaginal epithelium and can be released from vaginal rings made out of polymers such as Silastic or ethylvinyl acetate. As a delivery system, the vaginal ring is the only long-acting method that is under the user's immediate control. It can be easily inserted, checked, removed, and replaced by the user. Other advantages include the following:

- its use is not related to coitus
- it provides a constant rate of drug release, resulting in a steady plasma level of the minimum dose required for contraception
- metabolic side effects are reduced by avoiding the first-pass effect through the liver
- in the case of accidental pregnancy or if protection is no longer required, plasma levels fall rapidly to zero.

Fertility returns promptly after the ring is removed. In 2001, the FDA approved the first contraceptive ring for use in the United States. The ring, which releases 15 µg ethinyl estradiol and 120 µg etonogestrel daily, is left in place for 3 weeks and then is removed for 1 week to allow for withdrawal bleeding. Like the pill, it acts mainly by inhibiting ovulation and it is highly effective when used correctly. Experience to date suggests that it is well accepted by users and their partners and that it does not cause untoward local effects.

IUDS

Although IUDs are the most commonly used reversible method of contraception worldwide, their use in the United States has plummeted from 7.1% of married women in 1981 to just 0.5% of women between the ages of 15 to 44 years in 1995. Much of the decrease in use of this long-term, highly effective method of contraception can be attributed to concerns about the risk of pelvic infections stemming from studies of IUDs in the 1970s. In particular, the Dalkon Shield IUD was associated with an increased risk of infection and was removed from the market in 1975. Today, pelvic infection among users of modern IUDs is primarily associated with exposure to

sexually transmitted infections; the risk among IUD users at no risk for sexually transmitted infections is extremely low.

Currently, two IUDs are available for use in the United States. The most commonly used IUD is the copper T 380A, which is made of polyethylene with fine copper wire wound around the stem and copper sleeves on the two arms of the “T”. It remains effective for at least 10 years. The copper IUD is the most cost-effective method of contraception in the United States over 5 years of use. The FDA approved a progestogen-releasing IUD in 2000; this IUD releases 20 µg levonorgestrel per day for 5 years. The progestogen plays a role in the mechanism of action and decreases the amount and duration of menstrual bleeding and dysmenorrhea. Both IUDs are highly effective, with typical use failure rates ranging between 0.1% and 0.8% in the first year of use (see Table 30.1). Over the long term, IUD failure rates are similar to those of tubal sterilization, which makes it an ideal reversible alternative to sterilization for many women. Both the copper and levonorgestrel IUDs also protect against ectopic pregnancy. However, among women who become pregnant while using an IUD, the proportion of pregnancies that are ectopic is higher than it is among women who use no contraception.

The primary mechanism of action of IUDs appears to be prevention of fertilization as demonstrated by studies finding significantly decreased numbers of fertilized ova in the fallopian tubes of copper IUD users compared with women who use no contraception. IUDs also act by stimulating an inflammatory response in the uterine cavity, which decreases sperm transport, impedes the ability of sperm to fertilize the ovum, and may be spermicidal. The copper in copper-bearing IUDs enhances this response. In the progestogen-releasing IUD, the hormone also acts on the cervical mucus and ovarian function to prevent fertilization. IUDs may also act to prevent implantation if fertilization occurs.

The primary health concern with the use of IUDs has been the risk of upper genital tract infection. Early studies overestimated the association between IUD use and PID due to inappropriate control groups and lack of control for confounding factors. However, studies of modern IUDs among women at low risk for sexually transmitted infections have shown that the risk of infection is primarily associated with insertion of the IUD, is low (1 per 1,000 woman-years), and is largely limited to the first 20 days after insertion (Fig. 30.1). A randomized clinical trial of 1,833 U.S. women having IUDs inserted compared antibiotic prophylaxis to placebo and found very low rates of infection (1 participant in each group) during the 90 days after insertion. A large international cohort study reported an incidence rate of acute PID of 0.6 per 1,000 woman-years of copper IUD use. Some studies of levonorgestrel IUDs have shown decreased risk of PID compared with copper IUDs, possibly due to thickening of the cervical mucus, which could act as a barrier to bacteria; this finding needs to be confirmed in future studies. In addition, recent studies reduce concerns about any association between IUD use and tubal infertility.

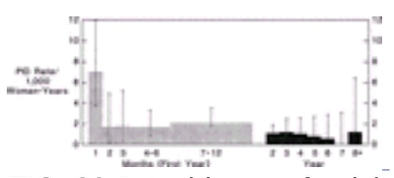

FIG. 30.1. Incidence of pelvic inflammatory disease (PID) by duration of intrauterine device use. The 95% confidence intervals are shown. (From Farley TMM, Rosenberg MJ, Rowe PJ, et al. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet* 1992;339:785–786.)

The IUD is an appropriate method of contraception for many women. Advantages of IUD use include it being a long-term, highly effective, reversible method, with little action required of the user. Exposure to sexually transmitted infections is one of the most important factors to assess when a woman is considering IUD use, and women with current sexually transmitted infections, PID, or increased risk of sexually transmitted infections are generally not appropriate candidates for IUDs. Young age and nulliparity are not by themselves factors that restrict IUD use, although studies have shown a higher risk of expulsion among young and nulliparous women. Some studies have shown that IUD use in nulliparous women is not associated with tubal infertility, and there is no delay in return to fertility after IUD removal. Therefore, young women and nulliparous women may be appropriate candidates for IUD use, if they are at low risk of sexually transmitted infections. Conditions for which women should not use an IUD include the following:

- pregnancy
- puerperal sepsis
- immediate postseptic abortion
- anatomic abnormalities that distort the uterine cavity
- unexplained bleeding, suspicious for a serious condition
- malignant gestational trophoblastic disease
- cervical cancer
- breast cancer (for progestogen-releasing IUDs only)
- endometrial cancer
- uterine fibroids with distortion of the uterine cavity
- PID—current or within the last 3 months
- sexually transmitted infections—current or within the last 3 months
- known pelvic tuberculosis.

Other conditions for which women generally should not use IUDs are listed in Table 30.2.

IUDs can be inserted at any time during the menstrual cycle if the woman is not pregnant. For postpartum women, immediate IUD insertion (within 10 minutes of expelling the placenta) may reduce the risk of expulsion. The IUD can also be inserted after 4 weeks postpartum without an increased risk of perforation or expulsion. However, for breast-feeding women, the progestogen-releasing IUDs generally should not be inserted until 6 weeks postpartum because of theoretical concerns about exposing the newborn to steroid hormones. An IUD can also be inserted immediately after an uncomplicated first trimester spontaneous or induced abortion, but it is recommended that insertion be delayed until involution is complete after second trimester abortions.

A pelvic exam is necessary before IUD insertion to rule out pregnancy and pelvic infection and to identify the position and mobility of the uterus. Accurate determination of uterine position is necessary to prevent perforation; the incidence of perforations with IUD insertion is about 1 per 1,000 insertions. Because the main risk of infection occurs with insertion, careful aseptic technique is required. Randomized clinical trials have not shown differences in infection rates or early discontinuation of IUD use when comparing antibiotic prophylaxis with placebo; however, there was a significant decrease in unscheduled return visits among the group who received antibiotics in one trial. Use of NSAIDs before insertion may reduce discomfort; local anesthesia is another option that is infrequently needed. Once the IUD is inserted, the woman should check for the IUD string so that she will later be able to confirm its presence and length.

IUD users have high rates of continuation—approximately 80% at 1 year of use in the United States. Increased menstrual bleeding and pain are the most common side effects reported with copper IUD use and are a primary reason for discontinuing the method. Because levonorgestrel-releasing IUDs generally reduce the amount of cramping and bleeding, women with heavy menstrual bleeding or dysmenorrhea may benefit from these IUDs. Treatment with NSAIDs has been shown to effectively reduce pain and blood loss. In contrast, amenorrhea is a major cause of discontinuation of the levonorgestrel-releasing IUD; it occurs in about 5% of users in the first year of use.

IUD expulsions occur in about 5% of users. Risk factors for expulsion include young age, nulliparity, and heavy bleeding. IUD users should check for the presence and length of the IUD strings frequently, at least after every menstrual period, to confirm that the IUD is still in place. Although pregnancy in an IUD user is an unusual event, when it does occur and the IUD strings are visible, the IUD should be removed to decrease the risk of spontaneous abortion, preterm delivery, and sepsis.

MECHANICAL BARRIER METHODS

The male latex condom is the only method of contraception proven to be highly effective in preventing both pregnancy and HIV infection when used consistently and correctly. Male condom use also reduces the risk of gonorrhea and chlamydial infection. Inconsistent or incorrect use, however, undermines this great potential benefit. Polyurethane male and female condoms have been less fully evaluated for contraception and disease prevention but consistent and correct use of these methods should also provide substantial dual protection. The potential for condoms to be highly effective if used consistently and correctly is in stark contrast to the long-standing notion that condoms are not highly effective. In fact, as shown in Table 30.1, perfect use of male condoms is more effective than typical use of oral contraceptives, which highlights the role of male condom users. It is now clear that true condom failure is infrequent but that failure to consistently and correctly use condoms is not.

Diaphragms and cervical caps may also provide some protection against some sexually transmitted infections, particularly gonorrhea and chlamydial infections, but there is substantially less evidence for this protection than for male condoms. Pending further evidence, protection against sexually transmitted infections should be

presumed to be less complete than for male condoms and protection against HIV infection should not be assumed at all.

Male Condom

The Centers for Disease Control and Prevention provide the following instructions for correct use of male condoms:

1. Use a new condom with each act of sexual intercourse.
2. Handle the condom carefully to avoid damaging it with fingernails, teeth, or other sharp objects.
3. Put the condom on after the penis is erect and before any genital contact with the partner.
4. Ensure that no air is trapped in the tip of the condom.
5. Ensure adequate lubrication during intercourse, possibly requiring the use of exogenous lubricants.
6. Use only water-based lubricants with latex condoms (oil-based lubricants can weaken latex).
7. Hold the condom firmly against the base of the penis during withdrawal, and, to prevent slippage, withdraw while the penis is still erect.

Condom breakage rates in the United States are low, about 2 broken condoms per 100 used. Proper use reduces the risk of condom breakage. Condom slippage may be more likely to contribute to pregnancies than condom breakage, which highlights the importance of following instruction 7 given above. Most condom failures are the result of inconsistent or incorrect use rather than failures of the product per se.

Female Condom

In 1993, the FDA approved the female condom for marketing and distribution in the United States. The device is a prelubricated, loose-fitting polyurethane sheath that is 17 cm in length and has a flexible ring at each end. One ring is loose inside the condom and is used to insert the condom into the vagina; the other ring lines the opening of the condom, remains outside the vagina, and covers a portion of the external genitalia during intercourse. The woman should insert the condom by holding the sheath at the closed end and grasping the inner ring; the inner ring should then be inserted toward the apex of the vagina by the index finger, making sure that the sheath is not twisted and that the outer ring remains outside the vagina. It is important that the penis is guided into the opening of the sheath to reduce the likelihood that penetration around the sheath occurs during intercourse. Thus, although this condom is female inserted, its proper use, like that of the male condom, requires the cooperation of both partners.

Diaphragm

The diaphragm is a latex, dome-shaped cup with a flexible spring rim. Diaphragms range in size from 50 to 95 mm and require vaginal examination for proper fitting. An appropriately placed diaphragm should completely cover the cervix; the posterior rim should lie in the posterior fornix and the anterior rim should fit posteriorly to the symphysis pubis, with about 1 cm between the rim and the symphysis pubis. In general, the largest diaphragm that is comfortable for the woman should be prescribed. If the diaphragm is too small, it may be displaced during coitus; if it is too large, it may cause discomfort or trauma. Diaphragms are used with spermicidal creams or jellies applied to the inside of the dome. After insertion, the diaphragm substantially reduces the risk of pregnancy for about 6 hours. If coitus occurs after that time, additional spermicidal cream or jelly should be placed intravaginally without removing the diaphragm. Likewise, additional spermicide should be placed intravaginally if coitus is repeated within 6 hours. The diaphragm should remain in place for at least 6 hours after coitus but for no longer than 24 hours to reduce the risk of toxic shock syndrome.

Cervical Cap

The cervical cap is a latex cup with a firm rim that covers the cervix and fits snugly around its base. Four sizes of the cap are available (with inner diameters of 22, 25, 28, and 31 mm). The properly fitted cap has a rim with an inner diameter that is almost the same as the diameter of the base of the cervix, so the cap remains in close contact with the cervix. The cap should be long enough to cover the entire cervix without resting on the cervical os. If the cap is too large, it is more likely to be displaced during coitus; if it is too small, it may cause trauma. The device is used with spermicide placed in the cap before insertion and is effective for 48 hours after insertion. It should be removed no longer than 48 hours after insertion to reduce the risk of toxic shock syndrome.

SPERMICIDES

Spermicides, formulated as vaginal foams, gels, creams, film, suppositories, and tablets, usually contain the surfactant nonoxynol 9 in the United States; the surfactants octoxynol and benzalkonium chloride are widely available elsewhere. Spermicides are not highly effective for contraception when used alone, even when used consistently and correctly. When used alone, or with a mechanical barrier (condoms, diaphragms, or cervical caps), spermicides should be inserted just before coitus.

The hope that vaginal use of nonoxynol 9 would reduce the risk of sexually transmitted infections, including HIV infection, has met with disappointment. Three randomized, controlled trials have failed to demonstrate any benefit in preventing HIV infection and the most recent of these suggests that frequent use of spermicides containing nonoxynol 9 may actually enhance the risk of acquiring infection; the U.S. Centers for Disease Control and Prevention and the World Health Organization now recommend that spermicides containing nonoxynol 9 not be used for prevention of sexually transmitted infections, including HIV infection. Evidence suggests that vaginal spermicides containing nonoxynol 9 are not effective in preventing cervical gonorrhea or chlamydial infection.

FERTILITY AWARENESS-BASED METHODS

Fertility awareness-based methods use signs and symptoms to estimate a woman's fertile period, during which time the couple should refrain from unprotected intercourse. Calendar methods estimate the fertile days based on the length of a woman's usual menstrual cycle; the other three fertility awareness-based methods are based on monitoring physiologic changes throughout the menstrual cycle. About 25% of typical users of fertility awareness-based methods become pregnant in the first year of use. Failure rates are based on couples who abstain from sex during the fertile period and may be different for couples who choose to use barrier methods during that time. The relatively high failure rates are partially due to inconsistent use of the method, but they are also due to the lack of reliability in estimating the fertile window. One study that measured timing of ovulation with daily urine samples found that in only 30% of women did the actual fertile window fall within the days of the fertile window as estimated from calendar calculation. Training in how to use these methods, as well as monitoring the menstrual cycles for several months, is necessary for successful use.

Calendar Methods

Calendar-based methods require abstaining from unprotected intercourse during the woman's fertile period, which is estimated from the typical length of her menstrual cycle and from assumptions about the timing of ovulation, the length of time the ovum is capable of being fertilized, and the length of time sperm can survive in the female genital tract. One method estimates the fertile period to be from the length of the shortest cycle minus 18 to the length of the longest cycle minus 11. For example, if the woman's shortest cycle was 25 days and her longest cycle was 29 days, her fertile period (i.e., when abstinence is required) would be from day 7 through day 18. Another version, the standard days method, simply states that for women whose cycle lengths are between 26 and 32 days, the fertile period is from days 8 through 19 of the cycle.

Cervical Mucus Method

The cervical mucus method entails checking the quality and quantity of cervical mucus each day; the fertile period is indicated by clear, wet, and slippery mucus. Abstinence from unprotected intercourse is necessary during menses, every other day during the preovulatory period (as intercourse interferes with interpreting the cervical mucus signs), and from the time fertile mucus appears through 3 days after the last day of fertile mucus.

Basal Body Temperature Method

The basal body temperature method is based on temperature changes throughout the menstrual cycle. A rise of 0.4 to 0.8 degrees above the mean temperature of the preovulatory phase for 3 days indicates ovulation has occurred. Therefore, abstinence is required from the time of menses until 3 days after the rise in temperature.

Symptothermal Method

The symptothermal method is the use of at least two of the previously described methods and may also rely on other changes during the menstrual cycle, including

midcycle pain and bleeding, as well as position and texture of the cervix.

EMERGENCY CONTRACEPTION

Emergency Contraceptive Pills (ECP)

Emergency contraception was once called “the best kept secret of family planning.” In the early 1970s, Yuzpe and colleagues tested combinations of ethinyl estradiol and norgestrel for postcoital contraception, based on a single dose of 50 µg ethinyl estradiol and 500 µg norgestrel. Subsequent clinical trials led them to conclude that the most successful regimen consisted of two doses of 100 µg ethinyl estradiol and 500 µg levonorgestrel, with the first dose taken within 72 hours of unprotected intercourse, and the second dose taken 12 hours later.

When started within 72 hours of unprotected intercourse, combined ECPs prevent about 75% of pregnancies. About half of users report nausea and about 20% experience vomiting. A randomized clinical trial showed that pretreatment with 50 mg of meclizine significantly reduces the frequency and severity of nausea and vomiting.

Various doses of levonorgestrel have also been tested since the 1970s for emergency contraception. A large multinational, randomized, double-blind clinical trial was conducted comparing the Yuzpe regimen and levonorgestrel treatment (one 750 µg dose followed by a second 750 µg dose 12 hours later) when started up to 72 hours after unprotected intercourse. Results showed that levonorgestrel was not only better tolerated but was also more effective than the Yuzpe regimen, preventing 89% of expected pregnancies among women who correctly used the treatment. It also showed that the earlier either treatment was taken after the act of unprotected intercourse, the more effective it was. Since then, it has been demonstrated that both 750 µg pills can be taken together in a single dose (1.5 mg levonorgestrel) with the same effectiveness and side effects as the two dose regimen.

A primary mechanism of action of ECPs is to inhibit, delay or otherwise interfere with normal ovulation, thereby preventing fertilization. ECPs may also alter the endometrium and impair implantation, although one study found that use of levonorgestrel ECPs did not impair endometrial morphology. ECP use does not disrupt an established pregnancy.

ECPs are safe for use by almost all women. Concerns about ECP distribution have included those regarding advance provision and multiple administrations. Studies have shown that women who were given an advance supply of ECPs had the same rates of unprotected intercourse as controls, followed the treatment regimen correctly, were more likely to use one dose of ECPs, but were no more likely than the control group to use ECPs repeatedly.

Emergency Use of Copper-Bearing IUDs

Copper-bearing IUDs are extremely effective when used as emergency contraception (99%). The IUD must be inserted within 5 days of unprotected intercourse. This method is most appropriate for women who want long-term, highly effective contraception, and have no contraindications to IUD use.

STERILIZATION

Vasectomy and tubal sterilization are intended to be permanent and are appropriate only for women and men who have made a fully informed and well-considered decision to permanently prevent pregnancy. Although some sterilizations are potentially reversible, depending on factors including the sterilization procedure, the length of normal fallopian tube remaining, the age of the woman (tubal sterilization), and the length of time between the sterilization and reversal procedures (vasectomy), many sterilizations are not reversible. Further, the costs of sterilization reversal or in vitro fertilization are prohibitive for many who regret having had a sterilization procedure.

Although vasectomy and tubal sterilization have been shown to be safe and highly effective, vasectomy is somewhat safer, partly because most vasectomies are done with local anesthesia and tubal sterilizations are intraabdominal procedures. Vasectomy is believed to be somewhat more effective than tubal sterilization and its effectiveness is easily assessed by semen analysis. The long-term effectiveness of vasectomy, however, has been less completely studied than that of tubal sterilization; some trials suggest that the effectiveness of vasectomy, like tubal sterilization, may vary according to the method of occlusion.

Counseling of those considering sterilization is critically important. Such counseling should include not only the anticipated risks and benefits of the surgery but also the possibility of later regretting having had the procedure. The strongest predictors of later regretting tubal sterilization are young age at the time of sterilization and substantial conflict between the woman and man at the time of sterilization. Women considering tubal sterilization should understand that pregnancy is possible even remote from sterilization, and they should understand that a high proportion of pregnancies after tubal sterilization are ectopic gestations.

Vasectomy

Vasectomy, or transection and occlusion of the vas deferens, is usually performed in an outpatient setting with local anesthesia and without premedication. After incising or puncturing the skin of the scrotum, the vas is identified, dissected free of its fascial sheath, and divided. The cut ends of the vas are then occluded by ligation, coagulation of the mucosa, or, rarely, clip application. Fascial interposition is frequently performed after ligation or coagulation by pulling the sheath over one of the vas ends and suturing it—to reduce the likelihood of subsequent spontaneous anastomosis. The most frequent complications of vasectomy are hematoma formation and infection, each of which occurs in about 2% of procedures. Death and serious morbidity are rare. No long-term serious adverse health effects have been documented, and the best available evidence suggests no effect on risk of cardiovascular disease, prostate cancer, or testicular cancer.

Although there is a substantial decrease in the concentration of sperm in the semen by 3 days after vasectomy, complete absence of sperm may take 16 weeks or more, depending in part on the number of ejaculations. Semen analysis should be performed, where feasible, after 12 weeks or 20 ejaculations and temporary contraception should be used in the interim. The time to azoospermia after vasectomy is under study and may vary according to surgical technique.

Tubal Sterilization

The proportion of sterilizations done on an interval basis (not pregnancy-associated) varies from country to country. Approximately one half of tubal sterilizations in the United States are performed after vaginal delivery or at cesarean section and the other half are performed at a time unrelated to pregnancy. The timing of the procedure with respect to pregnancy can affect the surgical approach, the method of tubal occlusion, and the choice of anesthetic. For example, interval procedures are usually performed in the United States by laparoscopy using coagulation (the bipolar technique is illustrated in Fig. 30.2), silicone rubber bands (Fig. 30.3), or clips (the spring clip technique is illustrated in Fig. 30.4) under general anesthesia; laparoscopic sterilization can be even more safely performed with local anesthesia. By contrast, procedures at the time of cesarean section require no additional anesthesia and usually involve partial salpingectomies (the modified Pomeroy method is illustrated in Fig. 30.5); procedures postvaginal delivery are performed by minilaparotomy with subumbilical incisions and likewise usually involve partial salpingectomies.

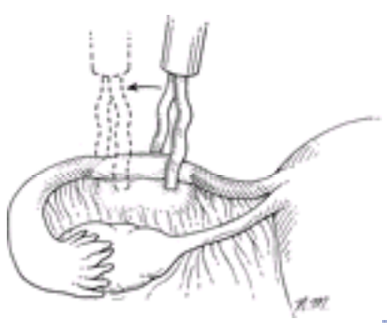

FIG. 30.2. Bipolar method. A 3-cm minimum zone of isthmic tube is desiccated with bipolar forceps. The paddles of the forceps extend across the tube onto the mesosalpinx. (From Peterson HB, Warshaw J, Pollack A. Tubal sterilization. In: Rock JA, Thompson JD, eds. *TeLinde's operative gynecology*, eighth ed. Philadelphia: JB Lippincott Co, 1997:529–547.)

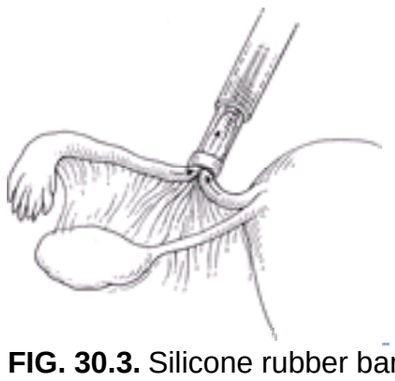

FIG. 30.3. Silicone rubber band method. The isthmic portion of the tube is retracted into the applicator barrel using grasping tongs, which should completely surround the tube. To avoid excessive traction on the tube and its mesentery, the applicator barrel is advanced toward the tube during this retraction process. (From Peterson HB, Warshaw J, Pollack A. Tubal sterilization. In: Rock JA, Thompson JD, eds. *TeLinde's operative gynecology*, eighth ed. Philadelphia: JB Lippincott Co, 1997:529–547.)

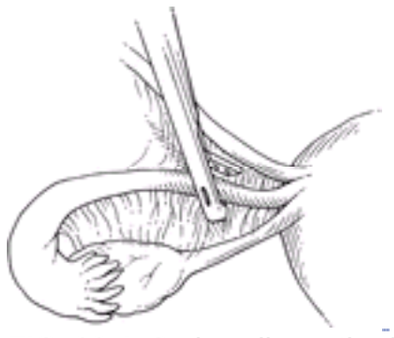

FIG. 30.4. Spring clip method. The clip is applied to the mid-isthmus at a 90-degree angle to the long axis of the tube. The hinge of the clip should be pressed against the tube, and the tips of the clip should extend onto the mesosalpinx. (From Peterson HB, Warshaw J, Pollack A. Tubal sterilization. In: Rock JA, Thompson JD, eds. *TeLinde's operative gynecology*, eighth ed. Philadelphia: JB Lippincott Co, 1997:529–547.)

FIG. 30.5. Pomeroy method. **A**: A loop of the isthmic portion of the tube is elevated and ligated at its base with one or two ties of no. 1 plain catgut suture. If performed through a minilaparotomy incision, these ties should be held long to prevent premature retraction of the tubal stumps into the abdomen when the loop of tube is transected. **B**: A fenestration is bluntly created through the mesentery within the tubal loop, and each limb of the tube on either side of this fenestration is individually cut. The cut ends of the tube are inspected for hemostasis and allowed to retract into the abdomen. (From Peterson HB, Warshaw J, Pollack A. Tubal sterilization. In: Rock JA, Thompson JD, eds. *TeLinde's operative gynecology*, eighth ed. Philadelphia: JB Lippincott Co, 1997:529–547.)

The likelihood of pregnancy after tubal sterilization varies according to age at the time of the procedure and sterilization technique (Table 30.3). The chance that pregnancies are ectopic varies by method. Among women in the U.S. Collaborative Review of Sterilization, the highest proportion of pregnancies that were ectopic occurred after bipolar coagulation (65%), followed by interval partial salpingectomy (43%), silicone rubber band application (29%), postpartum partial salpingectomy (20%), unipolar coagulation (17%), and spring clip application (15%). Further, the proportion of pregnancies that were ectopic for all methods combined increased over time, being three times as high (61%) in 4 to 10 years after sterilization as in the first 3 years (20%).

Age at sterilization	Probability of pregnancy (%) (Range)
18–27 y	
Bipolar coagulation	54.3 (28.3–80.4)
Unipolar coagulation	3.7 (0.0–11.1)
Silicone rubber band application	33.2 (10.6–55.9)
Spring clip application	52.1 (31.0–73.3)
Interval partial salpingectomy	9.7 (0.0–28.6)
Postpartum partial salpingectomy	11.4 (1.6–21.1)
28–33 y	
Bipolar coagulation	21.3 (9.6–33.0)
Unipolar coagulation	15.6 (0.0–31.4)
Silicone rubber band application	21.1 (6.4–35.9)
Spring clip application	31.3 (15.1–47.5)
Interval partial salpingectomy	33.5 (0.0–74.3)
Postpartum partial salpingectomy	5.6 (0.0–11.9)
34–44 y	
Bipolar coagulation	6.3 (0.1–12.5)
Unipolar coagulation	1.8 (0.0–5.3)
Silicone rubber band application	4.5 (0.6–8.4)
Spring clip application	18.2 (0.0–36.4)
Interval partial salpingectomy	18.7 (0.0–39.6)
Postpartum partial salpingectomy	3.8 (0.0–11.4)

[a]Cumulative probability per 1,000 procedures and 95% confidence interval.

Source: Adapted from Peterson HB, Xia Z, Hughes JM, et al. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996;174:1161–1170, with permission.

TABLE 30.3. *Life-table cumulative probability of pregnancy among women undergoing tubal sterilization in the U.S. collaborative review of sterilization by age* [a]

Death from tubal sterilization is rare, 1 to 2 deaths per 100,000 procedures, with most deaths attributable to complications of general anesthesia. Major complications, principally unintended laparotomies, occur in 1% to 2% of procedures.

The potential for late sequelae of tubal sterilization has been assessed. There is strong evidence against a purported post-tubal ligation syndrome of menstrual abnormalities. Sterilized women in the U.S. Collaborative Review of Sterilization were no more likely than women whose partners underwent vasectomy to have menstrual abnormalities within 5 years after sterilization. In the same study, sterilized women were more likely to undergo hysterectomy than women whose partners were sterilized, but nonbiologic factors were likely explanations.

Young age at sterilization, regardless of the number of children, is a strong predictor of later regretting having had the procedure. Among women sterilized at 18 to 24 years who were followed in the U.S. Collaborative Review of Sterilization, the cumulative probability of requesting information about reversal within 14 years was 40%.

SUMMARY POINTS

- The effectiveness of some contraceptive methods—including oral contraceptives, barrier methods, and fertility awareness-based methods—is highly dependent on whether they are used consistently and correctly. The effectiveness of other methods—including IUDs, implants, and injectables—is less dependent on user characteristics.
- Oral contraceptives have been studied more extensively than any other method. They are nearly 100% effective if taken daily, but they are substantially less effective with typical use. For healthy, nonsmoking women, the health benefits of oral contraceptive use far exceed the health risks.
- Four new contraceptive methods are available in the United States—a contraceptive patch, a combined injectable, a vaginal ring, and an IUD. The first three deliver both an estrogen and a progestogen; the fourth delivers a progestogen alone.
- Many women who desire contraception are also at risk for sexually transmitted infections, including HIV infection. For such women, consistent and correct use of a male latex condom is highly effective in protecting against both pregnancy and some sexually transmitted infections, including HIV infection. Spermicides containing nonoxynol 9 are no longer recommended for preventing sexually transmitted infections, including HIV; frequent use of spermicides may actually enhance the risk of acquiring HIV infection.
- IUDs are highly effective and provide long-term protection against pregnancy. Women at no risk of sexually transmitted infections are at exceedingly low risk of pelvic inflammatory disease from IUD use.
- Male and female sterilization are highly effective but should be chosen only by those who wish to permanently prevent pregnancy. Young age at sterilization is a key risk factor for regretting having had a tubal sterilization.

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Chapter 31

Suzanne R. Trupin

Induced Abortion

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Approximately 1.18 million abortions were performed annually in the United States in 1997. This number has decreased from the 1.61 million abortions in 1990. Each year, 2% of women of reproductive age (15–44) terminate a pregnancy legally in the United States. With the rate of abortion in the 1980s, it was estimated that 43% of women in the United States would have a pregnancy termination at some point in their reproductive life. The most recently published rate of abortion is approximately 20 per 1,000 women between the ages of 15 to 44. This rate has decreased from 25 per 1,000 women in 1990. The abortion ratio is about 306 per 1,000 live births. This ratio has decreased from 345 abortions per 1,000 live births in 1990 (Table 31.1). Regardless of contraceptive availability, about half the 6 million pregnancies occurring each year are reportedly unplanned. Of the unplanned pregnancies, approximately half are terminated by induced abortion. This rate has remained fairly constant since 1980. The typical patient seeking an abortion has been young, white, unmarried, and poor. Statistics from 1972 are indicative of the period prior to *Roe v. Wade* and the legalization of abortion in the United States (Table 31.1 and Fig. 31.1, Fig. 31.2 and Fig. 31.3). Worldwide, 53 million abortions are performed annually with 20 million reportedly being done illegally. Illegal abortions remain very unsafe and may account for 50,000 to 100,000 deaths each year.

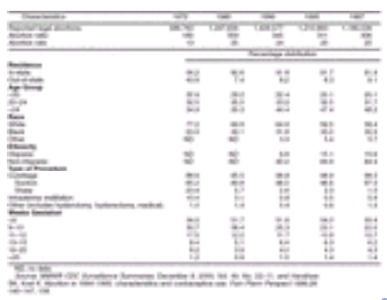

TABLE 31.1. *Legal abortions, abortion ratios, and abortion rates in selected years from 1972 to 1997 and characteristics of women who obtained legal induced abortions in those years*

FIG. 31.1. Fertility rate and abortion ratio and rate, by year—United States, 1972–1995. (From Koonin LM, MacKay AP, Berg CJ, et al. Pregnancy-related mortality surveillance—United States, 1987–1990. *MMWR CDC Surveill Summ* 1997;46:10.)

FIG. 31.2. Abortion ratio (per 1,000 live births) by age group (in years) of women who obtained a legal abortion, selected states—United States, 1974–1997. (From: Koonin LM, Strauss LT, Chrisman CE, et al. Abortion surveillance—United States, 1997. *MMWR CDC Surveill Summ* 2000;49:1–11.

FIG. 31.3. Rate of induced abortion by gestational week for 1997. *MMWR CDC Surveill Summ* 2000;49:1–11.

Abortion remains primarily a surgical procedure with 97% being done by suction curettage. The first medical abortion (in the U.S.) was done in the 1960s with antimetabolites. A medical abortion is accomplished by drug induction without primary surgical intervention. In September 2000, the U.S. Food and Drug Administration (FDA) approved a more effective yet more complex regimen, which includes mifepristone (initially developed under the manufacturer designation RU-486), an antiprogestin, as the initiating medication, followed by off-label use of misoprostol to be administered in the physician's office. Mifepristone, even if given with newer evidence-based medicine protocols using an equally effective 200-mg dose, carries a cost of $270 per 600-mg dose. This high cost has been one factor that has hampered the widespread use of this medical regimen for abortions. Nonetheless, about half of abortion providers were offering medical abortions within the first 6 months of 2001, and some centers reported that 10% to 15% of their terminated pregnancies were medical abortions. Drug protocols, with greater flexibility in dosage, timing of medication to decrease the interval from initiation to completion of the abortion, and home administration protocols to lower costs, will likely increase the number of providers offering medical abortions. These drug protocol modifications should also produce an overall shift from surgical to medical abortions.

LEGALIZATION

Since the landmark 1973 Supreme Court decision legalizing abortion, hundreds of laws, both federal and state, have been proposed or passed. This makes induced abortion the most actively litigated and highly publicized area in the field of medicine. The two most controversial topics of legislation involve debate on an appropriate definition for “viability” and the need for legislating parental involvement in a minor's decision-making process.

ABORTION COUNSELING

Some patients find the decision to have an abortion an easy one; for others it takes time and the consultation of a variety of providers and counselors. It may also take time to filter through multiple layers of providers to find a facility that performs pregnancy terminations, as over 80% of U.S. counties have no abortion providers. Statistics from the Alan Guttmacher Institute indicate that almost half of the women having abortions beyond 15 weeks of gestation state their procedure was delayed because of problems in funding or locating abortion services. Preoperative counseling for abortions should include a discussion of all options regarding the pregnancy within the context of the patient's concerns driving her decision to abort (Fig. 31.4). This should include discussion of medical versus surgical procedures, continuing the pregnancy, and the various options for legal adoption. Discussion should focus on the decision-making process and the patient's support system. Of utmost importance is to ensure that patients are not being coerced into their decision.

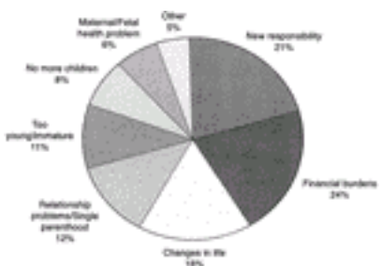

FIG. 31.4. Most important concerns driving the decision to abort. (From Torres A, Forrest JD. Why do women have abortions? Fam Plann Perspect 1988;20:169–176, with permission.)

Counseling sessions should also provide medical information, review pertinent medical and gynecologic history, and specifically discuss any previous abortion procedures. Statistics show that 47% of women who have an abortion have had a least one previous abortion. Medical personnel, such as obstetricians, perinatologists, and nurses, should be enlisted to review medical risks and benefits within the context of the patient's medical and pregnancy history. Patients should be informed of the risks of the procedure selected, and full isclosure of information includes discussing the risks of the abortion process as well as the risks of continuing the pregnancy. A full disclosure of methods regarding surgical versus medical abortions is mandatory. If a surgical abortion is preferred, the patient must then understand that the procedure is most often done under local anesthesia. Because the patient is awake during the procedure, she may verbalize a change of intent at this time. If this occurs, consent must be reestablished before the abortion may proceed.

The medical abortion counseling process takes longer than the surgical abortion counseling session. In the event the patient chooses a medical abortion, a description of the FDA protocol or any other evidence-based protocol must be presented to the patient. The patient will need to sign the mifepristone medication consent form. If the patient's medical abortion process will differ from the process described in this consent form, she must fully understand the differences. The patient needs to clearly appreciate that the passage of fetal tissue will present with bleeding, cramping, nausea and, in some cases, vomiting. There will also be some pain with the procedure. Patients will be told that they will be provided with sufficient pain medication and antiemetics. The patient needs to be given clear instructions on how to insert the misoprostol dose vaginally and to be taught how to differentiate bleeding from hemorrhage. This disclosure of information must be part of the consent process. There is a 2% to 8% chance of an incomplete abortion, which would require a follow-up surgical dilation and curettage for completion. Counselors must, therefore, indicate to the patient that follow-up examination visit(s) is (are) encouraged to ensure the completion of the pregnancy termination and the health of the patient. Finally, patients undergoing a medical abortion need telephone access and, more importantly, assistance with transportation in the event of an emergency during the abortion process (i.e., hemorrhage). Providers need to comply with all relevant applicable local, state and federal laws and ordinances.

In conclusion, the intent of the counseling session is to make sure that as much information as possible is available to the woman requesting a pregnancy termination in order for her to make an appropriate, informed, and independent decision. Counselors need to remain involved in caring for the patient throughout the abortion process. Preabortion counseling should also explore the subjects of future contraception and protection against sexually transmitted diseases (STDs).

INDICATIONS FOR ABORTION

Medical Indications

Medical indications for abortion have narrowed with advances in perinatal care. If data are available for a given indication, most perinatologists and abortion counselors prefer to put the risks in statistical perspective. In particular, these professionals are opposed to the concept of “recommending abortion” even in cases where maternal death is a possibility. Induced abortion is safer, with respect to mortality and morbidity, than a term delivery. The relative risk of death associated with childbirth may be ten times higher than that associated with abortion although the absolute risks for either are low (Table 31.2). Medical abortions in early pregnancy circumvent surgical and anesthetic risks associated with either delivery or surgical abortion. However, there is no evidence in the literature that suggests this makes medical abortion safer than surgical abortions. In the 1980s, it was estimated that maternal mortality was reduced seven-fold by a first trimester abortion compared to women carrying their fetus to term. More recent data indicate that a first trimester abortion may be even safer now; consequently, any discussion of risk must always be put in perspective.

Vacuum curettage[a] ≤12 weeks	0.05
Dilation and evacuation 13–15 wks[a]	2.00
Dilation and evacuation 16–20 wks[a]	6.5
Dilation and evacuation >21 wks[a]	11.9
Overall abortion mortality[b,c]	0.8
Overall maternal mortality[b]	10–20

[a]Deaths per 100,000 induced abortions.
[b]Maternal deaths per 100,000 live births; range accounting for reporting variances.
[c]*MMWR, CDC Abortion Surveillance—United States*, August 8, 1997, Vol. 46, No. ss–4.

TABLE 31.2. *Case-fatality rates for induced abortion and pregnancy*

Maternal conditions that may be considered a medical indication for an abortion include: renal failure, diabetic retinopathy, sickle cell disease, cardiac disease, neoplasia, autoimmune disease, and psychiatric disease. Cardiac conditions that may result in maternal death include severe mitral stenosis, coarctation of the aorta with vascular involvement, uncorrected tetralogy of Fallot, aortic stenosis, previous myocardial infarction, myocardial infarction during pregnancy, artificial heart valves, and Marfan syndrome with aortic involvement. A cardiac anomaly with potentially greater mortality is the Eisenmenger syndrome with pulmonary hypertension. Other medical indications include intrauterine infections, chorioamnionitis, and preterm premature rupture of membranes. Radiation treatments, chemotherapy, and live virus immunizations given inadvertently in early pregnancy are other reasons to discuss the risks and options of an abortion. However, nondirective factual counseling in this area is essential.

Fetal Indications

Despite progress in prenatal diagnosis, most anomalies identified have no real means of treatment other than abortion or, otherwise termed, *selective termination.* Maternal–fetal surgery involves surgical correction of fetal anomalies in utero. These anomalies are more easily detected with newer ultrasound technology increasing fetal assessment capabilities. Yet, this type of surgery remains experimental and controversial with little long-term outcome data. At present, fetal indications for induced abortion include those anatomic conditions incompatible with life (e.g., anencephaly) and major congenital abnormalities (e.g., hypoplastic left heart, severe neural tube defects). Recent literature studied the most common indications for selective termination. Parents are more likely to electively abort if a central nervous system (CNS) anomaly was discovered in utero compared to a non-CNS anomaly (Table 31.3.). This was true for all grades of severity within the CNS anomaly classification compared to all grades of severity for the non-CNS anomaly classification.

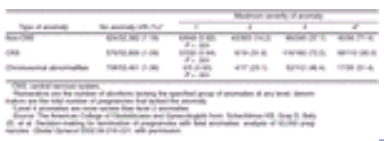

TABLE 31.3. *Abortion rate, by maximum severity of non-CNS anomalies, CNS anomalies, and chromosomal abnormalities*

When an anomaly is diagnosed in time to have a legal abortion, 50% to 80% of women selected abortion, although even the most severe cardiac conditions can theoretically be treated by cardiac transplantation. Most serious anomalies are not diagnosed until well into the second trimester as that is when complete anatomic surveys, by ultrasound, are performed.

SURGICAL ABORTION

Preoperative preparation for most women, after the focused history and consent process, can be fairly simple. The pregnancy is assessed for gestational age. (The abortion facility must be capable of performing the procedure for the gestational age.) Evaluation includes adequate cervical visualization, uterine palpation, and whether a local or general anesthetic is required. Testing for STDs is considered optional but may be beneficial for patients at high risk for an STD. A targeted physical examination is sufficient for a healthy woman. Laboratory analysis must include assessment of the hemoglobin or hematocrit and establishment of a patient's Rh factor status. Pap smears are recommended per usual protocols but are not specifically necessary for the abortion.

Ultrasonography establishes the pregnancy dating, as well as confirming fetal number, placental localization, and the presence of any uterine anomalies or fibroids. Sonography can guide the performance of the procedure by continually imaging the instruments as they are being manipulated within the uterine cavity (Fig. 31.5). For very early terminations, so little placental tissue exists that postprocedure ultrasound imaging is not always helpful in confirming the completeness of the procedure.

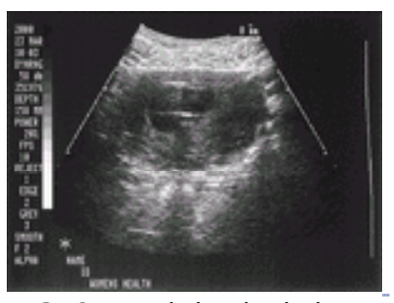

FIG. 31.5. Abdominal ultrasound anteroposterior view of 16-mm, straight vacuum curette visualized in an intrauterine location during a dilation and evacuation procedure for pregnancy termination.

Anesthesia for first trimester and early second trimester procedures is typically local infiltration paracervically with lidocaine, 12 cc of 1% to 2%, or chloroprocaine, 12 cc of 1% to 2%, with the physician and an assistant speaking to the patient to relax and reassure her throughout the procedure. Approximately 80% of women receive only local anesthesia during surgical termination. Preoperative preparation may include acetaminophen, or a nonsteroidal antiinflammatory drug (NSAID) or diazepam. Conscious sedation can be provided with 2.5 to 3.0 mg midazolam. In addition, rapid-acting narcotics, such as fentanyl, are occasionally used.

Cervical Dilation

Forceful cervical dilation can cause cervical lacerations, damage, or permanent incompetence of the internal os, all of which are extremely rare with modern techniques. Early first trimester procedures often require no dilation for the multiparous patient and little dilation with primigravidas. Initially, 400 µg of misoprostol, a cervical dilating agent, may be administered orally a few hours prior to the surgery. For procedures performed at less than 9 weeks from the last menstrual period (LMP), dilation is accomplished with progressive use of graduated cervical dilators. Pratt-type or Teflon Denniston dilators 3 mm and larger, are used serially to enlarge the cervical canal. Beyond this gestational age, medical or mechanical aids for dilation are very helpful. Most commonly employed is the seaweed *Laminaria japonica* (in singles or multiples), which expands over a 3- to 24-hour period to enhance dilation. Successive applications of increasing numbers of *L. japonica* can be effective and used for longer than 24 hours. Once the dilators are inserted, patients should understand that the abortion process has begun and must be completed, and failure to do so can result in life-threatening infection. Failure to be able to dilate the cervix is rare, but if the os is so stenotic that it cannot admit even a 3-mm dilator, preoperative use of misoprostol 400 to 800 µg intravaginally or 200 to 400 µg orally, up to 24 hours prior to the surgical procedure, can be helpful. When the cervix is easier to dilate, be aware that misoprostol has a fairly rapid onset so its use, earlier than 4 to 6 hours prior to the procedure, may lead to a spontaneous pregnancy expulsion. Another option is waiting until the pregnancy progresses to a later gestational period when the cervix may be more easily dilated.

First Trimester Abortion Procedure

Early first trimester abortions are almost exclusively performed by suction curettage. The earliest surgical abortions are performed between 3 to 5 weeks after the LMP. In some institutions, early abortion is performed before sonographic visualization of the gestational sac, but most are performed after the intrauterine location of the pregnancy is confirmed by ultrasound.

To rule out ectopic pregnancy, two to three ß-human chorionic gonadotropin (ß-hCG) titers should be taken at 48-hour intervals. Beta-hCG titers greater than 2,000 IU/L for a patient without an intrauterine sac visualized sonographically suggest an ectopic gestation. A sonogram should again be performed to definitely ascertain presence or absence of an intrauterine gestational sac. If an ectopic pregnancy is still suspected, the woman may undergo a medical abortion using the methotrexate protocols, which will treat an ectopic pregnancy as well.

To begin the suction curettage procedure, the anterior lip of the cervix, optionally anaesthetized at 12 o'clock first, is grasped with a single-tooth tenaculum that effectively stabilizes the cervix and straightens the cervical–uterine axis to facilitate cannula insertion. Local anesthetic is circumferentially infiltrated submucosally in the paracervical region. The cervix is dilated commensurately with the length of gestation and the need of cannula aperture. For a 7- to 9-week post-LMP gestation,

cannulas of 5 to 9 mm in width are used; they can be soft, flexible cannulas or rigid plastic, either straight or bent. Use of a uterine sound should be avoided, as it increases the incidence of uterine perforation, and depth of the endometrial cavity can be assessed by other means. The actual evacuation is accomplished by suction generated by a self-locking, handheld syringe or a machine aspirator; both may generate pressures of 60 to 70 mm Hg. Completeness of the procedure is confirmed by the appearance of bubbles in the suction cannula and the characteristic uterine sound of the catheter against the uterine wall, denuded of the decidual tissue. Completeness of the procedure can be confirmed by looking at the uterine cavity under ultrasound (Fig. 31.6A, Fig. 31.6B and Fig. 31.6C).

FIG. 31.6. A: Longitudinal view of the uterine cavity within minutes after a surgical abortion showing the endometrial stripe and constricted endocervical canal. **B:** Transvaginal ultrasound image taken in a longitudinal view of an 11-week gestation 1 hour after uterine evacuation shows evidence of procedure completion, but the endometrial stripe is less prominent due to the natural accumulation of blood within the endometrial cavity. **C:** Two weeks after suction curettage, transvaginal endometrium shows 16 mm of endometrial tissue, likely to be decidua and a few chorionic villi consistent with the normal involution process and warrants observation if clinically stable.

After the procedure, a surgeon can reliably confirm the pregnancy contents were obtained by inspecting the tissue. Washing the villi for the early suction curettage and then observing them through backlighting can enhance tissue visualization (Fig. 31.7). For procedures farther along in pregnancy, assessment of the primary skeletal fetal parts must be done. Visual confirmation of tissue must be done before the patient leaves the facility. Histologic evaluation of the products of conception can identify the rare woman with gestational trophoblastic disease (i.e., a molar gestation). In cases of known fetal anomalies, pathologic tissue examination is even more important. Blood loss is usually low, varying from 15 to 50 mL in most cases.

FIG. 31.7. Transillumination of villi floating in saline allows visualization for placental tissue confirmation after pregnancy termination.

Second Trimester Abortion Procedure

Dilation and Evacuation Dilation and evacuation (D & E) is the most common method of second trimester abortion. The procedure requires additional dilation of the cervix (up to 2 to 3 cm), and some of the evacuation needs to occur with the use of Sopher and Beirer type forceps. The forceps are most safely manipulated in the lower portion of the uterus or the midcavity region. Occasional use of uterotonic agents enhances the ability to reach the products of conception. Blood loss with these procedures is typically in the 100- to 300-mL range. Vasopressin, 4U, added to the paracervical block, significantly reduces bleeding. The use of ultrasound during the procedure to ensure the forceps are within the uterine cavity and afterward to verify complete removal of the products of conception may be helpful.
Intact Dilation and Extraction Procedures removing an essentially intact fetus have been termed *intact dilation and extraction.* Very few of these procedures have been performed in the United States.
Saline- and Prostaglandin-induced Abortions After 16 weeks gestation, abortions can still be performed with intrauterine abortifacient injection. Several solutions have been used for intrauterine injections, including hypertonic glucose, saline, urea, or uterotonics, such as prostaglandins or oxytocin. The uterus is relatively resistant to oxytocin induction at this point in the gestation, thus high doses of oxytocin are typically required and even those may not cause adequate uterine contractions. Labor induction with prostaglandins is the preferred strategy for second trimester pregnancy evacuation. The most widely used prostaglandin is PGE_2, dinoprostone, 20-mg suppositories, or 15-methyl-PGF_2, carboprost 250 g and tromethamine, for intramuscular injection. Misoprostol protocols using 25 g to 800 g orally or intravaginally, 4 to 8 hours prior to the procedure, can speed up delivery, although this drug regimen alone may take 24 to 72 hours. As saline and urea are hypertonic, the instillation procedure kills the fetus. Isolated reports of fetal survival in cases of prostaglandin induction exist. To avoid delivery of a nonviable but living fetus, intracardiac injection of digoxin or potassium chloride can be given prior to induction. Induction techniques may offer some advantages for the postmortem evaluation of fetal anatomic abnormalities, but 97% of anomalies can be evaluated after D & E. Preoperative karyotyping through amniocentesis is the best assurance of accurate chromosomal evaluation as this avoids more terminal cell contamination (i.e., the deciduas) and the requirement for optimal handling of the tissue to maintain viability.
Hysterotomy Hysterotomy may rarely be required for some cases of induced abortion. An indication for a hysterotomy would be large leiomyomata blocking cervical access. However, D & E procedures, even preceded by laminaria insertion, can safely be done in cases of placental previa as the laminaria do not need be inserted through the internal os to dilute the cervix. It is important to note that all hysterotomies are done with the classic uterine incision because the uterine segment is not developed well enough early in pregnancy to put the incision in the lower uterine segment.
Surgical Sterilization At the time of first or second trimester induced abortions, bilateral tubal ligation (using minilaparotomy), tubal fulguration, or tubal device occlusion are all considered to be safe. This option should be discussed during preoperative counseling.
Postoperative Care Antibiotic prophylaxis against infection reduces the incidence of postoperative salpingitis and endometritis, since cultures are not typically available preoperatively. Doxycycline has a broad spectrum of coverage and is the agent of choice. If the patient is allergic to doxycycline, metronidazole or ampicillin can be considered as alternatives. Prophylaxis regimens vary, but two doses of 100 mg of doxycycline should be administered with termination and again in 12 hours. Postoperative pain management is relatively straightforward. Contraction pain is usually mild and responsive to acetaminophen. An alternative regimen includes the use of NSAIDs. Both the acetaminophen and the NSAIDS, if over-used, can potentially mask a postoperative fever. Prior to the procedure, the provider must take note of the Rh(D) antigen status of the patient. Then immunoglobulin D must be offered to all Rh(D)-negative women. Rho(D) immunoglobulin should be administered to the Rh-negative patient on the day of the procedure or within 72 hours. For gestations less than 13 weeks, a dose of 50 µg is given. This amount is effective in preventing sensitization. For gestations =13 weeks, a dose of 300 µg is required. This dose may be excessive, but is considered the standard dose used in the United States. An intrauterine device, or intrauterine system, can be inserted immediately after a first trimester procedure, although the expulsion rate is slightly higher than if it is inserted after complete uterine involution. Injections of the contraceptives medroxyprogesterone acetate or estradiol–medroxyprogesterone as well as inserting levonorgestrel implants can be done on the day of the procedure or within the next 5 days. Postoperative appointments, 1 to 3 weeks later, can ensure and confirm that the induced abortion has been completed, evaluate for complications, reassess psychological status, and continue contraceptive and gynecologic care. As the ß-hCG has a long half-life, sensitive pregnancy tests may stay positive for weeks after an adequately evacuated pregnancy. However, compliance with follow-up visits is low due to a variety of factors. These include the distances patients have to travel, the fact that most women usually feel very well after their abortion, and the negative emotional response associated with a return to the site of the procedure. Women often seek care elsewhere but do not verbalize they had an abortion due to possible negative feedback.

MEDICAL ABORTION

Medical abortions can benefit a woman seeking pregnancy termination by increasing her control over the process and may allow abortions to be more widely available

in terms of the number of physicians that could provide this service in their offices. Both providers and patients can be shielded from the highly politicized abortion debate, allowing women to have an abortion without delay compared to waiting for an assigned scheduled surgery. Medical abortion reduces the risk of cervical laceration and uterine perforation and eliminates any anesthetic risk. Three abortifacients are currently being used for medical abortions: Prostaglandins (misoprostol), antiprogesterones (mifepristone), and antimetabolites (methotrexate). Misoprostol has been reported to be a teratogen when used in the first trimester. The mechanism of misoprostol action may be due to alteration of transplacental oxygenation or possibly a direct effect of the drug. The most common anomaly reported is a frontal facial set of lesions, termed *Möbius syndrome*, but over two dozen healthy pregnancies have been reported after failed medical abortion regimens. Mifepristone may be a teratogen but its effects have not been well studied. Methotrexate is a potent teratogen and its use in the first trimester is associated with major congenital malformations.

The FDA-approved regimen is initiated with mifepristone, followed by misoprostol (Table 31.4). This protocol is for women up to 49 days from the first day of the LMP. The literature, establishing the safety and efficacy of procedures up to 63 days from the LMP, indicates the procedures are less effective at this time but safe if clinicians and patients completely understand the process and the need to intervene with surgical uterine evacuation when necessary. Although the counseling process has been reviewed earlier in this chapter, patients given methotrexate and misoprostol need to comprehend that neither medication has been formally approved for medical abortions.

Visit 1: day 1—clinic or office
▪ Counseling and signing informed consent ▪ Medical history and physical examination, specific attention to medical contraindications ▪ M.D. and patient signing the provided medication agreement and patient receiving copy ▪ Blood samples taken for determination of hemoglobin level and Rh factor ▪ Pregnancy dating with sonogram or hCG titers if no gestational sac present ▪ Make sure no ectopic pregnancy ▪ Administer Rho_(D) immunoglobin if patient is Rh-negative ▪ Administer mifepristone 600 mg p.o.
Visit 2: day 3—clinic or office, 4-h observation
▪ Use sonography to check if patient has aborted ▪ If incomplete, administer 400 µg misoprostol orally and observe until heavier bleeding or passage of fetal tissue ▪ Repeat sonography for completion at end of 4-h observation ▪ If complete, schedule follow-up visit ▪ If still incomplete, discharge home ▪ Instruct patient on self-care
Visit 3: day 12–20—clinic or office
▪ Confirm abortion by sonography ▪ Surgical abortion, if necessary ▪ Assess level of bleeding and cramping since last visit, evaluate hemoglobin if medically indicated ▪ Administer birth control of patient's choice

ß-hCG, human chorionic gonadotropin.
Source: Medscape Woman's Health eJournal. Available at http://www.medscape.com/viewarticle/429755. 2001, WebMD, Inc., with permission.

TABLE 31.4. *U.S. Food and Drug Administration-approved mifepristone and misoprostol regimen summarized*

Misoprostol

Misoprostol, an E_1 prostaglandin analog, is FDA-approved as a treatment to aid in the prevention of gastric ulcers in persons taking NSAIDs. For pregnancy termination, the pharmacologic consequence of misoprostol administration is two-fold, softening the cervix and causing uterine contractions. The strong uterine contractions aid in the expulsion of the intrauterine contents. Misoprostol has excellent absorption orally or with vaginal administration. Oral absorption peaks in 30 minutes and then significantly drops at 120 minutes. The vaginal absorption does not peak for almost an hour, but high levels are sustained. The primary side effects of misoprostol are nausea, vomiting, diarrhea, abdominal pains, chills, fever, and shivering (Table 31.5). Misoprostol has been used for well over a decade with the antimetabolite methotrexate for medical abortions based on evidence-based protocols. As a single agent, misoprostol is considered less than adequately effective in terminating a pregnancy. Contraindications to misoprostol are glaucoma, anemia, mitral stenosis, and hypersensitivity.

	Mechanism of action	Side effects	Contraindications	Pharmacokinetics
Prostaglandins Misoprostol 400–800 µg p.o. or p.v.	Interact with myometrial cell receptors causing strong myometrial cell contractions leading to expulsion of embryonic or fetal tissue. Also causes cervical softening and dilation.	Diarrhea Vomiting Nausea Cramping Bleeding	Glaucoma, sickle cell anemia, hypotension, mitral stenosis, pregnancy not intended for termination, hypersensitivity to misoprostol	Half-life = 30 min p.o.: Time to peak plasma concentration =30 min Onset of uterine tonus = 8 min Time to peak uterine tonus = 25 min p.v.: Time to peak plasma concentration = 80 min Onset of uterine tonus = 21 min Time to peak uterine tonus = 86 min Time to peak serum levels = 90 min Half-life = 20 h Percent protein bound = 88% Oral bioavailability = 88%
Antiprogesterones Mifepristone (RU-486) 200–600 mg p.o.	Five times greater affinity for progesterone receptors. Binds to progesterone receptors and blocks progesterone from binding thus inhibiting its action and leading to increased uterine contractility. Also softens and dilates cervix.	Abdominal pain Uterine cramping Nausea Vomiting Diarrhea	Severe anemia, adrenal disease, chronic corticosteroid administration, severe kidney disease, severe liver disease, severe pulmonary disease, cardiovascular disease, inherited porphyria, clotting disorder, anticoagulant therapy, ectopic pregnancy, undiagnosed adnexal mass, IUD in place, hypersensitivity to mifepristone	
Antimetabolites Methotrexate 50 mg/m² i.m. 25–50 mg p.o.	Blocks dihydrofolate reductase thus inhibiting folate production and DNA synthesis. Affects rapidly dividing cells first (including trophoblast cells).	Nausea Vomiting Diarrhea Hot flushes Headache Cramping Dizziness	Severe anemia, inflammatory bowel disease, clotting disorder, acute liver or kidney disease, alcoholism, immunodeficiency syndrome, bone marrow hypoplasia, leukopenia, thrombocytopenia, hypersensitivity to methotrexate	Time to peak serum levels = 1–2 hours Terminal half-life = 10–17 hours Percent protein bound = 30%

IUD, intrauterine device.
Source: Medscape Women's Health eJournal. Available at: http://www.medscape.com/viewarticle/429755. 2001, WebMD, Inc., with permission.

TABLE 31.5. *Medications used in pregnancy termination*

Mifepristone (RU-486)

In 1988, the French released the progesterone antagonist RU-486, later named mifepristone, a derivative of norethindrone, for use as an abortifacient. It was noted that efficacy was improved if mifepristone was given in combination with a prostaglandin analog. Mifepristone has a potent receptor affinity for the progesterone receptor and a less potent affinity for glucocorticoid receptors. Once bound, it does not activate the progesterone receptor, rendering the progestin receptor inactive, thus making it an effective antiprogestin. Many prostaglandin analogs have been successfully used worldwide, but the FDA, in approving the drug, specifically mandated the requirement for mifepristone administration to be in conjunction with the misoprostol. The fundamental principle is that progesterone support of trophoblast attachment to the decidua in early pregnancy is essential, and withdrawal of this support causes detachment. Once trophoblastic separation occurs, ß-hCG levels will begin to decline. Mifepristone softens and dilates the cervix causing decidual necrosis, increasing uterine contractions, and enhancing the sensitivity of the uterus to prostaglandin administration.

Medical abortions have long been available in France, China, Sweden, and the United Kingdom. Before mifepristone was available for medical abortions in the United States, regimens in use worldwide varied. The FDA regimen specifies the dosage and timing of both the approved mifepristone and the misoprostol; the drugs are not currently individually approved for abortion (see Table 31.4). The regimen also specifies that the mifepristone is given on day 1 after the provider and the patient sign the informed consent. Then on day 3, misoprostol administration occurs in the provider's office with 4 hours of observation. The mifepristone must be directly purchased from the manufacturer after the provider signs a statement that he or she is capable of diagnosing an ectopic pregnancy and can arrange for the patient to receive a surgical abortion in the case that the medical abortion is not complete. Evidence-based medical abortion protocols provide equal efficacy with greater patient convenience and lower medical costs. Many regimens have been reported in the literature as shown in Table 31.6. The regimen most widely used is shown in Figure 31.8.

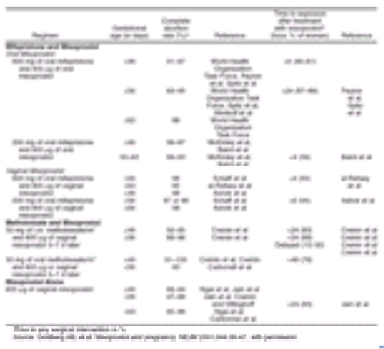

TABLE 31.6. *Efficacy of misoprostol regimens for medical abortion in the first trimester of pregnancy*

FIG. 31.8. Nonsurgical evidence-based mifepristone/misoprostol abortion sequence.

Patients undergoing medical abortion should be told to anticipate cramping, pain, and bleeding, and a third of patients may experience nausea, vomiting, diarrhea, dizziness, or fatigue (see Table 31.5). Abdominal/uterine cramping has been noted in 83% to 95% of patients; nausea has been observed in 12% to 61% of patients; vomiting in 9% to 47% of patients; diarrhea in 7% to 67% of patients; headache in 12% to 27%; dizziness in 1% to 37% of patients; chills in 14% to 89% of patients; mild to moderate pain in 50% to 95% of patients; and finally bleeding in 100% of patients. These symptoms are usually self-limiting and it is not necessary to treat them prophylactically. Narcotic-based analgesics are used, but many patients do well with NSAIDs.

The preabortion workup can be straightforward but should include a medical and obstetric history, allergies to medications, current patient medications, a pelvic exam, and a physical exam to obtain height and weight and blood pressure. All patients should be evaluated by pelvic ultrasound as all published studies to date have done this and it remains the standard of care. If a gestational sac is not seen, a clinical evaluation for an ectopic pregnancy should be initiated. A ß-hCG titer of = 2,000 IU/L and the absence of an intrauterine sac are consistent with either an ectopic pregnancy or an early spontaneous abortion. While patients could be treated based on ß-hCG titers alone (without the use of ultrasound), misdiagnosis of an ectopic pregnancy may occur and this clinical regimen is not generally recommended. Finally, Rho(D) immunoglobulin for Rh-negative patients can be administered on day 1.

Methotrexate

Methotrexate is an antimetabolite that blocks dihydrofolate reductase, an enzyme essential for the production of the DNA nucleotide thymidine during DNA assembly. As rapidly dividing cells are most affected, it causes trophoblastic cell death. Methotrexate has been used clinically for the treatment of gestational trophoblastic disease (i.e., molar gestation, ectopic pregnancy, and early medical abortion). Although methotrexate is not FDA-approved for early medical abortion, the protocols for abortion have been extensively studied. Toxicity is dose-dependent, and in the dosages given for these regimens, blood levels of methotrexate are undetectable 2 days after administration. At the low doses used in regimens for ectopic pregnancy, side effects of methotrexate are primarily gastrointestinal, with nausea, vomiting, and diarrhea, although there have been isolated reports of marrow suppression (leukopenia) and alopecia (see Table 31.5). At high doses, methotrexate can cause renal toxicity or damage to the gastrointestinal lining. Methotrexate in the 50- to 150-mg range should not induce ovarian toxicity and has no known long-term toxicity with regard to reproductive function. The protocols with methotrexate are more complex than those for surgical abortions, requiring more evaluation and more provider visits (Table 31.7 and Fig. 31.9). Failure rates are marginally higher than with mifepristone/misoprostol protocols.

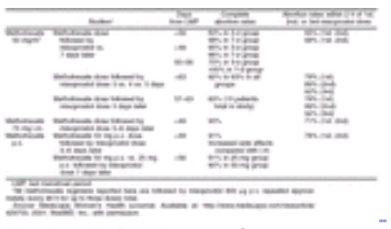

TABLE 31.7. *Methotrexate regimens used in pregnancy termination*

FIG. 31.9. Nonsurgical methotrexate/misoprostol abortion.

The National Abortion Federation (NAF) has revised the methotrexate/misoprostol protocol for early abortion. Two options have been recommended as guidelines for early medical abortion with these two abortifacients. Prior to the initiation of either of these protocols, counseling, education, and consent are completed. In addition, a medical history, physical exam, and sonography to confirm gestational age are necessary. The first option protocol begins on day 1 when methotrexate is administered. The dose can be 50 mg/m ^{2} intramuscularly (i.m.) or 50 mg p.o. Rho(D) immunoglobulin for Rh-negative patients can be administered on day 1 also or can be given any day prior to the misoprostol administration. The patient is provided with sufficient analgesic information and prescriptions and is also provided with 800 µg misoprostol, with instructions for self-insertion vaginally on either day 3, 4, 5, 6, or 7. On day 8 the patient returns to the office for a visit and the patient history is

obtained and ultrasound performed. With ultrasound, if a gestational sac is absent, treatment is complete. If a gestational sac is still present, repeat the misoprostol dose. This can be administered by the physician, self-administered in the clinic, or self-administered at home later that day. For follow-up, the cardiac activity in the gestational sac must be considered. If there is no cardiac activity in the gestational sac, the patient must return in 3 to 4 weeks. If there is cardiac activity, the patient should return in 1 week following this clinic visit. The visit on day 15 will include obtaining an interval history and an ultrasound. If a gestational sac is absent, the medical abortion is complete. If the gestational sac is present, with cardiac activity, a surgical evacuation is necessary at this time. If the gestational sac is present, with no cardiac activity, the patient should be given instructions on what to expect with regard to a delayed passage of the products of conception and scheduled for an appointment in approximately 3 weeks. On visit day 29 to 45 following methotrexate administration physicians must obtain another interval history and perform an ultrasound. If a gestational sac is absent, the treatment is complete. If a gestational sac is *still* present, a surgical evacuation is necessary at this time.

The other NAF-supported protocol is similar to the first protocol, but allows for an additional misoprostol administration (two 800 µg misoprostol doses total) for the patient (see Fig. 31.9). As a result, this may reduce the number of required clinic visits. Again this protocol begins on day 1 with 50 mg/m ^{2} methotrexate given i.m. or 50 mg p.o. The Rho(D) immunoglobulin for Rh-negative patients can be administered on this day or any day prior to the administration of misoprostol. The patient is provided with sufficient analgesic information and prescriptions and two doses of misoprostol at 800 µg each with instructions for vaginal insertion on day 3 to 7. The second dose of the misoprostol should be administered 24 hours later if little or no bleeding has occurred after the first misoprostol dose. The day 8 visit is optional if the patient has had bleeding. If the patient has not had bleeding at this point, then the day 8 visit includes obtaining an ultrasound to determine the status of the gestational sac and provide the woman with support and reassurance that all is well. On day 15, if a complete medical abortion process has not yet taken place, an interval history is obtained and an ultrasound is performed. If a gestational sac is absent, the treatment is considered complete. If a gestational sac is present with cardiac activity, a surgical evacuation is required at this time. If a gestational sac is present without cardiac activity, the physician should make arrangements to follow up with this patient in 3 to 4 weeks. At this next visit, the patient should be given adequate information with regard to a delayed passage of the pregnancy. At a subsequent visit between day 29 and 45, if a completed abortion has yet to be confirmed, the physician must obtain the interval history and perform an ultrasound. If the gestational sac is absent, the medical abortion process is then complete. If a gestational sac is still present, a surgical evacuation is necessary at this time.

With these two protocols, some patients take as many as 4 weeks to complete the abortion, and 4% to 6% of women will require surgical evacuation of the products of conception. Complication rates are similar to those with the mifepristone/misoprostol regimen. Although the ultrasonography assesses the presence or absence of an intrauterine pregnancy, the patient must be continually reevaluated clinically for stability and amount of blood lost. Contraception counseling is always given upon the completion of any medical abortion.

Contraindications for Medical Abortion

Contraindications to mifepristone include anemia, adrenal disease or chronic corticosteroid use, severe liver, cardiovascular, kidney or pulmonary disease, clotting disorders, anticoagulation therapy, pregnancy with an intrauterine device, or hypersensitivity to this drug (see Table 31.5). Preprocedure assessment of a hemoglobin or hematocrit, as well as Rh typing is required. Rho(D) immunoglobulin is to be given on day 1 of the regimen if the patient is Rh-negative. Patient selection for medical regimens should focus on the certainty of the decision to terminate the pregnancy, a willingness to comply with the instructions, and access to 24-hour emergency services. Factors that may affect a patient selecting a medical abortion are a desire to avoid a surgical procedure, falling within the medical dating criteria for the procedure, having no medical contraindications to the medications, access to telephone and transportation, a good support system, the ability to return for follow-up visits, being able to tolerate pain as it may be intense when passing tissue products, and the ability to give informed consent.

Patient Follow-Up for Medical Abortions

Patients who are undergoing a medical abortion are told that they must expect bleeding and cramping, especially after misoprostol administration. About 5% of women abort in the first 24 hours after mifepristone alone. About another 5% of patients abort within a few hours of the misoprostol (day 3), and almost 80% of patients have aborted within the next 24 hours. Patients are asked, however, to be patient as longer times to completion do occur and are not accompanied by a greater risk of complications. Once the sequence of events in Figure 31.8 has begun, ultrasonography assessments are essential in visualizing completeness of the medical abortion procedure as shown in Figure 31.10A, Figure 31.10B, Figure 31.10C. At the 8- to 10-day visit, ß-hCG levels may be measured. A decrease in ß-hCG levels more than 50% has been shown to be associated with a complete abortion process. Sonography is performed and is necessary to confirm absence of gestational sac. Some publications have indicated that bleeding, on average, lasts 14 days. Yet, bleeding may persist for 60 days in some patients, without untoward effects. More important, the patient must realize that heavy bleeding and severe cramping does not necessarily indicate a complete abortion has taken place. Therefore, the patient must realize that a third follow-up visit (day 12 to 20) is compulsory to confirm the completion of the procedure and observe the absence of a gestational sac. Sonography is again used for this confirmation. A further decrease in ß-hCG levels to more than 90% at this visit suggests, almost certainly, that the termination process is complete.

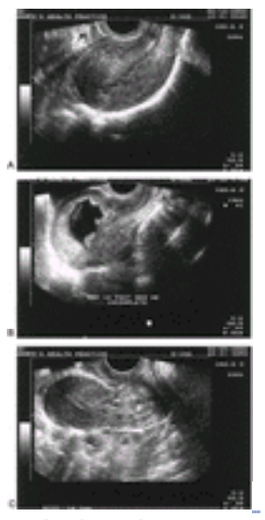

FIG. 31.10. A: Transvaginal ultrasound of a 42-day pregnancy 4 hours after misoprostol ingestion. Heavy bleeding and passage of tissue indicated the pregnancy termination had probably completed, the ultrasound confirms the absence of a gestational sac and that the medical abortion was effective. **B:** Day 14 after a medical abortion of a 47-day pregnancy. Transvaginal ultrasound shows retention of gestational sac although no fetal development or fetal cardiac activity is seen. This is consistent with an incomplete medical abortion. Follow-up or surgical termination are both options if the patient is medically stable at this point. **C:** Three-and-a-half weeks after medical abortion of a 35-day pregnancy. Transvaginal ultrasound shows a sac in the endocervix, not in the uterine cavity. Abortion is not yet complete.

In general, continuing pregnancy rates are low, and less than 1% of patients require curettage due to hemorrhage. However, one of the most important assessments the provider needs to ensure is a set of instructions for the patient to address severe bleeding. Because bleeding is expected, the provider needs to recognize, although rare, an actual episode of hemorrhage requiring surgery may be indicated. If the provider's bleeding threshold is low, it may be that potentially unnecessary surgical procedures are performed, and consequently an increased complication rate for the medical abortion procedure may result. Other indications for surgical intervention include a continuing intrauterine gestation of a retained nonviable pregnancy. A medical abortion is considered a failure if there is viable cardiac activity 2 weeks following the regimen. Additional rounds of misoprostol may be effective in accomplishing completeness at this time, but studies have yet to establish useful clinical guidelines. If the pregnancy is retained and nonviable, the patient will likely spontaneously abort within the next 3 weeks. Because there is always a risk, albeit low, of viable cardiac activity 2 weeks following the medical regimen, the provider must have arranged for a surgical evacuation as a back-up plan. It is important to note that surgical evacuation may be offered at any point in the medical abortion process if the pregnancy has not been spontaneously expelled and the patient is unwilling to wait any longer for completion.

COMPLICATIONS OF ABORTION

An induced abortion is a very safe procedure. Complications are rare (Table 31.8). During the abortion counseling session, the counselor should clearly state the known risks and benefits. The lay literature erroneously states that abortion causes cancer and reproductive dysfunction. Current medical evidence gives no indication that abortion causes either. There has also been no proven link between abortion and breast cancer. Future reproductive health is not affected by having a medically supervised legal abortion.

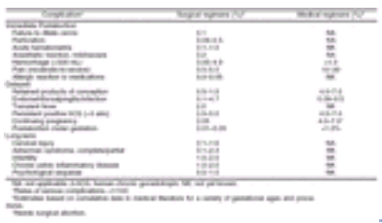

TABLE 31.8. *Complications of abortion and complication rates*

Surgical Procedures

Abortion procedures are extremely safe in the United States, with serious complications developing in only 1 in 100 patients and a mortality rate of less than 1 in 100,000 patients (see Table 31.2). The safest abortions are those performed at 7 to 10 weeks after the LMP (Table 31.9). Death rates for D & E have been reported at approximately 7 per 100,000, comparable to a term delivery. Concomitant sterilization, preexisting medical conditions, and general anesthesia may all contribute to an increase in postabortion complications. Immediate complications include acute cervical laceration, failure to dilate the cervix, failure to obtain the pregnancy tissue, postoperative pain, acute uterine hematometria, and, rarely, pulmonary embolism (Table 31.8 and Table 31.10). Other immediate complications can include moderate to severe pain, and allergic reactions to medications. More delayed complications include persistent bleeding secondary to retained products of conception, endometritis or salpingitis, and a continuing viable pregnancy. Longer-term complications include intrauterine adhesions and Rh sensitization. No long-term effects causing cervical incompetence have been documented in the literature. Rates of all the complications are extremely low.

TABLE 31.9. *Mortality rate with respect to gestational age*

Complication	Percentage	Number[a]
Hemorrhage	18.5	10
Embolism	11.1	6
Pregnancy-induced hypertension	1.2	1
Infection	49.4	25
Anesthesia	8.6	4
Other/unknown	11.1	6

Source: Abortion surveillance—United States, 1993 and 1994. *MMWR/CDC Surveill Summ* 1997;46:37–98.
[a]Per 100,000 abortions.

TABLE 31.10. *Abortion-related deaths: United States 1987–1990*

Uterine Hemorrhage

Rates of uterine hemorrhage (more than 500 mL blood loss) are low, occurring in less than 5% of cases, and the need for transfusion is exceedingly rare. Uterine atony can be decreased by complete evacuation of the uterus with the use of vasopressin injection in the paracervical block (4 U or 0.2 mL), or use of postoperative oral or intramuscular methylergonovine maleate (0.2 mg). Failure to respond to acute management of bleeding can be treated with carboprost tromethamine, oxytocin, or misoprostol. Continued atony can be treated with insertion of a large intrauterine Foley balloon to tamponade the uterine cavity.

Uterine Perforation

Uterine perforation is uncommon, occurring in approximately 1.3 in 1,000 terminations. It is usually not recognized even by an experienced surgeon at the time of the procedure. In first trimester fundal perforations, observation is all that is required. If the nature and extent of the perforation are unknown or if suction was applied during the perforation, evaluation by laparoscopy is necessary. In early first trimester abortions the procedure may be safely completed, even after perforation in experienced hands with sonographic guidance of the catheters. A perforation during D & E is a more serious complication, and the amount of bleeding may necessitate a laparotomy for uterine wall repair. One study from the literature established that 14 of 15 perforations during D & E were associated with major organ injury. Organs damaged include the uterus, bowel, and bladder. Surgical interventions, when necessary, should not be delayed.

Endometrial Adhesions

Asherman syndrome, or the development of endometrial surface adhesions or scaring, should be suspected in a patient with no menses for several cycles following a surgical abortion. This is a rare complication and may be avoided through the prevention of endometritis. This is done by complete evacuation of the products of conception.

Retained Tissue

Evaluation of the products of conception at the time of abortion can significantly reduce the number of cases of retained tissue. There have been case reports of very delayed retention of incompletely removed tissue, but a new pregnancy must be the first consideration in these cases. Persistence of a positive pregnancy test can signal retained products of conception, but careful postoperative evaluation by those experienced with the normal involution process typically reveals that this is a self-limited process. Normal resolution of the pregnancy test depends on the length of the pregnancy at the time of abortion and the sensitivity of the ß-hCG tests used. Beta-hCG persistence for a few weeks is not uncommon. A rapid decline in the quantitative ß-hCG is the rule. Sonography can be helpful, but many pregnancies have some intrauterine fluid accumulation that appears within a few hours of abortion and does not dissolve for several days in a first trimester pregnancy. Retained products of conception may be most effectively handled by endometrial aspiration (3- to 5-mm suction pipettes), which is also useful for treatment of hematometria and can be diagnostic for retained tissue. Alternatives that may be useful in selected cases are observation, uterotonics (with methylergonovine maleate or misoprostol), or repeat suction curettage. In some cases, the retained tissue can cause uterine hemorrhage and increase the incidence of infection.

Infectious Complications

Endometritis can occur with or without retained products of conception. Clinical signs are abdominal pain, increased cramping, fever, and increased bleeding. Endometritis is difficult to diagnose but can be presumed to be present when tenderness, especially associated with febrile morbidity (fever >38°C), or an elevated white blood cell count is present. It is expected to occur in about 0.5% of suction curettage procedures, 1.5% of D & E procedures, and 5% of uterine instillations, despite the use of prophylactic antibiotics. The organisms most likely responsible for endometritis are vaginal flora. A broad-spectrum oral antibiotic with anaerobic coverage is usually sufficient therapy. Repeat curettage may be indicated when it seems likely that retained products of conception are responsible for the endometritis.

Complications of Medical Abortions

Complications due to medical abortions exist but are rare. The most common complication from a medical abortion procedure is an incomplete abortion. Surgical evacuation is then required to complete the procedure. The incidence of hemorrhage is less than 1%. Bleeding from a medical abortion procedure can be heavy but only in rare instances does this bleeding become so severe that transfusion is warranted. In some instances, copious amounts of bleeding may need treatment with vasoconstrictor medications, curettage, and saline solution administration. More often less serious complications arise as indicated in Table 31.5. The incidence of intrauterine infection after surgical abortions is 0.1% to 5%, likewise infections after medical abortions are rare, occurring 0.09% to 0.5% of the time. Patients having experienced both medical and surgical abortion report greater satisfaction with the low risk of complications associated with medical abortion protocols.

Psychological Consequences of Abortion

Improvement in emotional health is the most common psychological consequence following abortion. However, women with a prior mental health diagnosis of depression may be at risk for depression following an induced abortion. The proportion of women experiencing clinical depression, up to 2 years after the induced abortion, is not significantly different from the population in general for this same age group (approximately 15–35 years old). Although occasional reports of posttraumatic stress disorder are documented, the incidence of posttraumatic stress disorder in the postabortion population is less than in the general population for

this age group. There is a subset of patients who do feel sadness, guilt, and regret after an abortion. Studies show this subset of patients to be 10% to 30% of all women who have experienced an abortion, but these feelings are usually mild. It is the job of abortion providers to be sensitive to the emotional support requirements for each woman undergoing pregnancy termination. Preabortion counseling should increase awareness for all patients with regard to their possible feelings after the abortion. Younger women (<24 years old) and women who have other children may be at higher risk for feelings of regret and distress after an abortion. It has also been noted that emotions of regret, sadness, and guilt may increase over time (years after the abortion). But whether these feelings were due directly to the abortion years before, or from another completely different emotionally draining event occurring since the abortion procedure, is difficult to ascertain.

SUMMARY POINTS

- An estimated 1.2 to 1.6 million elective abortions have occurred in the United States in each of the past 10 years, making this a very common procedure and choice for women with unwanted pregnancies.
- Extensive research indicates that induced abortions continue to be requested by women regardless of religious conviction or socioeconomic status.
- The most common surgical approach in the first trimester is suction curettage and in the second trimester, dilation and extraction.
- Medical abortion is performed by initial administration of mifepristone followed by misoprostol. A non-FDA approved alternative is the use of methotrexate.
- The complications of induced abortion are relatively few and the death rates remain less than 1 woman per 100,000, comparing favorably to maternal mortality.
- It is important for health care providers to understand the process of induced abortion and to recognize and be able to counsel women regarding the potential risks, benefits, and complications of both surgical and medical abortion procedures to keep these procedures safe and widely available.

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Chapter 32

David A. Eschenbach

Pelvic Infections and Sexually Transmitted Diseases

VULVA
Herpes
Human Papillomavirus
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Furunculosis
Bartholinitis
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SUMMARY POINTS
SUGGESTED READINGS

A large number of microbes are present in the female reproductive tract, and pelvic infections are common. Many pelvic infections are sexually transmitted (Table 32.1). This chapter provides data on usual presentations and updated treatment of pelvic infections.

Organisms	Diseases
Bacteria	
Neisseria gonorrhoeae	Gonorrhea
Chlamydia trachomatis	Chlamydia
Treponema pallidum	Syphilis
Haemophilus ducreyi	Chancroid
Calymmatobacterium granulomatis	Granuloma inguinale
Gardnerella vaginalis, anaerobes	Vaginitis
Group B β-hemolytic streptococcus	Group B streptococcal infection
Mycoplasmas	
Mycoplasma hominis	Mycoplasmosis
Ureaplasma ureatyticum	Mycoplasmosis
Viruses	
Herpesvirus hominis (herpes simplex virus)	Genital herpes
Cytomegalovirus (CMV)	CMV infection
Hepatitis B virus	Hepatitis B
Human papillomavirus	Condyloma acuminatum
Molluscum contagiosum virus	Molluscum contagiosum
Human immunodeficiency virus	Acquired immunodeficiency syndrome
Protozoa	
Trichomonas vaginalis	Vaginitis
Entamoeba histolytica	Proctitis
Fungi	
Candida albicans	Vaginitis
Parasites	
Sarcoptes scabiei	Scabies
Phthirus pubis	Pediculosis pubis

TABLE 32.1. *Sexually transmitted infections*

The impact of pelvic infections on women ranges from minor annoyance to serious illness and, rarely, even death. The cost of treating pelvic infections is enormous from both direct medical costs and indirect costs, including time lost from work. Using pelvic inflammatory disease (PID) as an example, previous estimates were that, by 2000, one of every four women who reached reproductive age in the 1970s had an episode of PID. Of women with PID, 25% will be hospitalized, 25% will have major surgery, and 20% will have tubal sterility.

Upper genital tract sites (endometrium, fallopian tubes, ovaries) formerly considered sterile are subject to ascending microbial traffic and occasionally infection from lower genital tract microbes. Some microbes preferentially infect certain sites and give rise to characteristic symptoms while other microbes cause few symptoms until major pathologic changes occur or until congenital neonatal infection or male-partner infection ensues. Clinicians should have special knowledge of the infections caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, group B streptococci, *Treponema pallidum*, anaerobic bacteria, bacteria associated with bacterial vaginosis, and *Mycobacterium tuberculosis*; these infections either are common or potentially produce severe sequelae. It is now appreciated that most viral infections of the genital tract are asymptomatic. Several viruses are common and produce severe disease in both adults and neonates, including herpesvirus, cytomegalovirus, hepatitis B virus, human papillomavirus, and human immunodeficiency virus (HIV).

VULVA

Herpes

Type-specific serologic assays indicate that one third of women 20 to 45 years of age have been exposed to herpes simplex virus type 2 (HSV-2). Between 60% and

85% of women with HSV-2 antibodies never have a recognized genital infection. Despite the frequency of asymptomatic infection, HSV infection is a common cause of vulvar ulcers. Genital ulcers also are caused by syphilis and chancroid. Ulcers from HSV usually occur 3 to 7 days after exposure. Symptomatic primary (first) genital infections typically consist of multiple vesicles that rapidly produce ulcerations of the vulva that can be exceedingly painful. The cervix and vagina may also be involved, producing a gray, necrotic cervix and profuse leukorrhea. External dysuria is common, and bilateral inguinal lymphadenopathy is usual. Vulvar lesions may last for 3 or more weeks before complete healing. Constitutional symptoms of fever, malaise, headache (i.e., aseptic meningitis), and urinary retention (i.e., myelitis) may persist for a week.

After primary infection, latent HSV usually localizes in the sacral ganglion and perhaps the dermis. Periodic asymptomatic viral shedding occurs, particularly in the first 6 months after primary infection. HSV is isolated on 1% of the days with no symptoms or physical evidence of infection. Most patients develop a secondary (recurrent) infection from latent virus weeks to months after the primary infection. Secondary lesions are less painful and more localized and last for a shorter time (3 to 7 days) than the lesions of primary infection. Systemic manifestations are unusual with secondary infection.

From 75% to 85% of genital herpes infections are caused by HSV-2, with the remainder caused by HSV-1, the primary cause of oral herpes. The two types of herpes infections are clinically indistinguishable except that genital recurrence is unusual from HSV-1. Vesicles and ulcers contain many highly infectious virus particles, and viral shedding occurs until the lesions disappear. Thus, direct contact with either genital or oral HSV lesions leads to a high rate of infection. Transmission usually occurs by direct contact with ulcerative lesions. Transmission is greatest during a primary infection, intermediate during a secondary infection, and probably least with asymptomatic shedding.

The diagnosis of herpes can be made clinically if typical, painful, shallow multiple vulvar ulcers are present. However, many HSV lesions are atypical. Laboratory confirmation of atypical lesions and lesions that appear during pregnancy is best attained by virus isolation (which can usually be achieved within 48 hours) or by polymerase chain reaction (PCR) identification. Other direct HSV identification methods, including Pap smear, fluorescein tagging, and immunoperoxidase staining, are insensitive. Accordingly, a negative direct Pap smear does not exclude HSV infection. Complement fixing and neutralizing antibodies appear within 1 week of the onset of infection; failure of an experienced laboratory to identify antibodies within 3 weeks is evidence against HSV infection. However, even high antibody levels do not protect against recurrent HSV infection, although antibody passively transferred to the fetus offers considerable protection against neonatal infection.

The rising incidence of herpes infection and the potentially serious fetal infection caused by HSV make this an important infection in pregnancy. New guidelines for herpes are discussed in Chapter 19.

Oral acyclovir (Zovirax), 400 mg three times daily, famciclovir (Famvir), 250 mg three times daily, or valacyclovir (Valtrex), 1 g twice daily all for 7 to 10 days, shortens the ulcerative phase. Antiviral therapy does not eradicate HSV or prevent recurrence. Patients with episodic recurrent herpes should be provided a supply of drugs to take for 5 days beginning with prodromal symptoms or within a day of the lesion appearance. Patients with six or more yearly recurrences may benefit from suppressive therapy of acyclovir, 400 mg twice daily, famciclovir 250 mg twice daily, valacyclovir, 500 mg daily, or valacyclovir, 1 g daily for up to 1 year. The expense of this drug limits routine or prolonged use. Local therapy of genital herpes is limited to pain relief. Local treatment neither penetrates into virus-containing cells nor influences epithelial damage from HSV. Corticosteroids and antimicrobial ointments offer no benefit as they prevent drying and, thus, delay healing. Wet-to-dry therapy is often helpful (i.e., 10-minute sitz bath three or four times daily followed by drying with hair dryer).

Human Papillomavirus

Genital human papillomaviruses (HPV) are DNA viruses that are distinct from papovaviruses that cause the common wart. HPV thrives in the moist genital area and usually is sexually transmitted. HPV infection is common and typically subclinical. HPV DNA is found in the genitalia in 30% to 45% of women by PCR DNA amplification. The vulva is positive for HPV DNA in more than 40%, and the cervix in over 30%. Only 1% of the women have visible warts, and only 9% have a history of genital warts. The average incubation period for visible warts is 3 months. Genital warts most commonly occur on the labia and posterior fourchette (Fig. 32.1). They originally appear as individual lesions, although large confluent growths can occur if neglected. Vaginal and cervical warts are even more common than labial warts, although most of these are flat lesions visible only by colposcopy. Over 30 HPV types infect the genital tract. Visible genital warts are usually caused by HPV types 6 and 11; 3% of college women had these types. The flat-wart variant is caused by HPV types 16, 18, 31, 33, and 35 (found in 22% of college women tested) and is visible only by colposcopy. A biopsy of flat or atypical-appearing cervical warts is required to exclude cervical neoplasia. Biopsies of warts also should be performed for pigmented, unresponsive, or fixed lesions, or in immunocompromised patients. HPV types 16, 18, 31, 33, and 35 are associated with high-grade cervical dysplasia and cervical cancer where the HPV DNA is integrated into the cancer cell. Women with flat warts should have frequent Pap smears. At present, routine typing of HPV is not recommended to aid PAP smear interpretation or predict cervical dysplasia.

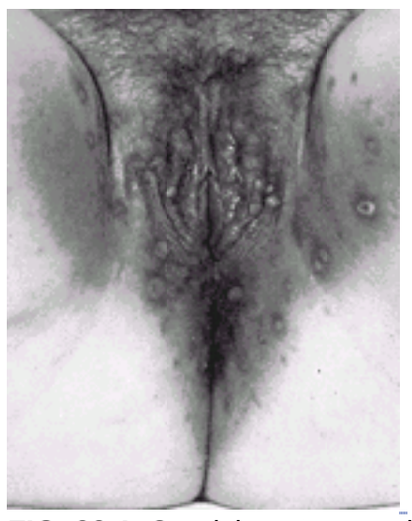

FIG. 32.1. Condylomata acuminata of the vulva.

Vulvar warts must be differentiated from the less verrucous, flatter growths of syphilitic condyloma latum (Fig. 32.2) and from carcinoma in situ of the vulva; dark field examination or punch biopsies may be required to differentiate these lesions. Small to medium-sized verrucous lesions can usually be treated with patient-applied podofilox (Condylox), imiquimod (Aldara), or by providers (cryotherapy, podophyllin, or trichloroacetic acid). Intralesional interferon and laser surgery represent alternative regimens. Small amounts of podophyllin (0.25 mL) should be used to avoid severe burns. Podophyllin, imiquimod, and podofilox are contraindicated during pregnancy. Large amounts of podophyllin have produced coma in adults and fetal death in pregnancy. A biopsy should be done on atypical lesions before therapy is initiated because podophyllin causes bizarre histologic changes that persist for months. Cryotherapy, trichloroacetic acid, or laser ablation can be used on vaginal warts during pregnancy. Recurrence rates of 50% probably relate to the failure of these methods to kill the virus in adjacent untreated areas. Severe burns have occurred from the use of 5-fluorouracil (5-FU) to treat warts; as a result its use is not recommended. Large warts may not respond to surgical or laser removal alone but also may require regional interferon therapy. Examination of sexual partners is unnecessary because most are already infected.

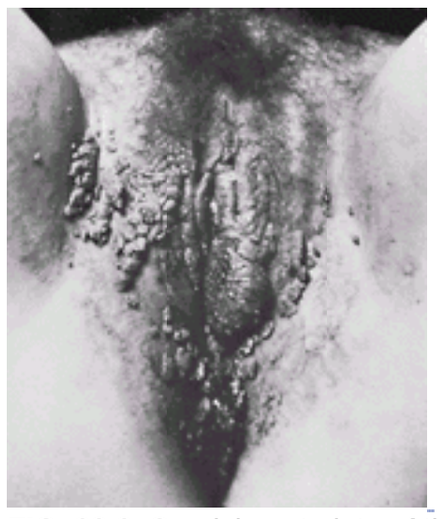

FIG. 32.2. Condylomata lata of the vulva and perineum. (From Curtis AH, Huffman JW. *A textbook of gynecology*, sixth ed. Philadelphia: WB Saunders, 1950, with permission.)

Vestibulitis

Patients with vestibulitis characteristically have pain with vaginal penetration (i.e., intercourse or tampon insertion) and, in extreme cases, have difficulty sitting or wearing tight clothing. This condition is frequently treated as vaginitis because acidic vaginal discharge increases local irritation. Patients typically have an erythematous area, most commonly at the 4-o'clock and 8-o'clock positions just outside the hymenal ring. There is no clear evidence that HPV or bacteria cause the inflammation, but an accelerated inflammatory response to *Candida* is suspected in many patients. Treatment is often not effective, but regimens include topical corticosteroids (i.e., without an alcohol base), local corticosteroid injection, oral tricyclic antidepressants, pelvic floor muscle physical therapy, and, in severe cases, skinning vulvectomy.

Furunculosis

Hair follicles or areas of hidradenitis in the vulva may become infected by staphylococci or other bacteria, giving rise to pustules. This condition must be distinguished from herpetic and syphilitic lesions. The diagnosis can be made by culture or by the finding of Gram-positive cocci in Gram stains of pus. If only a few small lesions are present, treatment with hot, wet compresses or hexachlorophene scrubbing helps. If a larger area is involved, administration of antistaphylococcal antibiotics is required until infection subsides, which may take weeks. Daily low-dose suppressive antibiotic therapy (e.g., erythromycin, 250 mg) can reduce frequent recurrences.

Bartholinitis

Two stages of Bartholin gland infection occur. The first is an acute infection of the duct and gland, usually caused by either *N. gonorrhoeae* or *C. trachomatis*. If infection causes obstruction of the duct, an abscess stage can result. Anaerobic bacteria can be isolated from most abscesses. Rarely, synergistic vulvar gangrene results from bartholinitis.

Cultures and a Gram stain of material expressed from the duct may identify gonococci. Cervical gonococcal and chlamydial cultures should be obtained, and treated, if present. Patients with an abscess usually require abscess marsupialization or incision with placement of a catheter in the abscess cavity for 3 to 6 weeks to establish a new duct. Simple incision and drainage should be avoided, since it does not address the drainage of mucus from a functioning gland. Recurrent infection from vaginal flora and mucus cyst formation are common sequelae of bartholinitis.

Chancroid

The soft chancre of chancroid is a painful ulcer with a ragged, undermined edge and a raised border. In contrast, the syphilitic chancre is painless and indurated. “Kissing ulcers” on opposing surfaces of the vulva occur. Tender, unilateral adenopathy is common, and node suppuration occurs in about 50% of patients with lymphadenopathy. The incubation period of this sexually transmitted disease (STD) is 2 to 5 days. The infection is caused by *Haemophilus ducreyi*, a Gram-negative bacterium that forms a school-of-fish pattern on Gram-stain preparation. The organism is fastidious, and it is best identified by culture of material from aspirated lymph nodes or from the chancre using special selective media or PCR tests. The differential diagnosis includes syphilis, genital herpes, and lymphogranuloma venereum.

Preferred treatment is azithromycin (Zithromax), 1 g orally, or ceftriaxone sodium (Rocephin), 250 mg intramuscularly, in single doses, or ciprofloxacin, 500 mg twice daily for 3 days or erythromycin, 500 mg three times daily for 7 days. Sexual partners should be examined and treated.

Granuloma Inguinale

Granuloma inguinale is rare in temperate climates and is usually considered an STD, although gastrointestinal transmission can occur. The initial papular lesion typically ulcerates and develops into a soft, painless, progressive granuloma that may be covered by a thin, gray membrane. The granuloma may spread over the course of many months to involve the anus and rectum (Fig. 32.3). Lymph nodes are moderately enlarged and painless, but they do not suppurate. The infection can become chronic, and long-standing disease may cause genital scarring and depigmentation, as well as lymphatic fibrosis with consequent genital edema.

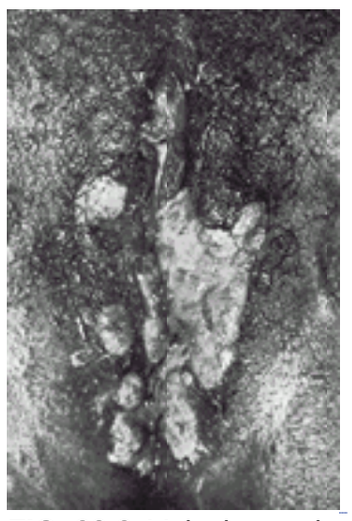

FIG. 32.3. Vulval granuloma inguinale of relatively recent origin. Some lesions are separate, others confluent. The margin of lesion is raised and scrolled; the base is granular and covered imperfectly by thin, gray slough. (From Demis DJ, Crounse RG, Dobson RL, et al, eds. *Clinical dermatology*, Vol 3. Hagerstown, MD: Harper & Row, 1972, with permission.)

Infection is caused by a gram-negative bacillus, *Calymmatobacterium granulomatis*, which is difficult to culture because it is an intracellular parasite. The identification is usually made from scraped material or a biopsy specimen obtained from the periphery of the lesion. Bipolar-staining bacteria are best identified within mononuclear cells (i.e., Donovan bodies) by Wright or Giemsa staining.

Therapy of choice is a 3-week course of doxycycline, 100 mg, or trimethoprim/sulfamethoxazole (double strength) or ciprofloxacin, twice daily. Erythromycin and azithromycin offer alternative therapies.

Lymphogranuloma Venereum

The incubation period for lymphogranuloma venereum (LGV) is 2 to 5 days. Thereafter, a transient, primary, painless genital or anorectal ulcer develops. Multiple, large, confluent inguinal nodes develop 2 to 3 weeks later and eventually suppurate. Acute infection may cause generalized systemic symptoms. If untreated, the infection enters a tertiary phase that can lead to extensive lymphatic obstruction. This development, together with continued infection, causes fistulae or strictures of the anal, urethral, or genital area. Women with LGV are particularly susceptible to rectal stricture. Edema and elephantiasis of the external genitalia and lower extremities are other serious sequelae.

The infection is caused by the sexually transmitted organism *C. trachomatis*, an intracellular bacterium. Only L $_{1\text{-}3}$ Chlamydia serovars, which produce accelerated in vitro tissue destruction, typically cause LGV. The diagnosis can be made by culturing chlamydiae from genital lesions or lymph nodes. The most specific and sensitive serologic test is the microimmunofluorescent antibody test, in which the specific L immunotypes are identified. The results of complement fixation (CF) tests are positive in 95% of patients with LGV, but the CF test lacks specificity; test results are often falsely positive in patients who do not have LGV but have previously been exposed to *Chlamydia.* High (=1:64 CF) titers offer some specificity.

LGV responds to 3-week regimens of doxycycline or erythromycin in the usual doses. Large lymph nodes should be aspirated to avoid chronic drainage. Surgical excision of scarred areas may be necessary.

ACUTE URETHRAL SYNDROME

Acute cystitis is present in approximately 50% of women with symptoms of dysuria and urinary frequency. Cystitis is defined by pyuria and midstream urine cultures that contain more than 10^5 organisms per milliliter of coliform or staphylococcal organisms. It is now apparent that about one-half of the remaining symptomatic women also have cystitis, but with less than 10^5 coliforms or *Staphylococcus saprophyticus* organisms per milliliter of urine obtained by suprapubic aspiration or urethral catheterization. Virtually all of these women have pyuria of eight or more leukocytes per high-power field of urine. The pyuria that occurs among another 25% of women with recent onset of internal dysuria and urinary frequency and negative urine cultures is termed acute urethral syndrome. These patients usually have *C. trachomatis*. The remaining 25% of patients with these symptoms have no pyuria, bacteriuria, or chlamydial infection and a variety of diseases are involved, including candidal or herpetic vulvitis, or no infection origin. Treatment of acute urethritis consists of therapy for the infectious agent, whether it is coliform or *S. saprophyticus* cystitis, or *C. trachomatis* urethritis.

VAGINITIS

Vaginitis is the most common reason for a gynecologic visit. Symptoms of vaginitis include increased vaginal discharge, vulvar irritation and pruritus, external dysuria, a foul discharge odor, and a yellow discharge color. However, symptoms are very poor indicators of the specific cause of vaginitis. Women with infectious vaginitis have either an STD (i.e., trichomonads) or a quantitative increase in normal flora (i.e., *Candida*, *Gardnerella vaginalis*, anaerobes). At least four types of infectious vaginitis are found: candidal, trichomonal, bacterial vaginosis, and, in children, gonococcal. Every effort should be made to establish the diagnosis of one of these specific infections and to avoid the diagnosis of a nonspecific vaginitis. A specific diagnosis is mandatory to select effective therapy. Treatment of nonspecific vaginitis inevitably fails.

Other conditions that may cause excessive vaginal discharge include cervicitis, normal cervical mucus from cervical ectopy, vaginal foreign bodies (most commonly, retained tampons), and allergic reactions to douching or vaginal contraceptive agents. Atrophic vaginitis among postmenopausal women can produce burning and dyspareunia, but an infectious cause is not established.

A small amount of vaginal discharge may be normal, particularly midcycle, when large amounts of cervical mucus production produce a clear vaginal discharge. A normal vaginal discharge should not have a foul odor or produce irritation or pruritus.

Examination

External genitalia may be normal or edematous, erythematous, excoriated, or fissured. Local vulvar disease, especially vestibulitis, must be excluded from a secondary effect of vaginitis.

On speculum examination, the vaginal mucosa may be erythematous. Discharge characteristics that are important to observe are viscosity, floccular appearance, color, and odor. Vaginal pH status must be determined. A pH less than 4.5 indicates *Candida* or a normal vaginal discharge. A potassium hydroxide (KOH) odor test and a microscopic examination consisting of a normal saline and 10% KOH wet mount should be done. A drop of each solution is mixed with discharge. Before placing a cover glass over the two separate drops, the KOH portion is tested for the presence of a fishy amine odor. Microscopic examination of the KOH portion is made for hyphae under the 100× objective, and examination of the saline portion is made for trichomonads and clue cells under the 400× objective. Multiple causes of vaginitis are frequent.

Vaginal cultures are not particularly helpful except when used selectively to identify Candida. Microscopy is specific, but only 80% sensitive in identifying various types of vaginitis. When infectious vaginitis is suspected in patients in whom a specific diagnosis cannot be established, a repeat examination should be performed 2 weeks later.

Candidiasis

The most prominent symptom of candidiasis is vulvar and vaginal pruritus. Increased vaginal discharge is infrequent. Vulvar signs of edema, geographic erythema, and fissures may occur. Classically, the vaginal walls are red and contain adherent, white, curdy plaques. However, most women with candidiasis have atypical symptoms, little discharge, and no erythema.

Candida albicans causes about 90% of vaginal yeast infections. Noncandidal species cause the remaining infections. These saprophytic fungi are isolated from the vagina in 15% to 25% of asymptomatic women. Thus, the mere presence of vaginal *Candida* does not always identify an infection, but large numbers of organisms lead to symptomatic vaginitis. However, severe symptoms develop in some women with only a few organisms but with an accelerated immune response to *Candida.* Candidiasis occurs because changes in host resistance or immune response allow organism detection or cause inflammation. The most widely accepted risk factors for candidiasis include pregnancy, diabetes, and use of immunosuppressive drugs and broad-spectrum antibiotics. Frequent vaginal intercourse and vaginal douching also are risk factors. Because cellular, not humoral, immunity is required to resist candidal infections, pregnant women and patients receiving immunosuppressive drugs that decrease cellular immunity are predisposed to candidiasis. Candidal overgrowth is also favored by high urine glucose levels that can occur in diabetes or pregnancy. Broad-spectrum antibiotics cause suppression of the normal vaginal and gastrointestinal bacterial flora, allowing fungal overgrowth. The role of oral contraceptives in candidal infection remains controversial.

Most women have uncomplicated infection defined as a sporadic, mild, *C. albicans* infection in a host with normal immunity. About 5% of women have complicated infection defined as recurrent, severe, or non- *albicans* infection. Many of these occur in immunosuppressed women (pregnant, diabetic, or debilitated or immunosuppressed).

Candidiasis is best diagnosed in KOH wet-mounts. Vaginal plaques, vaginal discharge, or vulvar scrapings from the edge of the erythematous border are mixed with 10% KOH (Fig. 32.4). The mycelial form is usually found only during an infection; mycelia can be identified by KOH wet mount in 80% of cases. The pH of vaginal discharge is normal (i.e., 4.7 or less). Fungi can readily be isolated on various media. However, Candida is part of normal vaginal flora, and a positive culture does not necessarily indicate infection. Cultures for Candida should be limited to KOH wet-mount–negative patients with symptoms or signs of candidiasis. In fact, 50% of women with candidiasis have a negative wet mount, but a positive Candida culture.

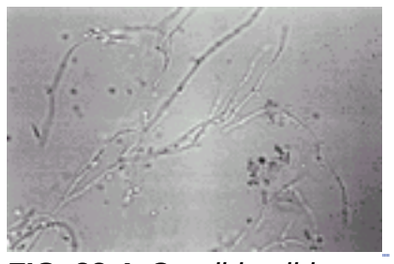

FIG. 32.4. *Candida albicans* growing as hyphae and pseudohyphae within infected tissue (×320). (From Monif GRG. *Infectious diseases in obstetrics and gynecology*. Hagerstown, MD: Harper & Row, 1974, with permission.)

Local vaginal therapy is used because most antifungal preparations are not absorbed from the intestinal tract. For uncomplicated infection, various intravaginal azole agents used for 3 to 5 days are equally effective for women with primary and infrequent candidal vaginitis. These agents include miconazole, clotrimazole, butoconazole (Femstat), tioconazole (Vagistat-1), and terconazole (Terazol). Azole drugs are not absorbed to any degree from the vagina, and the same local regimens can be used safely in pregnancy. The insertion of boric acid powder in capsules into the vagina is also effective. A one-time dose of fluconazole (Diflucan), 150 mg orally, or itraconazole (Sporanox), 400 mg initially then 200 mg for 2 days, is also effective for those with uncomplicated infection. Patients with complicated infection from severe symptoms need 7 to 14 days of intravaginal azole therapy or fluconazole 150 mg with the dose repeated in 4 days. Oral nystatin administration to decrease gastrointestinal colonization does not markedly improve therapeutic cure rates or diminish recurrence rates. About 15% of male sexual contacts of women with candidiasis have symptomatic balanitis; symptomatic males should be identified and treated to prevent recurrent female infection.

The number of non- *albicans* candidal infections appears to have increased. These infections respond poorly to azole therapy, including fluconazole. Boric acid or nystatin therapy works best. Even gentian violet 1% aqueous solution has a limited place in such patients.

Patients with frequently recurrent candidiasis represent the most difficult problem in treatment. Extended 2- to 3-week vaginal therapy, male therapy, and reduction of sugar intake are usually ineffective. A glucose tolerance test and HIV testing should be performed in recurrent or resistant cases to exclude unrecognized diabetes and HIV infection. In addition, some women with candidiasis have other concurrent vaginal infections; a repeat physical and wet-mount examination may clarify the problem.

Complicated infection from frequently recurring candidiasis (four or more times a year) should be treated first with standard anticandidal therapy for 2 weeks, followed by suppressive therapy with an intravaginal azole or boric acid twice weekly or an intravaginal azole daily for 5 days once a month, oral fluconazole, 150 mg weekly, or oral itraconazole, 400 mg monthly. Suppressive treatment should continue for at least 1 year; recurrent candidiasis is usually reduced to no or one infection yearly, but recurs in 30% to 40% of patients upon cessation of suppression.

Trichomoniasis

Characteristic symptoms of trichomoniasis include a profuse, yellow, malodorous, often uncomfortable vaginal discharge with vulvar irritation. *Trichomonas vaginalis* is a common sexually transmitted organism, present in 3% to 15% of asymptomatic women and in up to 20% of women who attend clinics for STDs. *T. vaginalis* is most likely identified in symptomatic women with recent acquisition. However, about 50% of all women with trichomoniasis are asymptomatic. Most male contacts of women with trichomoniasis asymptomatically carry the organism in the urethra and prostate.

A classic profuse, frothy, yellow vaginal discharge is present in only about one-third of women. The vulva may be edematous and inflamed by the discharge. Sometimes, subepithelial redness of the cervix (i.e., strawberry cervix) is seen with the naked eye; smaller red areas are more commonly identified colposcopically. The discharge in women with symptomatic trichomoniasis often has a pH greater than 4.5 and forms an amine odor with 10% KOH. Motile trichomonads are demonstrated in the saline wet-mount smear (Fig. 32.5). Trichomonads are larger than white blood cells (WBCs) and have a jerky motility. The wet mount usually also contains many polymorphonuclear leukocytes. Although the wet mount can identify trichomonads with 80% sensitivity among symptomatic women, less than 50% of all women with trichomoniasis by culture have positive wet mounts. Trichomonads also can be seen occasionally on a Pap smear.

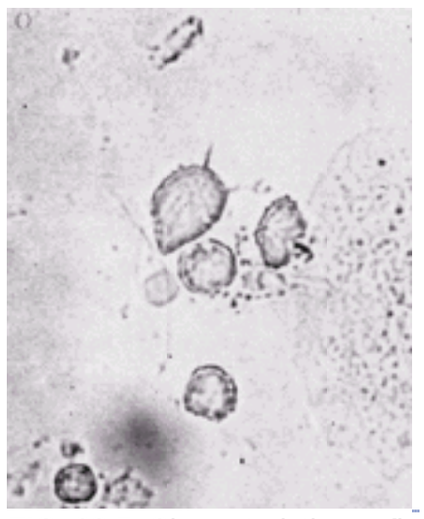

FIG. 32.5. Characteristic configuration of a trichomonad seen in wet smear at high-power magnification. (From Monif GRG. *Infectious diseases in obstetrics and gynecology.* Hagerstown, MD: Harper & Row, 1974, with permission.)

T. vaginalis is an anaerobic protozoan. A culture of this organism is easy to perform but not readily available, and culture should be limited to cases where the diagnosis is suspected, but cannot be confirmed by wet mount. Screening cultures in asymptomatic women are not recommended, except for certain high-risk populations. Women with trichomoniasis should also be cultured for *N. gonorrhoeae* because of a close association between the microbes.

T. vaginalis resides not only in the vagina but also in the urethra, bladder, and Skene glands, so systemic, rather than local, therapy is needed. Metronidazole is effective in treating trichomoniasis; the preferred regimen is 2 g in one dose because of complete patient compliance and high effectiveness. Extended 7-day metronidazole therapy, 500 mg twice daily, does not increase the 95% cure rate of a single dose. Simultaneous treatment of the male sexual partner is recommended. Recurrent trichomoniasis is usually attributable to either a lack of compliance or reexposure to an untreated sexual partner. A single recurrence should be treated with the recommended regimens. However, increasing in vitro and in vivo resistance of *T. vaginalis* to metronidazole exists, and repeated treatment failure should be treated with metronidazole, 2 g daily for 3 to 5 days. The Centers for Disease Control and Prevention (CDC) has consultation available for patients who fail this regimen (see Sexually Transmitted Disease Treatment Guidelines, 2002).

Metronidazole therapy is controversial because of its tumor-causing potential in humans. In animals, large doses (equivalent to 350 to 1,000 human doses) cause tumors. The drug also causes mutation of salmonellae associated with carcinogenic potential. No increased tumor rates were found in a small series of women evaluated for up to 10 years after metronidazole therapy for trichomoniasis. However, these data are only slightly reassuring that the drug does not cause cancer because longer, larger studies are needed to exclude this possibility. A meta-analysis and other studies show no consistent evidence of teratogenesis from use of metronidazole in pregnancy. The CDC Sexually Transmitted Disease Treatment Guidelines, 2002 no longer advise avoiding metronidazole in pregnancy. Treatment of asymptomatic *T. vaginalis* has not reduced prematurity and should be limited to symptomatic women. Persistent discharge after adequate treatment for trichomoniasis should lead to repeat examination for *Trichomonas*, candidiasis, and gonorrhea.

Bacterial Vaginosis

Bacterial vaginosis describes the vaginal condition resulting from overgrowth of both anaerobic bacteria and *G. vaginalis*. Both anaerobes and *G. vaginalis* are normal inhabitants of the vagina, but overgrowth of the normal Lactobacillus-dominant flora by these bacteria results in a thin, homogeneous, fishy-smelling, gray vaginal discharge that adheres to the vaginal walls and often is present at the introitus. In contrast to findings in other causes of vaginitis, the vaginal epithelium appears normal, and WBCs are usually not present. The fishy amine odor produced by anaerobes is accentuated when 10% KOH is added to the discharge.

The diagnosis of bacterial vaginosis is based on the presence of three of the following four characteristics of the discharge: pH greater than 4.5, a homogeneous thin appearance, a fishy amine odor with the addition of 10% KOH, and clue cells. Clue cells are vaginal epithelial cells with many organisms attached. The cell border of clue cells is so obscured by adherent bacteria that it is not identifiable. In bacterial vaginosis, 20% to 50% of the epithelial cells are clue cells. Polymorphonuclear leukocytes and lactobacilli are notably absent. Gram stains used for diagnosis rely on a reduction in *Lactobacillus* morphotypes and an increase in small Gram-negative rods and Gram-positive cocci. Commercially available card tests for high concentrations of *G. vaginalis* (Affirm), pH and trimethylamine (FemExam), and proline aminopeptidase (PIP Activity Test Card) are available. Cultures are not helpful because anaerobes and *G. vaginalis* can be recovered from women without bacterial vaginosis. In fact, up to 40% of asymptomatic women without vaginitis carry *G. vaginalis*. The distinguishing feature of bacterial vaginosis is the 10- to 1,000-fold increased concentration of anaerobic bacteria and *G. vaginalis*.

Factors leading to the overgrowth of anaerobes and *G. vaginalis* are poorly established but include the absence of Lactobacillus and a new sexual partner. Sexual transmission of the infection is considered a risk factor, but is unproven, especially since the treatment of sexual contacts does not prevent recurrence.

Treatment is not advocated for most asymptomatic women with bacterial vaginosis because it can spontaneously disappear. However, the 10- to 1,000-fold increased concentration of potentially virulent bacteria in the vagina is related to upper genital tract infection after surgery. A significant, increased relative risk (RR) of postoperative infection has been reported in patients with bacterial vaginosis following cesarean section (RR = 6), hysterectomy (RR = 3 to 4), and induced abortion (RR = 3). Bacterial vaginitis has also been associated with spontaneous PID and postpartum endometritis after vaginal delivery. Treatment of bacterial vaginosis is particularly beneficial for those undergoing elective surgery. Bacterial vaginosis in pregnancy has also been related to premature delivery (RR = 2 to 4), amniotic fluid infection (RR = 2 to 3), and chorioamnionitis (RR = 2 to 3); treatment of women with prior preterm delivery has reduced the incidence of preterm delivery, but treatment of low-risk asymptomatic women had no effect on preterm delivery.

Metronidazole, 500 mg orally twice daily for 7 days, metronidazole gel, intravaginally once daily for 5 days, and clindamycin cream, intravaginally at bedtime for 7 days are the recommended regimens for bacterial vaginosis. Alternative regimens include 2 g oral metronidazole in a single dose, 300 mg oral clindamycin twice daily for 7 days, and clindamycin ovules intravaginally at bedtime for 3 days. Metronidazole and clindamycin are particularly effective against the anaerobes. Fluoroquinolones, tetracycline, sulfonamides, and erythromycin are ineffective. Treatment of the male sexual contact with metronidazole does not prevent recurrent bacterial vaginosis and is not recommended.

Toxic Shock Syndrome

Toxic shock syndrome is an acute illness caused by toxin-producing *Staphylococcus aureus*. About 6% of women carry *S. aureus* in the vagina, but only 2% of women have *S. aureus* capable of producing the toxic shock toxin. The syndrome is highly associated with menstruation and probably with tampon use, but it has also occurred from *S. aureus* infection of the breast and endometrium after delivery and from abdominal surgical wounds. Characteristic features include a high fever (>102°F [38.9°C]), a diffuse rash, hypotension, skin desquamation (usually 1–2 weeks later), and a wide variety of systemic effects, including gastrointestinal (vomiting, diarrhea), muscular (myalgia), mucous membrane (hyperemia), renal (elevated blood urea nitrogen or creatinine level), hepatic (enzyme abnormalities), hematologic (thrombocytopenia), and neurologic (disorientation, coma). Vaginal or specific-site cultures recover *S. aureus*. Blood, throat, and cerebrospinal fluid cultures, together with serologic tests for Rocky Mountain spotted fever, leptospirosis, and measles, are usually indicated to exclude diseases with similar clinical presentations.

A vaginal tampon, if present, should be removed. Patients should be hospitalized and, when indicated, given large fluid volumes for blood pressure maintenance. Beta-lactamase–resistant antibiotics are recommended, and if other causes of bacterial sepsis such as meningococcemia cannot be excluded, additional antibiotics are necessary. Other life-supporting measures such as intubation, vasopressor administration, and dialysis are often necessary. The case:fatality ratio has been reduced from 15% to 3% with supportive therapy. Antibiotics are of no proven benefit in the acute stage, but they do reduce recurrence rates from 30% to 5%.

Although the effectiveness is uncertain, it is prudent for all women to avoid the prolonged and overnight use of tampons. It is recommended that postpartum women not use tampons for 6 to 8 weeks after delivery. Women with toxic shock syndrome should be warned of recurrent episodes and advised against resuming tampon use.

SYPHILIS

Physicians must constantly be aware of possible syphilitic infection, particularly in populations with high rates of HIV infection. Most women with syphilis are asymptomatic and have only serologic evidence of infection. *T. pallidum* rapidly enters lymphatics after exposure, but a primary chancre lesion usually takes about 3 weeks to develop. The classic chancre ulcer is painless and firm with sharply defined, raised edges; however, most syphilitic ulcers are atypical. Any suspicious genital ulcer should be studied by dark field examination. Serous material expressed from the ulcer base is mixed with saline solution, and because *T. pallidum* is an anaerobe, this mixture must be immediately placed under a cover slip with the edges occluded by petroleum jelly. Identification of typical spirochetes by dark field microscopy establishes a diagnosis of primary syphilis. Dark field examination of ulcer material from possible syphilitic ulcers should be done on 3 consecutive days. VDRL test or rapid plasma reagin (RPR) and fluorescent treponemal antibody (FTA) serology should be performed for a patient with a suspicious lesion. If the serologic results are nonreactive and spirochetes cannot be demonstrated by dark field examination, serologic tests should be repeated in 1 month.

Secondary syphilis appears 6 or more weeks later and is characterized by a symmetric, macular, papular, or papulosquamous rash and generalized, nontender lymphadenopathy. Condylomata lata (see Fig. 32.2) are highly infectious, hypertrophied, wartlike lesions of secondary syphilis that usually occur in moist areas such as the vulva or perineum; they must be distinguished from other vulvar lesions. Superficial, painless mucosal erosions of the mouth or vagina, called mucous patches, develop in one-third of patients. Systemic symptoms of fever, weight loss, and malaise may occur. Serologic tests are positive in the secondary stage.

Untreated patients will enter a latent phase of syphilis during which clinical and physical manifestations are absent. Diagnosis in the latent phase is established by serologic tests. Intermittent spirochetal bloodstream invasion may occur in the early latent phase (first 4 years). In pregnancy, the risk of congenital fetal infection in the primary and secondary phases of syphilis is 80% to 95%; the risk during the early latent phase is 70%. During the late latent phase, immunity develops, which reduces blood invasion, and the risk of congenital syphilis decreases to 10%. Congenital syphilis is reported to be on the rise, affecting 1 in 10,000 live-born infants. Fetal or perinatal death occurs in 40% of those with congenital syphilis. About one-third of adult patients with untreated late syphilis manifest central nervous system or cardiovascular symptoms of tertiary syphilis.

VDRL and RPR tests detect a nontreponemal, nonspecific reagin antibody. The tests can be titrated, and the titer either falls or disappears after therapy for early or secondary syphilis. Thus, the VDRL test can be used to judge the activity of either a first episode or reacquired infection in a patient with documented syphilis. Treated patients with latent syphilis may retain high, stable VDRL titers. Acute bacterial or viral infections can give rise to acute false-positive serologic reactions that last for up to 6 months. Several conditions, such as aging, addiction to drugs, autoimmune disease, and pregnancy, can lead to chronic, nonspecific, false-positive VDRL reactions. False-positive VDRL titers usually are 1:8 or less. By contrast, the FTA test involves a specific antitreponemal antibody, and false-positive FTA reactions are rare. Patients with a positive VDRL reaction must have a confirmatory FTA test to exclude a false-positive VDRL reaction. Patients with a false-positive VDRL reaction will have a negative FTA reaction. In patients with syphilis, the FTA test remains positive indefinitely, and because the test is not titrated, repeat FTA testing should not be done in a known positive patient.

The treatment schedules for syphilis currently recommended by the U.S. Public Health Service's CDC are as follows:

- Early syphilis: Early syphilis is defined as primary, secondary, or latent syphilis of less than 1 year's duration. The drug of choice is penicillin G benzathine, 2.4 million U intramuscularly in a single dose. Alternative choices for penicillin-allergic patients include 2-week regimens of doxycycline, 100 mg twice daily, or tetracycline, 500 mg four times daily. Ceftriaxone, 1 g daily intramuscularly for 8 to 10 days, may be used if close follow-up can be ensured.
- Syphilis of longer than 1 year's, or of unknown, duration: Penicillin G benzathine, 2.4 million U intramuscularly each week for 3 successive weeks (7.2 million U total), is the drug of choice in this situation. Alternative choices for the penicillin-allergic include doxycycline and tetracycline for 4 weeks. Intravenous aqueous penicillin G or penicillin G procaine is recommended for neurosyphilis. Erythromycin is not recommended for neurosyphilis. Spinal tap to exclude asymptomatic neurosyphilis is recommended for those with neurologic or ophthalmologic signs, other evidence of active disease (aortitis, gummas), HIV infection, treatment failure, and infection for more than 1 year with a titer of 1:32 or greater. Neurosyphilis and syphilis in HIV-positive patients should be treated by infectious disease specialists.
- Syphilis in pregnancy: Parenteral penicillin is the only documented efficacious treatment in pregnancy. Treatment with penicillin is the same as for the corresponding stage of syphilis among nonpregnant women. For pregnant patients who are allergic to penicillin, tetracycline is not used because of toxicity and erythromycin is not used because of high failure rates to cure the fetus. Penicillin is so superior to other antibiotics for treating syphilis in pregnancy that pregnant, penicillin-allergic patients should be desensitized. The Jarisch-Herxheimer reaction commonly occurs in early syphilis, and pregnant women should be hospitalized in anticipation of this possibility for monitoring of themselves and the fetus. The reaction is ascribed to the sudden massive destruction of spirochetes by antibiotics; it is marked by fever, myalgia, tachycardia, and occasionally hypotension. The reaction usually begins within 24 hours and subsides spontaneously in the next 24 hours. All patients need to be followed with quantitative serologic tests to monitor treatment results and offered HIV testing. All sexual partners need to be contacted and tested for syphilis.

CERVICITIS

Acute cervicitis is defined as the presence of yellow cervical mucopus or an increased number of WBCs in cervical mucus. Symptoms are usually limited to a purulent vaginal discharge. Physical findings include mucopus in the endocervical canal or bleeding after swabbing of the cervix. Organisms that infect the cervical columnar epithelium, *C. trachomatis* or *N. gonorrhoeae*, can be isolated separately or in combination from about one-half of women with purulent cervicitis. Unknown microbes cause the other cases. The diagnosis can also be established by the finding of more than 10 WBCs per 1,000× microscopic field.

Infectious ulcers of the cervix caused by herpesvirus, syphilis, and chancroid must be distinguished from erosion and the other conditions described in Chapter 33. Depending on the nature of the lesion, Gram stain, Pap smear, culture, dark field examination, colposcopy, and, in some cases, biopsy may be required.

If *N. gonorrhoeae* is found by culture or DNA technique, treatment should be the same as for gonorrhea, including treatment for coexisting *C. trachomatis*. If *N. gonorrhoeae* is not found, azithromycin or doxycycline regimens used for *C. trachomatis* are recommended. Ofloxacin or levofloxacin can also be used.

ENDOMETRITIS

Lymphocytes and neutrophils normally appear in the endometrium in the second half of the menstrual cycle; their presence does not necessarily constitute endometritis. However, plasma cells are not normally in the endometrium, as they represent an immune response, usually to a bacterial antigen.

Endometritis produces nonspecific symptoms, and it should not be diagnosed unless plasma cells, neutrophils within glands, or a specific causative infection is found. Endometritis may occur in the following situations:

- puerperal endometritis (see Chapter 19)
- chlamydial or gonococcal endometritis, often occurring among patients with salpingitis
- endometritis after endometrial instrumentation or surgery
- tuberculous endometritis
- purulent endometritis, occurring in pyometra caused by a cervical stricture or after radium insertion
- endometritis occurring characteristically in the presence of an intrauterine device (IUD).

The fact that chronic endometritis is associated with the use of IUDs is well documented; it results from organisms attached to the IUD surface rather than from the foreign body per se. Transfundal endometrial cultures of hysterectomy specimens from women who had used tailed IUDs for more than a few weeks uniformly recovered bacteria, while cultures from women who did not use an IUD were negative. Bacteria that can be recovered are usually of low pathogenicity, but more virulent intrauterine bacteria occasionally cause malodorous discharge and salpingitis. In addition, an anaerobe, *Actinomyces israelii*, has been found in Pap smears from about 5% of women using IUDs, but not in those who do not use IUDs. This organism appears to colonize the IUD, and when it is found on a Pap smear, asymptomatic patients should be warned of abnormal discharge or abdominal pain, representing infection. If symptomatic infection occurs, the IUD should be removed, and patients treated with ampicillin for 2 to 4 weeks. Asymptomatic patients should not have the IUD removed because of *A. israelii*.

Chronic plasma cell endometritis in nonpregnant women who do not use an IUD is often related to endometrial infection with *C. trachomatis* and, to a lesser extent, *N. gonorrhoeae*. Plasma cell endometritis occurs in up to 50% of women with acute cervicitis and over 80% of women with acute salpingitis. Symptoms are abnormal uterine bleeding and mild uterine tenderness. Untreated endometritis can progress to clinically evident salpingitis.

GONORRHEA

Gonorrhea is caused by the Gram-negative diplococcus *N. gonorrhoeae* which attach only to columnar or transitional cells by pili and are rapidly brought intracellularly by pinocytosis. They attract leukocytes, commonly giving rise to purulent discharge. Gonorrhea is usually sexually transmitted, although organisms can be acquired by neonates passing through an infected cervix, causing gonorrheal ophthalmia.

Course of the Disease

N. gonorrhoeae in the lower genital tract infects the urethra, Bartholin glands, and endocervix. The anus and rectum can also be infected either from cervical infection or during anal coitus. Urinary frequency, dysuria, and a purulent vaginal discharge are the first symptoms to appear 2 to 5 days after exposure. At least 50% of women with *N. gonorrhoeae* infection have no symptoms. Many women do not seek medical attention if these symptoms are mild. The discharge occasionally is locally irritating and causes vulvar edema and soreness. Pharyngitis may result from gonorrheal pharyngeal infection. In 2% of infected women, disseminated gonococcal infection occurs, causing fever, septicemia, dermatitis, arthritis, endocarditis, or meningitis, in various combinations. Untreated gonorrhea is associated with premature delivery and premature rupture of membranes.

In 10% to 17% of women with untreated gonorrhea, the organisms ascend to produce upper genital tract infection or acute PID (Fig. 32.6). Acute PID is the most common serious sequela of gonorrhea. The mechanical and antibacterial properties of cervical mucus probably provide a barrier against upward extension, but during menstruation the mucus barrier is lost, and gonococci can disseminate to the uterus and fallopian tubes. A transient endometritis occurs as the organisms pass through the uterine cavity and reach the fallopian tubes, where they produce an acute and usually bilateral inflammatory reaction of tubal mucosa. The tubes characteristically become swollen and reddened when the muscularis and serosa become inflamed. If exudate drips from the fimbriated ends of the tubes, pelvic peritonitis occurs that ultimately can cause peritoneal adhesions. The swollen and congested fimbriae may adhere and produce tubal occlusion.

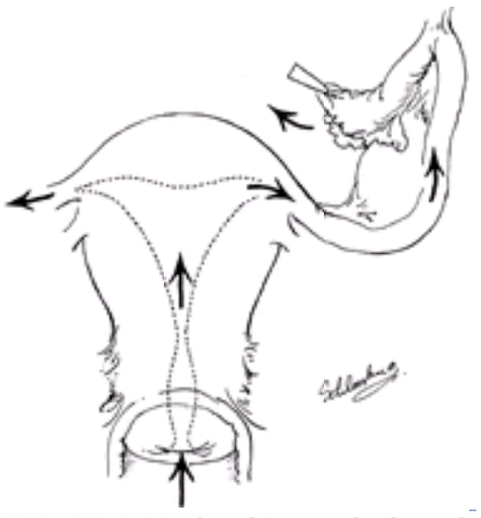

FIG. 32.6. Mode of transmission of gonococcal pelvic infection. Portal of entry is external genitalia. The organism enters cervix, following mucous membrane, passes up through the uterine cavity, and attacks the fallopian tube. Pelvic peritonitis results from escape of pus from tubal fimbria. (From Wharton LR. *Gynecology and female urology.* Philadelphia: WB Saunders, 1943, with permission.)

The process can take any of the following courses. With prompt, appropriate antibacterial therapy, the infection may subside with little permanent damage to the reproductive tract. The fimbriae may occlude, producing permanent tubal infertility. The swollen and congested fimbriae may adhere to one another or to the ovary, trapping the exudate in the tube and giving rise to pyosalpinx or, if the ovary becomes infected, a tuboovarian abscess. The mucosal folds may adhere to one another, forming glandlike spaces that are filled at first with exudate and later, as the process becomes chronic, with watery secretion in follicular salpingitis (Fig. 32.7). If the infection subsides after agglutination of the fimbriae and closure of the distal tube, watery secretion accumulates and distends the tube, forming a hydrosalpinx (Fig. 32.8).

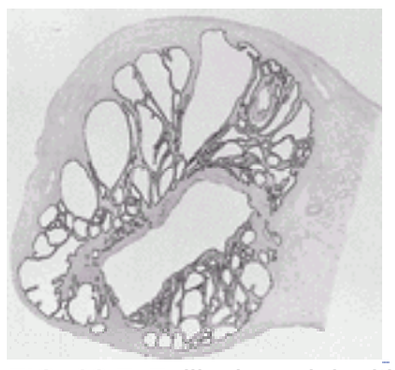

FIG. 32.7. Follicular salpingitis, an end stage of gonorrheal salpingitis. Mucosal folds are adherent, giving rise to innumerable round or irregular cystlike cavities lined by cuboidal epithelium. (From Kelly HA. *Operative gynecology*, Vol 2. New York: Appleton, 1898: plate XI; drawing by Max Brodel, with permission.)

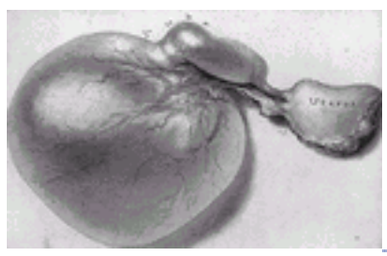

FIG. 32.8. Hydrosalpinx. (From Curtis AH, Huffman JW. *A textbook of gynecology*, sixth ed. Philadelphia: WB Saunders, 1950, with permission.)

Symptoms and Signs

Except for the discharge, which can be milked from the urethra or is present in the vagina or cervix, there are few signs of acute gonococcal infection in women. Bilateral, mild to severe lower abdominal pain may occur with acute salpingitis. Pelvic peritonitis can cause pain on movement of the cervix, direct and rebound abdominal tenderness, muscle guarding that prevents abdominal palpation, and tender adnexa to various degrees on bimanual examination. However, a sizable proportion of women with salpingitis experience either mild or no symptoms. In subacute salpingitis, infection continues with signs and symptoms that are even less overt than those of the acute stage. In the end stage of salpingitis, the uterus and the adnexa can be fixed by pelvic peritoneal adhesions. The adnexa may be either adherent to the posterior aspect of the uterus or prolapsed in the cul-de-sac, which may pull the uterus into a retroverted position. Notable features are dyspareunia, sterility, and chronic, aching pelvic pain that increases before menstruation.

Diagnosis

The diagnosis of gonorrhea depends on a culture of *N. gonorrhoeae* or identification of *N. gonorrhoeae* by DNA tests. The finding of intracellular Gram-negative diplococci in the Gram stain of cervical or urethral exudate points to gonorrheal infection, but Gram stains for gonorrhea are insensitive. Gonococcal testing should be performed on women with positive Gram stains, symptoms or signs suggestive of gonorrhea (e.g., cervicitis, undiagnosed vaginitis, dysuria), other STDs, bartholinitis or skenitis, acute lower abdominal pain suggestive of acute salpingitis, or suspected disseminated gonococcal infection, as well as on women with male sexual contacts with gonorrhea.

Sites to be tested in order of importance are: cervix, anal canal, pharynx, and urethra. Vaginal discharge should be wiped away from the cervix before mucus is obtained for testing. Genital samples must be cultured on Thayer-Martin or similar media containing antimicrobial agents that inhibit growth of the normal bacterial and fungal flora. Patients with gonorrhea should also receive a test for chlamydial infection because 10% to 30% of women with *N. gonorrhoeae* also have *C. trachomatis*.

Because gonorrhea is an STD, it usually is present in the male partner. The fact that more than 40% of the male contacts of women with gonorrhea are asymptomatic carriers who otherwise do not seek treatment underscores the importance to identify and treat male sexual contacts.

Drug Therapy of Uncomplicated Lower Genital Tract Gonorrhea

The CDC-recommended treatment schedules for gonorrhea reflect increased resistance to penicillin and tetracycline and in Asia, the Pacific rim, and the West Coast to quinolones, frequent coexistence of chlamydial infection with gonorrhea, potentially serious complications, and frequently no testing for *C. trachomatis*. Penicillin is no longer recommended to treat gonorrhea because ß-lactamase production by extrachromosomal plasmids destroys ß-lactam antibiotic activity in a large number of gonococcal strains. Resistance to quinolones will likely increase.

The recommended drug therapy regimens are given in Table 32.2. A loading dose of cephalosporin or quinolones is used to inhibit *N. gonorrhoeae*. Patients allergic to penicillin should receive spectinomycin (Trobicin) or other cephalosporins or quinolones. If *C. trachomatis* is not excluded, azithromycin or doxycycline is indicated. Quinolones and doxycycline should not be given to pregnant women. Special antibiotic regimens are recommended for patients with complicated gonococcal infections. These regimens are published in the widely circulated CDC Sexually Transmitted Disease Treatment Guidelines 2002. Prophylactic regimens to prevent ophthalmia neonatorum include silver nitrate, erythromycin, and tetracycline applications.

Gonorrhea
Recommended loading dose regimen (choice of one plus treatment for chlamydia)
Ceftriaxone (Rocephin), 125 mg i.m.
Cefixime (Suprax), 400 mg p.o.
Ciprofloxacin (Cipro), 500 mg p.o.
Ofloxacin (Floxin), 400 mg p.o.
Levofloxacin (Levaquin) 250 mg p.o.
Alternative regimen (choice of one)
Spectinomycin (Trobicin), 2 g i.m.
Ceftizoxime (Cefizox), 500 mg i.m.; cefotaxime (Claforan), 500 mg i.m.; or cefoxitin (Mefoxin), 1 g i.m. with probenecid
Norfloxacin (Noroxin), 800 mg p.o. or gatifloxacin (Tequin) 400 mg p.o.; all in a single dose
Chlamydia
Follow-up regimen to treat chlamydia (choice of one)
Azithromycin (Zithromax), 1 g p.o., in a single dose, *or*
Doxycycline, 100 mg p.o., b.i.d. for 7 d
Alternative regimen (choice of one)
Ofloxacin, 300 mg p.o., b.i.d. for 7 d
Erythromycin (see "Pregnant patients" below)
Levofloxacin 500 mg p.o. for 7 days
Pregnant patients (choice of one)
Preferred regimen
Erythromycin base 500 mg p.o. q.i.d. for 7 days, *or*
Amoxicillin 500 mg p.o. t.i.d. for 7 days, *or*
Azithromycin, *or*
Erythromycin base, 250 mg p.o., q.i.d. for 14 d, *or* azithromycin
Alternative regimen
Erythromycin ethylsuccinate, 800 mg p.o., q.i.d. or 400 mg q.i.d. for 14 d

TABLE 32.2. *Treatment regimens for gonorrhea and chlamydia*

The first-choice regimens are so effective that test-of-cure cultures are not recommended. A rescreening culture in 1 to 2 months is reasonable. Patients treated with alternative regimens should have a test-of-cure culture in 4 to 7 days after therapy. All male sexual contacts need referral for evaluation and treatment.

Patients with gonorrhea should have serologic tests for syphilis. Those with incubating syphilis (i.e., seronegative, without clinical signs of syphilis) are likely to be cured by all the regimens mentioned, except for quinolones and spectinomycin. Patients treated with these regimens need a follow-up serologic test for syphilis.

CHLAMYDIAL INFECTION

C. trachomatis is a sexually transmitted bacterium that is often associated with gonorrhea. Chlamydiae infect the same tissues and produce the same symptoms and

diseases as gonorrhea. Chlamydial infection causes urethritis, bartholinitis, cervicitis, endometritis, salpingitis, Fitz-Hugh and Curtis syndrome (i.e., perihepatitis), and LGV. Treatment of *C. trachomatis* in pregnancy reduces premature delivery. Neonates born of mothers with chlamydial cervical infection have up to a 40% risk of chlamydial conjunctivitis and a 20% risk of chlamydial pneumonia. As with gonococcal infection, male sexual contacts have both symptomatic and asymptomatic urethritis.

C. trachomatis is an obligate intracellular bacterium that attaches to columnar or transitional epithelial cells, is engulfed by pinocytosis, and remains within a phagosome membrane that protects it from host defense mechanisms. The bacteria replicate until they replace most of the cell and, ultimately, cause the cell to rupture. Infective particles are released into the extracellular space, and the process is repeated. Replication time is a relatively slow 24 to 48 hours, explaining the characteristically long latent period between the time of exposure and the onset of symptoms, which ranges from weeks to months.

C. trachomatis is three to five times more common than *N. gonorrhoeae* in developed countries because it is not routinely sought in asymptomatic patients. Chlamydial infection is most often asymptomatic and frequently not identified until overt infection occurs. Infection is particularly common among teenagers. *C. trachomatis* is associated with serious sequelae, including tubal infertility and ectopic pregnancy and it appears able to produce permanent tissue damage more readily than *N. gonorrhoeae*. Permanent tissue damage appears largely related to the immune response to infection. Reinfection, chronic infection, and infection in the presence of antibody to chlamydial heat shock protein are particularly associated with tissue damage.

Chlamydial infection should be suspected with acute urethritis, mucopurulent cervicitis, and salpingitis. The rate of chlamydial salpingitis approximates that of gonorrhea. Chlamydial infections can be diagnosed by culture, a direct monoclonal antibody slide test, an enzyme-linked immunosorbent assay, or DNA techniques. New DNA methods using ligase chain reaction or PCR offer both sensitivity and specificity not achieved with older tests. Samples should be taken from the cervix or from urine with DNA tests.

Azithromycin and doxycycline are the most effective drugs to treat chlamydial infection (see Table 32.2). Erythromycin, ofloxacin (Floxin), and levofloxacin (Levaquin) are alternatives. In pregnancy, erythromycin and amoxicillin are preferred, but reports document the effectiveness and safety of azithromycin.

GENITAL MYCOPLASMAS

Genital mycoplasmas have often been thought a microbe in search of a disease because they are ubiquitous and not highly virulent. *Mycoplasma hominis* is recovered from the vagina in 15% to 70% of women, and *Ureaplasma urealyticum* is recovered from 40% to 95% of women. A third isolate, *Mycoplasma genitalium*, is now associated with endometritis. These organisms are phylogenetically positioned between bacteria and viruses.

The most convincing role for mycoplasmas in human female infections is as a pathogen in postpartum fever. Mycoplasmas are recovered from the blood of 10% to 15% of women with postpartum fever, and antibodies to *M. hominis* are demonstrated in 50% of such women. Their role in salpingitis is less clear. Mycoplasmas are recovered from the tubes of 5% to 15% of women with salpingitis, but in primate model studies, *M. hominis* produces an adnexitis and not salpingitis.

Maternal lower genital tract *U. urealyticum* is not associated with low birth weight, and treatment of *U. urealyticum* does not reduce preterm births. However, organisms are found in intraamniotic infection and cause cerebrospinal fluid and lung infection in premature neonates. Recovery of *U. urealyticum* from fetal tissue of mid-trimester spontaneous abortuses also suggests a relationship with abortion. The role of *U. urealyticum* in fertility is unsettled, but in some reports, mycoplasmas were not related to infertility or to higher pregnancy rates in infertile women.

Both *M. genitalium* and *M. hominis* are sensitive to tetracycline. Erythromycin inhibits *U. urealyticum* in vitro but not *M. hominis*. However, neither antibiotic very effectively eradicates mycoplasmas from the vagina.

ANAEROBIC BACTERIA

Anaerobic bacteria are highly associated with pelvic infections. Multiple anaerobic species, usually together with one or more aerobic bacteria, typically combine to form a polymicrobial infection. Intraabdominal abscess and postoperative, postpartum, and bacterial vaginosis infections are the most important examples of anaerobic infection.

Anaerobic bacteria are part of the normal vaginal flora. Although many mechanisms by which anaerobic bacteria become pathogenic are unknown, two mechanisms known to cause anaerobic infection include (a) reduction of the redox potential that occurs with tissue trauma from surgery and (b) antibiotic selection that preferentially inhibits aerobic bacteria. Clinicians can virtually assume the presence of anaerobes in infections with a foul-smelling odor as only anaerobes produce odorous metabolic products. Anaerobes are virtually always isolated from an abscess. Anaerobic infections can also produce gas and cause thromboembolism.

The anaerobic bacteria most commonly found in genital infections include anaerobic Gram-positive cocci (*Porphyromonas* and *Peptostreptococcus* species), gram-negative rods (*Prevotella* [*P. melaninogenicus, P. bivia*], *Bacteroides* [*B. fragilis*], and *Fusobacterium* species), and Gram-positive rods (*Clostridium* species).

Cultures should be obtained before antimicrobial therapy is begun. Because anaerobes are part of the normal flora, deep tissue cultures are required that are not contaminated by surface bacteria. Because 48 or more hours are required for anaerobe isolation, antibiotic selection is usually based on clinical signs. Anaerobic infection should be particularly suspected with abscess formation, a foul odor, gas formation, tissue necrosis, sterile cultures from obviously infected sites, and thromboembolism. Antibiotic sensitivity testing is only a rough guide to antibiotic susceptibility, but in vitro and in vivo experience has shown that clindamycin, metronidazole, imipenem/cilastatin sodium (Primaxin), second- and third-generation cephalosporins (cefoxitin sodium [Mefoxin], cefotaxime sodium [Claforan]), and extended-spectrum penicillins (ticarcillin disodium/clavulanate potassium [Timentin], amoxicillin/clavulanate potassium) are effective to treat anaerobic infections.

SALPINGITIS

Acute primary salpingitis results when pathogenic bacteria in the cervix invade the fallopian tubes. *N. gonorrhoeae*, *C. trachomatis*, normal flora aerobic and anaerobic bacteria, and, perhaps, *M. genitalium* are known causes of tubal infections. Virtually all primary salpingitis occurs among sexually active, menstruating, nonpregnant women. Gonococcal and chlamydial infections account for 50% to 60% of cases. Tuberculous, parasitic, or fungal salpingitis is rare in industrialized countries. Salpingitis usually occurs without instrumentation or trauma to the genital tract; however, approximately 15% of cases occur after instrumentation (e.g., IUD insertion, dilation and curettage, abortion, hysterosalpingography). Perisalpingitis secondary to acute appendicitis or other intraabdominal infections accounts for less than 1% of cases.

Acute salpingitis is a common event that annually develops in up to 1% of women between 15 and 39 years of age. Young, sexually active women between 15 and 24 years of age have the highest rate of infection. This infection has tremendous cost consequences. At least $1 billion is required to treat the 800,000 women with acute salpingitis in the United States annually, and $40 billion is spent to diagnose and treat tubal infertility.

Epidemiology

Most women are infected with sexually transmitted organisms. The rate of salpingitis is increased in women with multiple sexual partners. The high rate of salpingitis in young women is due to their increased rates of gonorrhea and chlamydial infection. Routine screening for *C. trachomatis* and *N. gonorrhoeae* has reduced salpingitis in Europe and the United States. Sexually active women at increased risk for STDs, especially women younger than 25 years and with multiple sexual partners, should be annually screened for chlamydial infection and gonorrhea. Such screening will prevent salpingitis and subsequent tubal infertility and ectopic pregnancy more effectively than any other measure. Previous salpingitis also predisposes women to subsequent salpingitis, probably because mucosa damaged from prior infection is more susceptible to infection than normal tissue. Patients with previous uncomplicated gonorrhea have a high rate of subsequent salpingitis, in part because of increased rates of subsequent gonorrheal infection. Prior chlamydial infection predisposes patients to salpingitis if a second chlamydial infection occurs. Repeated chlamydial infections produce a hyperimmune response that increases the chance and severity of tissue damage.

The presence of an IUD is an independent risk factor for salpingitis. IUD users have a two-fold to four-fold increased rate of both salpingitis and tubal infertility, compared to non–IUD users. The highest rate of salpingitis in IUD users occurs within a few weeks of insertion as a result of the introduction of cervical bacteria into the endometrial cavity along with the IUD. Most infections in IUD users, however, occur long after insertion, probably because bacteria wick along the IUD tail from the vagina to the uterus and adhere to the IUD surface. IUDs also appear to enhance anaerobic bacterial growth, and their use is associated with *Actinomyces* and bacterial vaginosis infection. Because IUD use is also associated with tubal infertility, an IUD should not be inserted in women who desire future pregnancy. By contrast, barrier or oral contraceptive methods appear to protect against salpingitis. The protective effect of oral contraceptives on salpingitis appears to exist only for patients with chlamydial infection, possibly due to a down-regulation of the hyperimmune response caused by the organisms.

The role of male contacts with untreated gonococcal or chlamydial urethritis is often ignored by gynecologists. Only 25% of male contacts of women with gonococcal salpingitis are treated by the time the female partner develops symptomatic salpingitis. Over 50% of the male contacts with gonococcal urethritis are asymptomatic, and *N. gonorrhoeae* is isolated from 40% of these asymptomatic males. Men with nongonococcal urethritis represent reservoirs of chlamydial salpingitis. To reduce the rate of new and recurrent salpingitis, all male contacts of women with any type of salpingitis should be examined and cultured. If infectious organisms are found, males should be appropriately treated.

Bacteriology

Neisseria gonorrhoeae In most studies in the United States, *N. gonorrhoeae* is recovered from 40% to 50% of women with acute salpingitis. However, gonococcal prevalence varies greatly: *N. gonorrhoeae* is isolated from less than 20% of salpingitis cases in Sweden and from 80% of cases in certain urban populations in the United States. In women with both cervical gonorrhea and salpingitis, *N. gonorrhoeae* is the most frequent intraabdominal isolate, but the sole isolate in only 30% of these cases. The remainder have either no organisms or other organisms isolated alone or together with *N. gonorrhoeae* in the abdomen. Chlamydial infection frequently coexists with gonorrhea; in some studies, more than 50% of women with gonorrhea also had *C. trachomatis* in the cervix. Positive tubal gonococcal cultures are usually obtained during the early stages of infection, but not in the later stages of infection.
Chlamydia trachomatis *C. trachomatis* is as important as the gonococcus in causing acute salpingitis. From 30% to 60% of women with salpingitis have *C. trachomatis*, and in most of these women the organisms can be isolated from the fallopian tube. Application of new DNA tests for *C. trachomatis* identifies even more chlamydial infections. Chlamydial salpingitis is under-diagnosed because many patients have mild symptoms and are not identified. It is now evident that women with mild symptoms and signs have the same amount of severe tubal damage as those with severe symptoms. Chlamydial salpingitis often produces mild symptoms and signs but may produce more severe tubal damage compared to gonococcal salpingitis.
Nonsexually Transmitted Aerobic and Anaerobic Bacteria Nonsexually transmitted aerobic and anaerobic bacteria are normally present in cervical and vaginal flora and particularly include organisms associated with bacterial vaginosis. These organisms can be a direct cause of salpingitis, but they also cause secondary infection in combination with *N. gonorrhoeae* and *C. trachomatis*, IUD use, or instrumentation. Polymicrobial infection with these agents is common in salpingitis. In such cases, many different Gram-positive and Gram-negative aerobic and anaerobic organisms are isolated, particularly *Porphyromonas*, *Prevotella*, and *Bacteroides* spp, including *B. fragilis*. Anaerobic organisms are especially common in serious infections, and they are virtually always found in abscesses.
Mycoplasmas Genital mycoplasmas have been recovered from the tubes or cul-de-sac in 2% to 20% of patients with salpingitis. In addition, more than 20% of patients with salpingitis have changes of mycoplasmal antibody titer suggestive of invasive infection. These organisms lack the virulence of *N. gonorrhoeae* and *C. trachomatis*, and they appear to cause an adnexitis rather than salpingitis. *M. genitalium* identified by DNA technology is related to endometritis.

Pathogenesis

Salpingitis occurs from vaginal and cervical bacteria ascending into the endometrium and fallopian tubes. The ascent of bacteria probably increases during menses, as evidenced by the onset of pain within 7 days of starting menses in one-half to two-thirds of patients with gonococcal salpingitis. Virulent gonococci also proliferate at menstruation, and less virulent gonococci are present at other times of the cycle. Other risk factors for salpingitis exist. Virulent bacteria in the cervix are more likely to cause salpingitis than nonvirulent bacteria, and *C. trachomatis* and *N. gonorrhoeae* are two virulent organisms capable of causing salpingitis. Virulence is occasionally evidenced by bacteria in the normal flora.

Specific bactericidal antibodies to *N. gonorrhoeae* appear to reduce salpingitis. Clinically recognized salpingitis develops in only 10% to 17% of women with cervical gonorrhea, and most of these women probably develop tubal infection during the first one or two menstrual periods between gonococcal acquisition and the development of specific bactericidal antibodies.

C. trachomatis may not depend on menses for ascent into the endometrium. Endometritis caused by *C. trachomatis* appears to be a common chronic intermediate infection that exists through several menstrual cycles. Tubal damage from chlamydial infection appears to occur from the immune response to infection. As mentioned, repetitive chlamydial infections elicit a hyperimmune response that accelerates tissue damage. The presence of chlamydial heat shock protein also contributes to an acceleration of tissue damage.

The usual route of infection with either organism is the contiguous spread along mucosa from the cervix to the endometrial cavity and fallopian tubes (see Fig. 32.6). Lymphatic or hematogenous dissemination of organisms from the uterus to the adnexa is uncommon in nonpregnant women. It also is possible that organisms may be transported along the fallopian tubes by cilia or even carried by their attachment to spermatozoa or to other organisms.

Fitz-Hugh and Curtis Syndrome Perihepatitis consisting of liver capsule inflammation without liver parenchymal damage is referred to as Fitz-Hugh and Curtis syndrome (Fig. 32.9). Swelling of the liver capsule produces pain with inspiration, usually in the right upper quadrant. A purulent or fibrinous exudate appears on the capsular surface. Violin-string adhesions between the liver capsule and the anterior abdominal wall are a late manifestation of capsular inflammation.

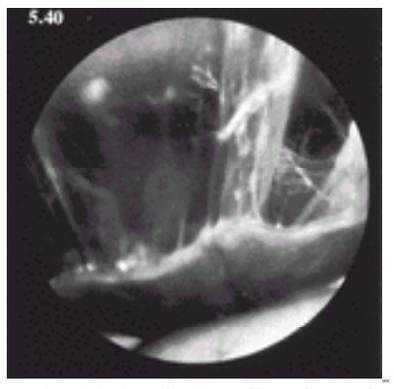

FIG. 32.9. Liver adhesions in Fitz-Hugh and Curtis syndrome.

Perihepatitis was formerly believed to be caused solely by *N. gonorrhoeae*, but *C. trachomatis* also causes this syndrome. Chlamydial heat shock protein is associated with perihepatitis, indicating that the syndrome is another manifestation of a hyperimmune response to chlamydiae. Some organisms travel transperitoneally from the fallopian tubes to reach the liver surface, but organisms may also reach the liver by lymphatic and hematogenous routes. The syndrome occurs virtually exclusively in women, although two men with this syndrome have been reported. Salpingitis is invariably the source, but the syndrome occasionally follows appendicitis and other causes of peritonitis. The Fitz-Hugh and Curtis syndrome is frequently misinterpreted as cholecystitis, viral pneumonia, or pyelonephritis. Liver enzyme levels may be mildly elevated. In women with salpingitis, 5% to 10% developed symptoms, but another 5% of women have asymptomatic perihepatitis. This latter group may have the violin-string adhesions recognized as an incidental finding at a subsequent surgery. Many women with Fitz-Hugh and Curtis syndrome note the onset of lower abdominal pain before or with the upper abdominal pain, but some develop such severe upper abdominal pain that they fail to complain of lower abdominal pain. Given the frequency of salpingitis and the infrequency of acute cholecystitis in women 15 to 30 years of age, Fitz-Hugh and Curtis syndrome is a more likely cause of upper quadrant pleuritic pain than cholecystitis and should be suspected in any woman with pleuritic upper quadrant pain and physical signs of salpingitis. Laparoscopy is useful to diagnose unclear cases.

Diagnosis

The largest unsolved problem with salpingitis is the lack of sensitive and specific diagnostic criteria. For an estimated one-half of women, salpingitis does not cause sufficiently typical symptoms to be diagnosed. In Table 32.3 women are presented who, despite not having a recognized episode of salpingitis, had severe enough tissue damage to cause infertility from tubal obstruction. Thus, patients with mild abdominal pain and other mild manifestations are often not identified. An emphasis must be placed on increasing the sensitivity for the diagnosis. The problem is the very broad spectrum of clinical severity among patients with salpingitis. Although severe manifestations are usually recognized as salpingitis, they occur in only 30% of patients. Insistence on rigid criteria, such as fever, severe tenderness, leukocytosis, and an elevated erythrocyte sedimentation rate (ESR), leads to a failure of diagnosis in nonovert cases.

Study	Infertile patients with tubal occlusion	No history of salpingitis (%)
Punnonen et al. (1979)	23	9 (37)
Moore et al. (1982)	33	15 (45)
Jones et al. (1982)	77	62 (81)
Kane et al. (1984)	70	42 (60)
Conway et al. (1984)	48	36 (75)
Brunham et al. (1985)	18	11 (61)
Total	269	175 (65)

Source: From Wolner-Hanssen P, Kiviat NB, Holmes KK. Atypical pelvic inflammatory disease: subacute, chronic or subclinical upper genital tract infection in women. In: Holmes KK, Mårdh P-A, Sparling PF, et al., eds. *Sexually transmitted diseases*. New York: McGraw-Hill, 1990.

TABLE 32.3. *Proportions of patients with tubal occlusion from salpingitis with no history of salpingitis*

On the other hand, a clinical diagnosis of salpingitis that relies on the history, physical examination, and nonspecific laboratory tests also has a large false-positive error rate. Several studies demonstrate that a clinical diagnosis of salpingitis can be confirmed by laparoscopy in about 65% of patients (Table 32.4); about 20% of patients had no disease observed, and another 15% had other pelvic conditions, most commonly ovarian cyst, ectopic pregnancy, appendicitis, or endometriosis.

TABLE 32.4. *Laparoscopic observations in patients with a clinical diagnosis of pelvic inflammatory disease*

History

Important history and physical findings in patients with presumed PID are listed in Table 32.5. However, none of these findings distinguish women with salpingitis from those with other causes of pelvic pain. Lower abdominal pain is the most consistent symptom in women with overt salpingitis, although it may be mild or even absent. Acute pain is present for less than 15 days in 85% of patients who present with PID. Most women with gonococcal salpingitis experience acute pain during menses; in chlamydial salpingitis, the onset of pain is often insidious and not associated with menses. The abdominal pain is usually continuous and most severe in both lower quadrants. It increases by movement, the Valsalva maneuver, and intercourse. Abnormal vaginal bleeding occurs in 15% to 35% of women with salpingitis. Symptoms of appendicitis and ectopic pregnancy overlap with those of PID. The risk of STD can be helpful in forming a tentative opinion. An increased risk of PID would be expected for women with multiple sexual partners, other STDs, symptomatic male partners, and prior gonorrhea or prior PID.

TABLE 32.5. *Clinical findings in 176 women with suspected acute pelvic inflammatory disease (PID)*

Physical Examination

Most patients with salpingitis have lower abdominal, cervical, and bilateral adnexal tenderness (see Table 32.5). Cervical motion tenderness is a sensitive indicator of salpingitis. However, none of these findings is specific for PID and patients with other disease or with no apparent disease may have similar physical findings. Other associated findings lack the sensitivity to be useful. For example, although a temperature of 100.4°F (38°C) or higher is present more often in patients with than in those without salpingitis, only 45% of patients with laparoscopically confirmed salpingitis have a temperature greater than 100.4°F.

Laboratory Tests

Nonspecific tests as the peripheral WBC count and the ESR are helpful only if the results are abnormal, but they are often normal. Of patients with laparoscopically confirmed salpingitis, 50% have a normal WBC count and 25% have a normal ESR. C-reactive protein levels may be more useful.

Laboratory signs such as yellow cervical mucopus and a cervical Gram stain with an increase of polymorphonuclear leukocytes of more than 30 per high-powered field appear to offer a more specific indication of salpingitis in patients with pelvic tenderness. It is mandatory to obtain a culture for gonorrhea and a test for chlamydial infection. Cervical culture for other organisms is not recommended.

Endometrial Biopsy

Endometrial biopsies are easy and safe to obtain. Histologic evidence of endometritis is based on finding plasma cells and polymorphonuclear leukocytes migrating through the epithelium. Histologic endometritis has a 90% sensitivity and specificity for diagnosing salpingitis, compared to laparoscopy.

Ultrasound and Computed Tomography

Abnormal vaginal ultrasound findings correlate with a diagnosis of salpingitis made by laparoscopy, but these findings remain too insensitive with mild tubal abnormalities and too nonspecific for a certain diagnosis. Ultrasound is useful to distinguish an abscess from an inflammatory mass within the adnexa, define a mass in obese or excessively tender patients, and follow the size of a mass with treatment. Computed tomography has successfully been used for the same purposes; it may be especially helpful if ultrasound is difficult to perform, as in peritonitis or a recent abdominal incision.

Laparoscopy

Laparoscopy provides the most accurate way to diagnose salpingitis. It should be used when the diagnosis is unclear, particularly in patients with severe peritonitis, to exclude a ruptured abscess and appendicitis. It is estimated that for every 100 times a clinical diagnosis of PID is made without visual confirmation, three patients with appendicitis are treated for PID (see Table 32.4), resulting in a critical delay in the correct diagnosis. Pain and tenderness from acute PID should abate 3 or 4 days after antibiotics begin. Patients without reduced tenderness on antibiotic therapy also benefit from laparoscopy. About 20 of 100 women with a clinical diagnosis of PID have no abnormality at laparoscopy. All cases where laparoscopy is performed should have cultures taken from the fimbriated ends of the tubes, regardless of the findings, to detect the small number of patients with endosalpingitis and normal-appearing tubes.

Open laparoscopy is used to identify and percutaneously drain pelvic abscesses. The abscess is visualized, and a 14-French catheter is placed into the abscess, which is drained of pus and carefully rinsed with sterile bacteriostatic water. A closed drainage system is then connected to the catheter for 1 to 3 days until drainage ceases. About 90% of abscesses are successfully treated by percutaneous drainage.

Examination of the Male Partner

Examination of the male sexual partner helps establish the diagnosis of PID and treat STDs. At least 80% of male contacts of women with PID are not treated by the time PID occurs in the female partner. If there is no urethral discharge, a Gram stain and urethral material for *N. gonorrhoeae* and *C. trachomatis* identification should be obtained.

Treatment

Adequate treatment of salpingitis includes an assessment of severity, antibiotic therapy, additional general health measures, close patient follow-up, and treatment of the male sexual partner. Patients with the mildest manifestations can be treated as outpatients. Specific indications for hospitalization include severe manifestations of salpingitis (i.e., severe peritonitis, severe nausea, or fever higher than 100.4°F [38°C]), a suspected abscess, outpatient antibiotic failure, and an uncertain diagnosis

with severe symptoms.

Patients should be examined within 2 to 3 days and again at 7 and 21 days later to verify a satisfactory response to treatment. If an IUD is in place, it should be removed 24 to 48 hours after therapy is started. Ideally, the antibiotic should be selected according to the organism isolated, but, in salpingitis, empiric therapy is used. The treatment regimens recommended by the CDC were designed to treat gonococcal and chlamydial salpingitis and anaerobic salpingitis. Inpatient regimens include either intravenous cefoxitin or cefotetan disodium (Cefotan) and oral doxycycline or intravenous clindamycin and gentamicin, followed by oral clindamycin or doxycycline for a total of 14 days. The clindamycin regimen is also effective for patients with chlamydial infection. Parenteral therapy can be stopped 24 hours after clinical improvement. Outpatient regimens include a loading dose of an antibiotic recommended for gonorrhea and treatment of Chlamydia with an option to treat for anaerobic infection. One treatment regimen consists of ofloxacin 400 mg twice daily or levofloxacin 500 mg once daily for 14 days with or without metronidazole. A second regimen includes ceftriaxone or cefoxitin with probenecid in a single dose plus doxycycline with or without or metronidazole, 500 mg twice daily for 14 days. It is also possible to use other antibiotic regimens with similar antimicrobial activity. Gonococcal salpingitis responds more rapidly to antibiotics than nongonococcal salpingitis. Recommended agents must be used in full doses because partially treated, subacute salpingitis may result from the use of lower doses.

Hospitalized patients with peritonitis but no adnexal abscess usually respond rapidly to the regimens. An adnexal abscess, even if systemic manifestations are mild, should be treated with antibiotics that inhibit *B. fragilis* because of its frequency in pelvic abscesses. Clindamycin, metronidazole, cefoxitin, or imipenem/cilastatin should be used to treat a known or suspected pelvic abscess.

Abdominal surgery is indicated for a ruptured abscess. Colpotomy drainage is usually preferable for an unruptured midline abscess filling in the cul-de-sac. If laparotomy is performed for a presumptive diagnosis of appendicitis but instead acute salpingitis is found, the procedure should be limited to taking a tubal culture and closure of the abdomen. If laparotomy is required for an unresolved abscess or adnexal mass, surgery should be limited to the most conservative procedures that will be effective. Unilateral abscesses respond to unilateral salpingo-oophorectomy if appropriate antibiotic regimens are used; routine hysterectomy and bilateral salpingo-oophorectomy are seldom needed to treat acute salpingitis in young women. As mentioned, percutaneous drainage of abscesses is usually successful.

When chronic pain occurs, surgery should be deferred as long as possible to allow maximum healing. Analgesics and oral contraceptives to prevent ovulation may suffice until the swelling and fixation decrease. Surgery may be indicated for persistent pain that does not respond to conservative measures, for recurrent attacks of pelvic pain, or for a pelvic mass that does not resolve. Laparoscopy with lysis of adhesions usually suffices, but adnexectomy or, rarely, even hysterectomy is required. Surgery is also necessary for infertile patients.

OOPHORITIS

Most cases of oophoritis are secondary to salpingitis. The ovary becomes infected when purulent material from the fallopian tube enters the ovary. If the tubal fimbriae are adherent to the ovary, the tube and ovary together may form a large retort-shaped tuboovarian abscess. Antibacterial therapy, as previously outlined, is immediately indicated, and surgery is mandatory if the mass is considered to be leaking or ruptured or if it fails to resolve. Ovarian abscess after gynecologic surgery is particularly resistant to antimicrobial treatment.

Oophoritis may occur without accompanying salpingitis in mumps and septicemia. Oophoritis of this type usually results in lower abdominal pain that lasts for only a few days during an acute infectious illness. The ovarian infection usually subsides without incident, although abscesses may occur. If bimanual examination is not satisfactory, ultrasound scans may be used to detect abscesses.

GENITAL TUBERCULOSIS

Female genital tuberculosis remains relatively uncommon in the United States. Less than 1% of salpingitis cases can be attributed to *Mycoplasma tuberculosis*. Pulmonary tuberculosis remains a problem in many impoverished areas, and its rate is rising in parallel with the number of female patients with HIV infection. Although the spread of tuberculosis from the primary pulmonary infection to the pelvis usually occurs early in tubercular infection, early detection of genital infection is seldom feasible. Genital tuberculosis develops in about 10% of patients with pulmonary tuberculosis.

Pathogenesis

Virtually all genital infections are secondary to a pulmonary infection, which usually spreads by the bloodstream from the lungs to the fallopian tubes within 1 year of the primary pulmonary infection (Fig. 32.10 and Fig. 32.11). Direct extension occurs from the tube in several directions: to the pelvic peritoneum and ovary, to the endometrium, and to the cervix. Less common lymphatic extension to the genitalia can occur from abdominal sources or by direct extension from the intestinal tract. Genital tuberculosis is seldom caused by an ascending infection from a sexual partner with tuberculous epididymitis.

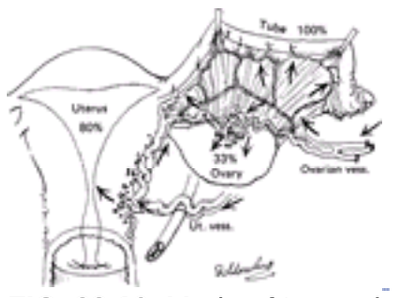

FIG. 32.10. Mode of transmission of tuberculous pelvic infection. Tubercle bacillus invades pelvic organs by way of bloodstream from distant focus in the lung or other organ. (From Wharton LR. *Gynecology and female urology.* Philadelphia: WB Saunders, 1943, with permission.)

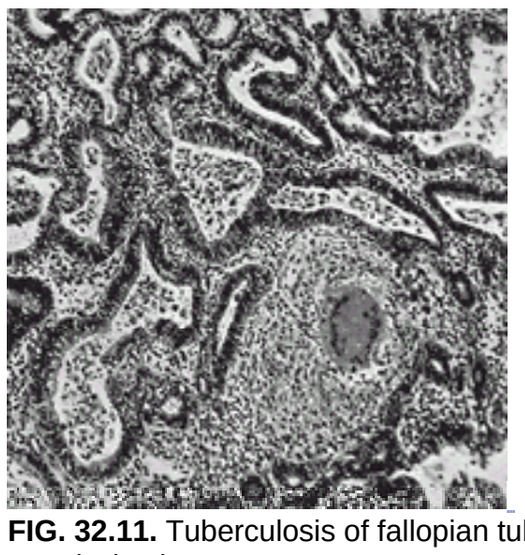

FIG. 32.11. Tuberculosis of fallopian tube (×105). (From Curtis AH, Huffman JW. *A textbook of gynecology*, sixth ed. Philadelphia: WB Saunders, 1950, with permission.)

The initial tubal lesion may remain localized for a considerable time (in some cases years), or it may extend to the interior tubal mucosa. Endosalpingitis results either in an exudative phase where ulcer formation at the site of caseous degeneration produces a typical moth-eaten pattern hysterosalpingogram, or in an adhesive phase, where large tubercles are present within the tubes. Dense perisalpingian adhesions are characteristic. In contrast to bacterial salpingitis, tubal occlusion, particularly fimbrial closure, does not occur early in tuberculous disease, and the tubes may remain patent despite relatively marked destruction of the tubal wall.

Tubal infection is present in virtually all women with genital tuberculosis. Endometrial infection is present in 50% to 80% of cases. Infected endometrium is shed monthly at menses and the endometrium becomes reinfected from tubal seeding. Myometrial infection occurs but only in advanced cases. Cervical infection occurs in

only 10% to 25% of patients, resulting in either a papillomatous or ulcerative lesion that grossly resembles cervical carcinoma.

Clinical Forms

Latent Genital Tuberculosis In the latent form, genital tuberculosis appears partially or completely arrested after the initial tubal infection, and patients have few or no pelvic complaints. Pelvic physical findings are normal. The diagnosis is usually made in the course of an investigation of infertility (by endometrial biopsy or dilation and curettage) or by chance at laparotomy. In the latent phase, a precarious balance exists between the disease and the host defense mechanisms. Active but latent infection has been documented 30 years after an initial infection.
Tuberculous Salpingitis Tuberculous salpingitis is a more advanced infection that may develop immediately after the primary hematogenous tubal spread, or it may follow a prolonged latent phase. The tubes are grossly enlarged by the inflammatory reaction. Although the symptoms and findings can mimic those of acute bacterial salpingitis, clinical manifestations are usually indolent and prolonged. Additionally, tuberculous salpingitis does not respond to the antibiotic therapy used for acute bacterial salpingitis. Despite these differences from bacterial salpingitis, tuberculosis is often discovered only by histologic examination of an excised tube.
Tuberculous Peritonitis In tuberculous peritonitis, widespread infection of all peritoneal surfaces produces ascites, adhesions, and innumerable small nodules (i.e., tubercles) throughout the abdomen. The serosal surfaces of the pelvic organs are typically involved, and the tubes are often patent. This form results from hematogenous or lymphatic spread.

Diagnosis

A history of pulmonary tuberculosis is often present in patients with genital tuberculosis, but simultaneous active pulmonary infection is uncommon. A normal chest film does not exclude genital tuberculosis because pulmonary lesions are found in only 30% to 50% of genital tuberculosis cases. The most common complaints are sterility and pelvic pain. Deteriorating health and menstrual abnormalities may also occur. Menorrhagia may be associated with abdominal pain, but amenorrhea or oligomenorrhea also occurs with tuberculous peritonitis. Most women with genital tuberculosis are in their 20s and 30s, but because of the frequent tendency for long latency periods, the disease may become active even after menopause. As mentioned, tubal tuberculosis may mimic acute bacterial salpingitis. However, when a pelvic problem does not conform to expected rules, the first consideration should be ectopic pregnancy and the second pelvic tuberculosis. Pelvic tuberculosis should be strongly considered when salpingitis occurs in a woman who is considered to be virginal.

A first-strength, purified protein derivative tuberculin skin test is important because a negative result virtually rules out the possibility of tuberculosis. Diagnosis is best established by endometrial biopsy, which should be performed in the week preceding menstruation, when the endometrium is thickest and is most likely to contain tubercles. A portion of the specimen should be cultured, and the remainder submitted for histologic examination. Repeated cultures of the menstrual blood can also be obtained. If cultures of either biopsy specimens or menstrual blood are negative, curettage may yield results. Antimicrobial susceptibility testing should be performed to predict drug resistance.

Endometrial biopsy, curettage, and culture of menstrual flow or endometrial tissue can provide an exact diagnosis of genital tuberculosis if the results are positive; if the results are negative, tuberculosis cannot be excluded. Diagnostic laparotomy is indicated if these measures fail to verify a diagnosis in a patient with a history and pelvic findings suggestive of genital tuberculosis. Diagnostic laparoscopy may be performed if there is minimal likelihood of tuberculous peritonitis, but caution must be used because of the possibility of perforating a loop of adherent bowel. Hysterosalpingography may reveal a characteristic tubal pattern, but it may also cause severe exacerbation of disease and should not be used if tuberculosis is possible.

The incidental discovery of reproductive tract tuberculosis may be the first indication that the patient has tuberculosis. In such patients, it must be determined whether or not other sites (e.g., lungs, urinary tract, bone, and gastrointestinal tract) also are infected.

Treatment

A three-drug therapy consists of isoniazid, 300 mg daily, rifampin, 600 mg daily, and pyrazinamide, 1,500 mg daily, for 18 to 24 months. In areas of high resistance, streptomycin or ethambutol (Myambutol) is added as a fourth drug. Patients without adnexal masses should have an endometrial biopsy for culture and microscopic examination 6 and 12 months after starting therapy. Persistent organisms need to be susceptibility-tested to identify drug-resistant strains. Laparotomy is performed if adnexal masses persist for 4 months and rifampin or streptomycin should be given preoperatively. Bilateral salpingectomy and removal of other tuberculous foci may be performed in young women with minimal disease. A bilateral salpingo-oophorectomy and total hysterectomy are indicated in those with advanced disease or advanced age. Pregnancy after tubal tuberculosis is rare, even in women with minimal disease. If the tubes are damaged by genital tuberculosis, efforts to improve fertility by tubal operations are usually futile.

SUMMARY POINTS

- STDs are common, particularly in young sexually active women with multiple sexual partners. However, most STDs occur among the larger population of women not at high risk for STDs.
- STDs are often asymptomatic for both women and their sexual partners.
- Many classic symptoms associated with various STDs are common in women without infection and, conversely, they are not present in many women with STDs.
- Many signs present in women with STDs also are common and they are present in women with no identifiable infection. Specific laboratory tests are usually required to confirm infection.
- The best course of treatment of STDs incorporates a combination of antimicrobial therapy directed at the patient and her partner, education about reducing STD exposure, and, when appropriate, careful follow-up examination and testing.

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Chapter 33

Edward J. Wilkinson

Benign Vulvovaginal Disorders

BENIGN DISEASES OF THE VAGINA
Vaginitis
Lichenoid Vaginitis
Congenital Vaginal Adenosis
Acquired Vaginal Adenosis
Vaginal Granulation Tissue
Vaginal Prolapse of the Fallopian Tube
VULVAR NONNEOPLASTIC EPITHELIAL DISORDERS
Lichen Sclerosus
Squamous Cell Hyperplasia
Squamous Cell Hyperplasia and Granular Cell Tumor
Lichen Planus
Cicatricial Pemphigoid
Psoriasis
Plasma Cell Vulvitis (Vulvitis of Zoon)
Vulvar Vestibulitis
Pruritic Vulvar Squamous Papillomatosis
Contact Dermatitis
Atopic Dermatitis
Fixed Drug Eruption (Dermatitis Medicamentosa)
Behçet Syndrome
Hidradenitis Suppurativa
Miscellaneous Inflammatory Conditions
ULCERS OF THE VULVA AND VAGINA
Dark Lesions of the Vulva
Compound Nevi
Other Benign Pigmented Lesions
Management of Pigmented Lesions
Depigmentation Disorders
BENIGN TUMORS OF THE VULVA
Condyloma Acuminatum
Leiomyoma of the Vulva
Benign Vulvar Tumors of Sweat Gland Origin
Papillary Hidradenoma
Mammary-like Tissue: Arising from the Specialized Anogenital Glands
Clear Cell Hidradenoma
Syringoma
Vascular Lesions
Angiokeratoma
Pyogenic Granuloma (Granuloma Pyogenicum)
Bacillary Angiomatosis
Kaposi Sarcoma
VULVAR CYSTS
Bartholin Cyst and Bartholin Abscess
Bartholin Abscess
Keratinous Cyst (Epithelial Inclusion Cyst)
Mucous Cyst
Columnar Cell Metaplasia
Vulvar Endometriosis
Apocrine Hydrocystoma/Cystadenoma of the Vulva
Mesonephric-like Cyst (Wolffian-like Duct Cyst)
Cyst of the Canal of Nuck (Mesothelial Cyst)

SUGGESTED READINGS
Benign Vaginal Conditions and Vaginitis
Vulvar Non-Neoplastic Epithelial Disorders Including Vulvar Lichen Sclerosus and Squamous Hyperplasia (Hyperplastic Dystrophy)
Ulcers and Infectious Diseases
Vulvar Vestibulitis, Vulvar Squamous Papillomatosis, Nevi, and Cysts
Additional Books and Book Chapters

This chapter addresses benign diseases of the vagina and vulva. Vaginal disorders including vaginal inflammation, vaginal adenosis, vaginal granulation tissue, and vaginal prolapse of the fallopian tube are discussed. Benign diseases of the vulva are presented in four major categories: nonneoplastic epithelial disorders, including vulvar lichen sclerosus and squamous cell hyperplasia; other inflammatory dermatoses, including vulvar vestibulitis; vulvar and vaginal ulcers, including infectious conditions that may cause ulceration; and a section on dark lesions of the vulva, including melanosis, lentigo simplex, nevi, and other benign pigmented lesions. The last section discusses the differential diagnosis of cysts of the vulva, including Bartholin cysts, and reviews common benign tumors of the vulva.

BENIGN DISEASES OF THE VAGINA

Vaginitis

Vaginitis may be of various causes and these have been classified in various ways; however, the classification outline of Sobel has been adapted for use here (Table 33.1).

Cause	Approximate % of total
Bacterial vaginosis	50%
Gardnerella vaginalis	
Mycoplasma hominis	
Mobiluncus curtisii	
Candidiasis	25%
Trichomonas vaginitis	20%
Other	5%
Atrophic vaginitis	
Postmenopausal	
Postpartum	
Physical agent-related	
Foreign body	
Allergic	
Chemical/caustic agents	
Desquamative inflammatory vaginitis	
Idiopathic	
Behçet syndrome-related	
Dermatosis-related or dermatosis-like	
Lichen planus, erosive	
Cicatricial pemphigoid	
Pemphigus	
Linear IgA disease	
Lichenoid vaginitis	
Ulcerative vaginitis/acute bacterial vaginitis	
Staphylococcus aureus infection	
Toxic shock syndrome	
Streptococcal vaginitis	
Beta-hemolytic streptococci	
Idiopathic vaginitis	
Causes unrelated to the above	

TABLE 33.1. *Causes of vaginitis in adults*

Lichenoid Vaginitis

Lichenoid vaginitis is primarily a descriptive diagnosis. Clinically these patients are usually of reproductive age and have symptoms of dyspareunia or vulvovaginal discomfort and pain. On examination vaginal mucosal atrophic-like changes are usually seen associated with punctate red areas.

Histopathologic findings include superficial chronic inflammation at the mucosal–submucosal interface (lichenoid in character), atrophic-like changes within the mucosa, and microscopic submucosal hemorrhagic areas. A number of these patients have had associated vulvar vestibulitis or a vulvar dermatosis. Treatment is directed toward the underlying cause of the inflammatory process, if known. If atrophy is present, vaginal estrogen cream may be effective.

Congenital Vaginal Adenosis

An association between a specific lesion of the lower genital tract and intrauterine exposure to diethylstilbestrol (DES) and related nonsteroidal synthetic estrogens has been established. Clear cell adenocarcinoma (carcinoma) of the vagina or cervix has been the most ominous but least frequently encountered sequel related to maternal administration of these drugs, with an estimated incidence of no more than 4 per 1,000 exposed young women. Benign anatomic anomalies, however, are exceedingly common and include vaginal adenosis and cervical vaginal ridges, including a cervical “hood” of vaginal tissue about the apparent ectocervix. Transverse vaginal septum and large cervical ectopian (eversion) involving the cervix and the upper vagina are also recognized abnormalities. The uterus may be small and the uterine cavity “T”-shaped.

Vaginal adenosis is defined as the presence of benign glandular epithelium in the superficial vaginal wall usually of endocervical and, more rarely, endometrial type. It is frequently accompanied by squamous metaplasia that may be extensive and can, over time, completely replace the columnar epithelium, leading to a “remodeling” of the upper vagina and cervix which results in a relatively normal-appearing vagina and cervix. The endometrial type of adenosis is more commonly associated with clear cell adenocarcinoma.

Acquired Vaginal Adenosis

Acquired adenosis of the vagina (columnar cell metaplasia, mucinous metaplasia, and ciliated cell metaplasia) represents an acquired metaplastic change of the nonkeratinized squamous epithelium of the vulva vestibule to columnar epithelium of mucinous or tubal–epithelial type. This has also been described within the vulvar vestibule (see “ Vulvar Cysts”).

Vaginal columnar cell metaplasia (acquired adenosis) presents as a somewhat red area in the upper vagina that may be associated with a mucoid vaginal discharge. This has been described associated with Stevens-Johnson syndrome as well as after vaginal laser or 5-fluorouracil (5-FU) therapy for vaginal intraepithelial neoplasia.

Within the vagina, topical estrogen cream and acidification of the vagina can promote squamous metaplasia of the columnar epithelium, with resulting squamous mucosa. Surgical excision is not necessary in such cases.

Vaginal Granulation Tissue

Granulation tissue within the vagina may be found in the vaginal suture line following hysterectomy or other vaginal operative procedure. It can also occur following vaginal treatment that ulcerated or resulted in the loss of the vaginal mucosa, such as laser therapy. The patient may complain of postcoital bleeding or of an unusual mucoid-appearing discharge.

On physical examination granulation tissue is relatively red to violet in color as compared to the normal adjacent squamous mucosa. The surface may be slightly elevated and have a granular or mucoid appearance as compared to the adjacent squamous epithelium. The tissue may be friable and bleed easily on contact or following biopsy. Histopathology demonstrates characteristic granulation tissue with small clustered capillary-like vessels and loose-appearing edematous stroma with acute and chronic inflammatory cells.

Treatment usually consists of excisional biopsy or electrofulgeration. Monsel solution can control bleeding and be used if the granulation tissue recurs. Acidification of the vagina can promote vaginal mucosal healing.

Vaginal Prolapse of the Fallopian Tube

Prolapse of the fallopian tube through an apical vaginal suture line following hysterectomy may occur. The patient may experience pain with coitus and postcoital bleeding. On examination a red elevated mass is usually identified within the suture line, and the mass may be tender or painful on palpation or with pressure. In some cases the entire fimbriae may protrude from the suture line. If biopsy is performed the findings are of tubal epithelium usually with associated tubal muscle or typical fallopian tube plical architecture. Treatment is vaginal excision of the prolapsed portion of the tube.

VULVAR NONNEOPLASTIC EPITHELIAL DISORDERS

As classified by the International Society for the Study of Vulvovaginal Disease (ISSVD), vulvar nonneoplastic epithelial disorders include lichen sclerosus, squamous cell hyperplasia (formerly hyperplastic dystrophy), and other dermatoses. This terminology replaced the ISSVD terminology, as reported in 1976, and does not use the term “vulvar dystrophy”.

Lichen sclerosus and squamous cell hyperplasia usually present as white lesions of the vulva. They are both symptomatic, associated with pruritus or burning pain. Biopsies, usually taken from several sites bearing the white epithelium, are necessary to definitively distinguish these lesions. Diagrammatic representation of vulvar anatomy is included in Fig. 33.1.

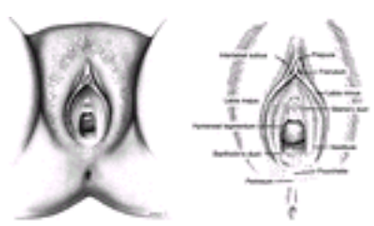

FIG. 33.1. Diagrammatic representation of vulvar anatomy. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with

permission.)

Lichen Sclerosus

Lichen sclerosus often presents as white, thin, parchment-like skin. Ecchymosis and superficial erosions or ulcerations may be seen, secondary to scratching (Fig. 33.2).

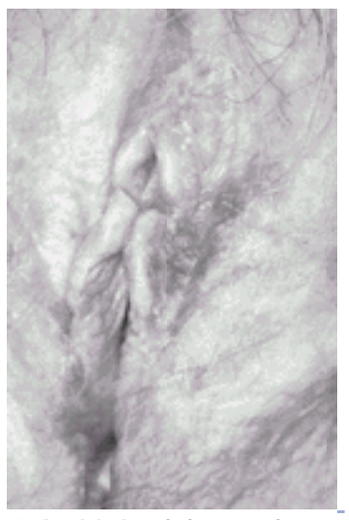

FIG. 33.2. Lichen sclerosus of the vulva with excoriation. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Long-standing lichen sclerosus may result in marked introital stenosis with atrophy of the labia and agglutination of the labia minora and frenulum of the clitoris. Perianal and perineal involvement is common and the involved areas are typically symmetric in location. Lichen sclerosus may occur at any age, including childhood. The involved skin is often thin and wrinkled, and areas of ecchymosis and ulceration may be seen. In children, perianal lichen sclerosus may present with pain or bleeding on defication, and may be misinterpreted as sexual abuse.

On histopathologic examination, lichen sclerosus is characterized by loss of rete ridges with marked thinning of the epithelium. Within the dermis loss of cellularity with subepithelial dermal fibrin deposition, edema, and chronic inflammation in the deeper dermis are characteristic features. The cause of lichen sclerosus is unknown; however there is a recognized familial occurrence. It is recognized that women with vulvar lichen sclerosus have some risk of squamous cell carcinoma within the vulvar areas involved. In prospective evaluations the frequency of squamous cell carcinoma arising within vulvar lichen sclerosus has been observed to be 3.5% or higher. The precursor epithelial changes are not well recognized, however epithelial hyperplasia is commonly associated. One known neoplastic change in the epithelium is referred to as “vulvar intraepithelial neoplasia; differentiated type.” This type of vulvar intraepithelial neoplasia (VIN) lesion is associated with keratinizing squamous cell carcinoma, but is not associated with human papillomavirus (HPV) as are the other VIN types and their associated carcinomas. Any suspicious lesion, such as an ulcer or markedly hyperkeratotic area, identified within an area of lichen sclerosus is best biopsied to exclude carcinoma.

Therapy for lichen sclerosus of the vulva includes topical high potency corticosteroids (e.g., halobetasol 0.05% or clobetasol propionate 0.05%). Application is usually once per day and continued until a response occurs. Tapering of the topical medication to one or two times per week is considered for long-term therapy, but does require medical observation. Therapy is continued indefinitely, recognizing that lichen sclerosus is not cured, but is controlled by this therapy. Topical testosterone is generally only used with topical high-potency corticosteroids in women with severe atrophic changes who do not respond to the topical corticosteroid alone. Topical testosterone is not recommended in children or those who may have unacceptable reactions to testosterone because it is absorbed systemically. Topical progesterone can be considered as a supplement to topical corticosteroid in children or in individuals where the side effects of testosterone exposure are not acceptable. In addition to the topical corticosteroid, sitz baths and mild tranquilizers or antihistamines may be needed initially to relieve acute symptoms.

Squamous Cell Hyperplasia

Squamous cell hyperplasia (formerly hyperplastic dystrophy) typically presents as white thickened skin, often with accentuated skin markings (Fig. 33.3). The skin is thickened with prominent wide and deep rete ridges (acanthosis), a nonspecific term used as a diagnosis only when HPV infection, fungal infection, and other known causative conditions have been excluded.

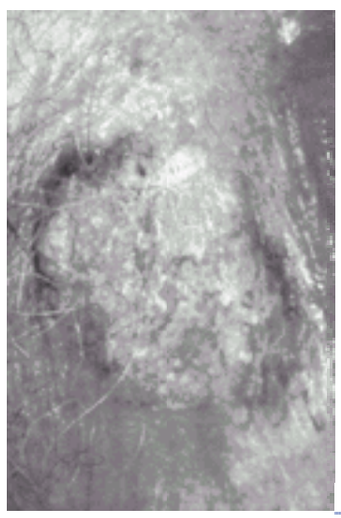

FIG. 33.3. Squamous cell hyperplasia of the vulva. Pruritic vulvar hypertrophied plaque of squamous cell hyperplasia with associated postinflammatory hyperpigmentation. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) See color figure 33.3.

Squamous cell hyperplasia (can include lichen simplex chronicus and neurodermatitis and previously referred to as hyperplastic dystrophy) is also characterized by white epithelium. The epithelium usually appears thickened with an irregular surface. Unlike lichen sclerosus, the process is typically not symmetric, and may be localized to a single site. Shrinkage and agglutination of the labia is not seen, nor are the focal areas of submucosal ecchymosis that may occur in lichen sclerosus secondary to scratching.

Squamous Cell Hyperplasia and Granular Cell Tumor

Squamous cell hyperplasia can be associated with granular cell tumor of the vulva. In some cases the hyperplasia is so marked as to resemble well-differentiated squamous cell carcinoma (pseudoepitheliomatous hyperplasia). Although this is a rare event, biopsy of the hyperplastic area, including some underlying dermis containing the tumor, is usually diagnostic. Granular cell tumors are usually benign tumors, although rare cases with recurrence and malignant behavior have been reported. The tumor is thought to be of nerve sheath origin. Treatment is local excision.

The pathologic changes seen in squamous cell hyperplasia include prominent acanthosis, with elongation, widening and deepening of the rete ridges, and thickening of the epidermis. Hyperkeratosis may be present. A mild chronic inflammatory infiltrate may be present within the dermis. This diagnosis is one of exclusion and if a specific histopathologic diagnosis such as lichen simplex chronicus or lichen planus can be made, a specific diagnosis should be given. Chronic candidiasis or dermatophyte infection may result in similar epithelial changes. The identification of the causative organisms by clinical evaluation and culture of skin scrapings, or

silver fungus stains on histologic sections, permits a precise diagnosis and specific therapy.

Squamous cell hyperplasia is responsive to topical corticosteroids (e.g., betamethasone valerate 0.1% ointment). Lesions usually respond within 2 weeks, and treatment can be tapered and discontinued after the lesion regresses. Long-term therapy is not necessary and may lead to problems related to chronic topical corticosteroid use such as epithelial atrophy. The avoidance or elimination of exogenous contact irritant factors is also beneficial.

Lichen Planus

Lichen planus (LP) presents most commonly in women over 40 years of age. Symptoms include pruritus and burning but some patients may be asymptomatic. The oral and vaginal mucosa also may also be involved by white, lacelike plaques (Wickham striae). Women with the vulvovaginal-gingival syndrome have an erosive form of LP and present with involvement of the oral, vaginal, and vulvar mucosa. Women with LP may present with vulvar pain, dyspareunia, burning, as well as postcoital bleeding. The bleeding is apparently related to vulvar vestibular or vaginal adhesions. Long-term changes include anal and vaginal stenosis.

Clinical findings may involve both the vulvar vestibule as well as the vagina (Fig. 33.4). The findings may initially be minimal with foci of reticulated papules. In later or more severe stages, LP may present as an erosive or desquamative process, with loss and agglutination of the labia minora, frenulum and prepuce, and shrinkage with stenosis of the vagina. Postinflammatory hypopigmentation of the involved vulvar skin may occur, resembling advanced lichen sclerosus. Vaginal and oral mucosal involvement help distinguish LP from lichen sclerosus. Histopathologic findings are related to the severity, age, and location of the process. Vaginal and vulvar vestibular mucous membrane findings may differ somewhat from cutaneous changes.

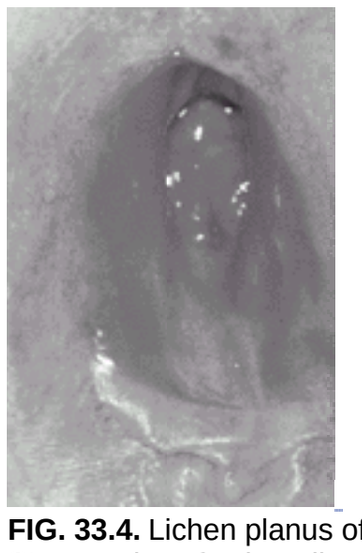

FIG. 33.4. Lichen planus of the vulva. The lichen planus involves the vagina and vestibule and was associated with severe dyspareunia for 8 months. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Microscopic features identified in the involved skin or mucosa include a bandlike, predominately lymphocytic, inflammatory infiltrate. Plasma cells are usually rare or absent in the skin, but may be found in mucosal lesions. Lichenoid inflammation involves the superficial dermis and overlying epidermis. Basal epithelial cells have liquefaction necrosis. Colloid bodies (Civatte bodies) are degenerated keratinocytes and valuable in the diagnosis of LP. Acanthosis, with wedge-shaped hypergranulosis and hyperkeratosis without parakeratosis, are typical findings. Immunofluorescent studies of a skin or mucosal biopsy submitted in Michelle fixative, or other appropriate fixative, or snap frozen, can be studied and characteristically will demonstrate fibrinogen deposits in the dermal–epidermal junction. Complement C3 and granular immunoglobulin M (IgM) and immunoglobulin G (IgG) deposits may be found. In the mucosa of the vestibule vagina, LP changes may include thinned epithelium, erosion, ulceration, and bullae.

The most common differential diagnoses include lichen sclerosus, plasma cell vulvitis, cicatricial pemphigoid, localized scleroderma (morphea), and contact dermatitis. Clinical history, examination of the patient's skin and oral mucosa, and biopsies of specific lesions, including unruptured bullae, for light and immunofluorescent studies are needed to definitively distinguish these processes. The treatment of LP is best undertaken with a dermatologist as consultant. The most difficult issue is the adhesion formation that leads to scarring and stenosis of the vestibule and vagina. Topical corticosteroids are the usual initial approach, and may include high-potency, fluorinated corticosteroids to gain initial response and relief. Other treatment may include topical or oral cyclosporine, oral dapsone, and oral griseofulvin.

Cicatricial Pemphigoid

Cicatricial pemphigoid can involve the vulva and the vagina and usually presents clinically with subepithelial blisters, which clinically may resemble the blisters of pemphigus vulgaris. Eosinophils are prominent in the vesicles of cicatricial pemphigoid. Immunofluorescence studies are needed to distinguish this bullous lesion from others, including pemphigus and linear immunoglobulin A (IgA) disease. Cicatricial pemphigoid has linear IgG and complement C3 deposits, which are usually absent in LP. Clinical management is complex and consultation with a dermatologist is recommended.

Psoriasis

Psoriasis affects about 2% of the U.S. population. It is inherited as an autosomal dominant trait with incomplete penetrance. When it involves the vulva, it often involves the lateral labia majora and genital intertriginous areas. Sharp-bordered, silvery-crusted erythematous papules and plaques characterize psoriasis (Fig. 33.5). Removing the loose silvery scale reveals multiple small punctate bleeding points. This finding is referred to as *Auspitz sign.* Presentation of psoriasis on the vulva may not demonstrate the typical silvery scales but rather red erythematous plaques, with the red plaques being the primary clinical finding. The lesions of psoriasis usually are somewhat symmetric. Without treatment the psoriasis typically has a long protracted course. The presentation of psoriatic lesions developing related to localized trauma is referred to as the *Koebner phenomenon.* The lesions present within 7 to 30 days following the localized trauma. Reiter syndrome may occur related to psoriasis although it not common in women.

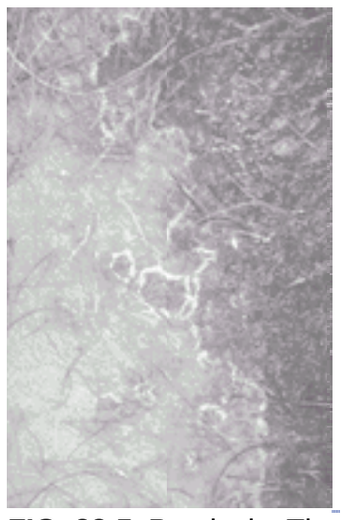

FIG. 33.5. Psoriasis. There is marked erythema and the lesion has sharply demarcated borders. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Histopathologic features of psoriasis include hyperkeratosis and parakeratosis, with uniform acanthosis evidenced by a relatively uniform increase of length of the rete ridges. The rete, at their base, are wide and “club-shaped.” There is a decreased granular layer, and intraepithelial abscesses, composed predominately of

granulocytes, are within the epidermis and referred to as *Munro abscesses.* There is increased epithelial turnover reflected in increased numbers of mitotic figures in the basal and parabasal areas. The dermal papillae have prominent vessels and also may be club-shaped. The associated papillary dermis is edematous with little or no significant inflammatory cell infiltrate.

The differential diagnosis includes squamous cell hyperplasia, seborrheic dermatitis, and chronic eczema. Although these all have acanthosis, unlike psoriasis, the rete ridges are not relatively uniform in length and Munro abscesses are not present. Seborrheic dermatitis usually has granulocytes about follicular ostia that can clinically resemble psoriasis, therefore biopsy is usually necessary for definitive diagnosis (Fig. 33.6). The clinical presentation and distribution of the cutaneous lesions can be similar when comparing psoriasis and seborrheic dermatitis and their distinction can be difficult.

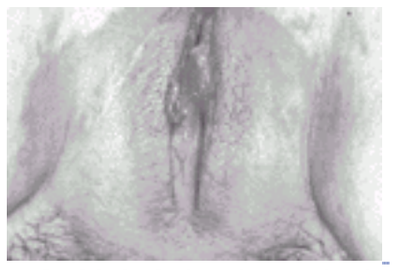

FIG. 33.6. Seborrhea. The involved vulvar skin is somewhat reddened. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) See color figure 33.6.

Plasma Cell Vulvitis (Vulvitis of Zoon)

Women with plasma cell vulvitis typically have symptoms of pruritus and burning. It should be distinguished from other red lesions including those of known etiology (Table 33.2). An erythematous macular lesion that is red to orange in color and may be hemorrhagic characterizes plasma cell vulvitis. The macular areas may be single or multiple, and may involve relatively large areas of the vulva.

Red lesion	Cause
Candida infection	*Candida albicans*
Tinea cruris	*Trichophyton rubrum*
Pityriasis versicolor	*Pityrosporum orbiculare*
Erythrasma	*Corynebacterium minutissimum*
Reactive vulvitis	Local irritants

TABLE 33.2. *Inflammatory red lesions of the vulva with known etiology*

Histopathologic features include a thinned epithelium with reduced rete ridge length and without a granular layer or keratinized surface. The horizontally orientated parabasal squamous cells have been referred to as “lozenge-shaped keratinocytes.” Superficial dermal inflammation is present involving the dermal–epithelial interface, and is lichenoid in character. The inflammatory cells present consist predominantly of plasma cells. Prominent blood vessels are found in the dermis, often associated with intradermal hemorrhagic areas and hemosiderin-laden macrophages.

The differential diagnosis includes lichen planus and related dermatosis, as well as some infectious conditions, especially syphilis. The prominent plasma cell infiltrate may include perivascular plasma cells, however the plasma cells are not associated with spirochetes or other organisms on silver stain and serologic studies for syphilis are negative. The cause of plasma cell vulvitis is not known.

Treatment is primarily topical corticosteroids but may include intralesional corticosteroids, as well as etretinate. Supportive care, to relieve acute symptoms, is also recommended.

Vulvar Vestibulitis

Vulvar vestibulitis is one of a number of conditions associated with vulvar vestibular pain. There remains controversy regarding the definition, diagnosis, and treatment of vulvar vestibulitis. For the purposes of defining vulvar vestibulitis it is defined in this chapter as originally described (Friedrich 1987), specifically as a symptom complex characterized by severe external dyspareunia (dyspareunia on entry), inflammation of the vulvar vestibule, and exquisite tenderness of the vulvar vestibule in the areas of inflamed minor vestibular glands. It is recognized that asymptomatic women may have some minor redness or pressure tenderness within the vulvar vestibule and this should not be interpreted as vulvar vestibulitis.

Histopathologic findings associated with vulvar vestibulitis are not specific. Within biopsies, or specimens obtained from partial vestibular excisions performed to relieve vestibulitis, a superficial inflammatory cell infiltrate is present consisting predominately of lymphocytes, but also usually also includes plasma cells, mast cells, and complement C3. The inflammation is within the superficial submucosa. If minor vestibular glands are present, the inflammation is also seen around the minor vestibular glands. The minor vestibular glands are simple glands lined by tall, mucus-secreting columnar epithelium. The inflammation usually does not involve the gland lumens.

No specific etiology has been identified as a cause of vestibulitis, and studies for HPV have not demonstrated a causal association.

Although no uniformly effective medical therapy has yet been defined, clinical management, including biofeedback, is sometimes effective in relieving symptoms. A list of some of the more common treatments follows. None of these treatments, however, have been proven to be uniformly effective in controlled trials.

Vaginal and introital lubricants with or without the use of vaginal dilators.
Vaginal and introital lubricants with or without the use of biofeedback.
Interferon local injections (3 million U/mL), 1 million units per injection site with up to 12 injection sites distributed about the vestibule. Injections are with a fine 25- or 33-gauge needle and an insulin syringe. Three courses of injections are given per week for 4 weeks.
Topical anesthetics (5% Xylocaine ointment or 2% lidocaine gel) applied to the tender sites p.r.n.
Systemic antifungal therapy is advocated as initial therapy by some (e.g., Diflucan, or similar medications).
Amitriptyline (Elavil) started at a low dose 10 to 25 mg orally, with increased doses up to 3 times per day in protracted or unresponsive cases.
Local excision of the involved inflamed vestibular areas has been used; however, long-term follow-up studies show recurrence or persistence of symptoms in about one half of the cases.

Pruritic Vulvar Squamous Papillomatosis

Pruritic vulvar squamous papillomatosis is a clinical complex that includes vestibular papillae and pruritus. Vulvar pain or burning may also be present and dyspareunia is common. On examination of the vulva, multiple small clustered squamous papillae are present on the medial aspects of the labia majus (Fig. 33.7). In some cases the papillae present following the onset of symptoms. The papillae are sometimes so small that magnification is necessary for identification (colposcopic magnification ×10).

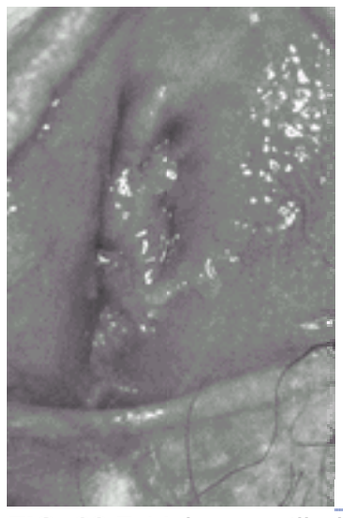

FIG. 33.7. Vulvar vestibular papillomatosis. Clustered vulvar vestibular papillary projections of squamous papillomatosis. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Histopathologic examination demonstrates small (1–2 mm) squamous epithelial covered papillae supported on delicate vascular stalks. The papillae usually are multiple and occur in clusters on the vestibule. Although initially thought to be secondary to HPV infection, more recent work does not support this association.

Contact Dermatitis

Contact dermatitis may be an allergic or an irritant-related entity. Allergic dermatitis is a cell-mediated response related to sensitizing agents. Topical medications and rubber are example agents. Irritant agents can include urine, stool, soaps, deodorants, perfumes, or other agents related to such reactions within the skin. Irritant dermatitis is more common than allergic dermatitis in most settings. The cutaneous or mucosal areas involved are usually confined to the area of exposure and the dermatitis often persists for weeks to months following exposure.

Histopathologic findings may be quite variable, and are related to whether it is an allergic or irritant-related process, the severity of the reaction, duration of the exposure, and length of time the inflammatory process has been present. Epithelial spongiosis with microvesiculation is usually present, and if the lesion is more severe or long-standing, erosion and ulceration may be seen. A superficial perivascular inflammatory infiltrate consisting predominantly of lymphocytes and histiocytes is often present. Eosinophils may be present, especially in allergic reactions. In long-standing contact dermatitis, epithelial thickening (acanthosis) with parakeratosis and hyperkeratosis can occur resulting in histopathologic features of squamous cell hyperplasia with or without features of lichen simplex chronicus.

Atopic Dermatitis

Atopic dermatitis of the vulva is usually associated with pruritus and burning. On examination the vulvar skin may appear dry and scaling. Scratching related to the pruritus can result in excoriation and thickening of the vulvar skin. Vulvar biopsy is generally not needed unless significant epithelial thickening or a questionable lesion is identified.

The histopathologic findings of atopic dermatitis may include epithelial thickening with features of squamous cell hyperplasia. The findings may be nonspecific with epithelial spongiosis and associated superficial dermal inflammation. The inflammatory infiltrate predominately includes lymphocytes and macrophages, however, eosinophils and mast cells also may be present. The extent of the inflammatory cell infiltrate tends to correlate with the severity and duration of the dermatitis. Immunofluorescent studies are generally not necessary but if performed may identify immunoglobulin E (IgE) on epidermal Langerhans cells.

Fixed Drug Eruption (Dermatitis Medicamentosa)

Fixed drug eruptions typically are related hypersensitive reactions to systemic drugs. The eruptions typically can recur at the same skin sites upon reexposure to the same drug. Multiple reexposure can be associated with lesions in new sites as well in the original locations. After the drug is stopped, the lesions usually heal completely in the mucosa, but in the skin, postinflammatory hyperpigmentation is common. Cutaneous fixed drug eruptions are a complex group of drug hypersensitivity reactions. They are subclassified into four distinct types that can be summarized as follows. Type I usually presents as urticaria and is mediated through IgE antibodies. Type II presents as purpura or bullous lesions and is mediated through IgG and IgM antibodies. Type III may present as an urticarial or maculopapular reaction and may be associated with vasculitis and is related to immune complexes. Type IV may present as a contact dermatitis, exanthem, or a maculopapular eruption.

The histopathological findings of fixed drug reaction may include epithelial interface vacuolar changes with associated necrotic keratinocytes. Within the dermis eosinophils may be identified. These findings may be otherwise nonspecific or only suggest drug eruption. Other testing, including patch testing for the suspect offending drugs, indirect and direct Coombs testing, as well as other laboratory testing, all maybe useful. In cases of suspect fixed drug eruption, a complete drug exposure history is essential.

Behçet Syndrome

Behçet syndrome is of unknown etiology and includes oral aphthous ulcers, genital ulcers, and ophthalmologic inflammation. In addition these patients may have colitis, acne, cutaneous nodules, thrombophlebitis, and, in severe cases, encephalopathy. Some cases lack the ocular changes (Table 33.3, on vaginal and vulvar ulcers). When Behçet syndrome involves the vulva, deep ulcerations are usually seen that, in severe cases, result in fenestration of the labia, and occasionally labial gangrene (Fig. 33.8). The disease is of unknown cause and may wax and wane, with vulvar ulcerations healing and then recurring. The vulvar ulcers are usually associated with oral ulcers

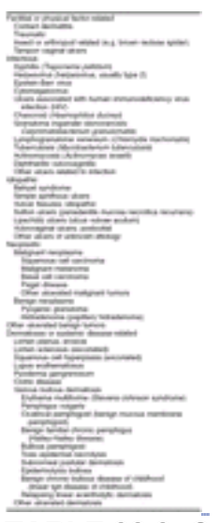

TABLE 33.3. *Causes of vulvar and vaginal ulcers*

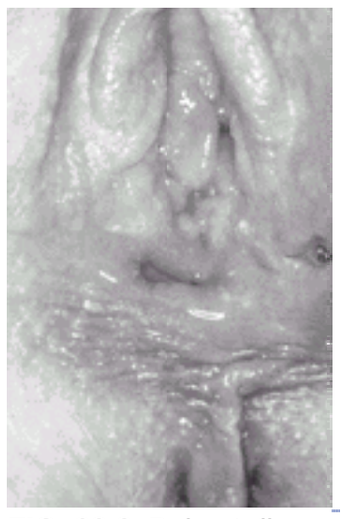

FIG. 33.8. Behçet disease. Painful vulvar ulcer in a woman who also had oral ulcers of a similar appearance. Serologic and microbiologic studies for other potential pathogens were negative. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

On histologic examination the involved vulvar skin or mucosa is involved with a necrotizing arteritis. This is associated with a chronic inflammatory infiltrate that is typically perivascular and may involve the vessel wall with damage to the arterial media. The arteritis is associated with endothelial cell swelling and can result in arteriolar occlusion or venous thrombosis.

Hidradenitis Suppurativa

Hidradenitis suppurativa is an apocrine gland–related chronic inflammatory disorder. The initial presentation is of a painful, tender, deep-seated subcutaneous nodule or nodules in the vulva as well as axillae and other sites where apocrine glands occur. Subcutaneous spread of the inflammatory process results in confluent masses that, in some point in their course, involve the overlying skin and result in ulceration and draining sinuses. This process, over time, subsequently causes extensive scarring of the vulva or other involved sites. Fox-Fordyce disease may be associated in some cases.

Histopathologic features in the early stages of hidradenitis suppurativa include perifolliculitis associated with acute and chronic dermal inflammation. In advanced cases severe inflammation results in the loss of the epithelial appendages with squamous epithelial ulceration with sinus tract formation.

Management includes medical as well as surgical approaches. Medical treatment may include long-term retinoids (e.g., isotretinoin), anti-androgen therapy, or treatment with leuprolide. Surgical approaches may include laser ablation by unroofing of the sinus tracts, or excision of involved areas. Surgical approaches are usually appropriate in severe or refractory cases.

Miscellaneous Inflammatory Conditions

Inflammatory infectious conditions that may occur in the vulva, that present as red lesions, with their known causative agent, are listed in Table 33.2.

ULCERS OF THE VULVA AND VAGINA

Table 33.3 lists the predominant causes of ulcers within the vulva and vagina.

Dark Lesions of the Vulva

Dark or pigmented lesions of the vulva are listed in Table 33.4.

Nevomelanocytic lesions
Lentigo simplex
Melanosis vulvae
Nevomelanocytic nevi
Junctional
Intradermal
Compound
Compound nevus without atypia
Atypical vulvar nevomelanocytic nevus
Malignant melanoma
Superficial spreading melanoma
Nodular melanoma
Lentigo maligna melanoma
Metastatic melanoma
Vulvar intraepithelial neoplasia
Seborrheic keratosis
Reactive hyperpigmentation
Dermatofibroma
Malignant fibrous histiocytoma

TABLE 33.4. *Dark lesions of the vulva*

Lentigo Simplex Lentigo simplex is one of the most common pigmented lesions biopsied on the vulva. Lentigo simplex clinically is a flat, non-elevated pigmented area on the skin that has normal surface skin markings (Fig. 33.9). Lentigo simplex represents an area of skin with increased melanin with associated melanocytes. The epithelium may be slightly hyperplastic and hyperkeratotic. Lentigo simplex by definition is 5 mm or less in diameter. Larger flat pigmented lesions with essentially identical histopathologic features are referred to as *melanosis vulvae.* No treatment is needed although biopsy is performed to determine the basis of the pigmented lesion.

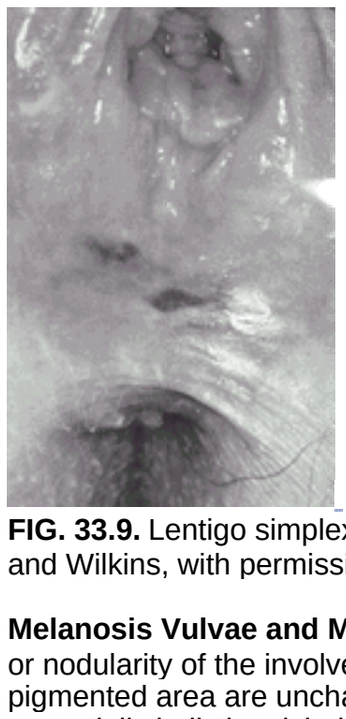

FIG. 33.9. Lentigo simplex. Several small flat pigmented lesions of lentigo simplex. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) See color figure 33.9.

Melanosis Vulvae and Melanosis Vaginae Vulvar melanosis is a benign pigmented condition that is characterized by pigmentation of the vulvar skin without elevation or nodularity of the involved skin in an area that is, by definition, larger than 5 mm in diameter. Like lentigo simplex the melanosis is flat and the skin markings over the pigmented area are unchanged and similar to the adjacent skin. Histopathologic examination of vulvar melanosis and lentigo simplex demonstrate that they are essentially indistinguishable. Therefore the size of the lesion is important and influences the clinical diagnosis and the pathologic interpretation. Similar pigmentation with similar findings when found in the vagina is referred to as *melanosis vaginae*, and in some cases melanosis of both the vulva and the vagina may be found.
Vulvar Nevomelanocytic Nevi The types of nevomelanocytic nevi identified on the vulva include junctional, compound, and intradermal. In most series compound and intradermal nevi are more common. Atypical vulvar nevi are a special category of nevus and these often have some features of compound nevi.

Junctional Nevi Junctional nevi have the nevus cells located within the epidermis as well as the dermal–epidermal junction. The nevus cells are immediately adjacent to the squamous keratinocytes. Junctional nevi are young and somewhat undifferentiated.

Compound Nevi

A compound nevus represents a continuum of maturation from a junctional to an intradermal nevus. In compound nevi, the nevus cells are within both the epidermis and the dermis. Nevus cells are seen within the dermal–epidermal junction, but also within the dermis, where dermal reticulum, collagen, and elastic fibers envelop the nevus cell nest. Compound nevi have elevated surfaces as compared to the surrounding skin.

Intradermal Nevi Intradermal nevi do not have a dermal–epidermal component and the nevus cells are completely surrounded within the dermis by connective tissue elements. Over time an intradermal nevus may entirely regress, or evolve into an acrochordon (fibroepithelial polyp).
Atypical Vulvar Nevi Of special interest are the atypical vulvar nevomelanocytic nevi that may clinically and histopathologically resemble malignant melanoma (Fig. 33.10). Atypical nevi are found predominately in adolescent and premenopausal women. Pathologically they have features of compound nevi, having both a junctional and an intradermal component, but they also have cytoatypia, especially in the more superficial nevomelanocytes.

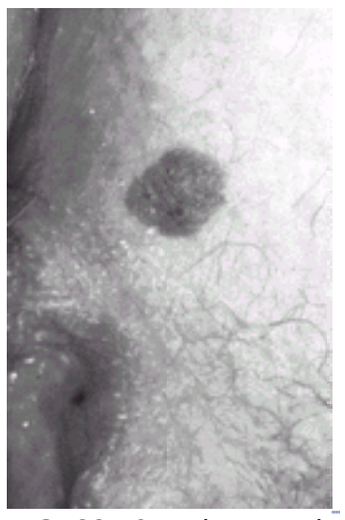

FIG. 33.10. Vulvar atypical nevus in an adolescent patient. The lesion is raised and has somewhat irregular borders. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

They can be distinguished histopathologically from malignant melanoma by three specific features. These include symmetry in horizontal and vertical dimensions, decrease in cell size with maturation of the nevus cells in the deeper levels, and lack of pagetoid single cell spread in the upper one-third of the epidermis.
Congenital and Giant Nevomelanocytic Nevi Congenital nevi occur in approximately 10% of newborns and most of these nevi are less than 4 mm in diameter. Giant nevomelanocytic nevi, which by definition are 20 cm or larger in diameter (“garment type” nevus), are rare but are associated with increased risk of developing malignant melanoma in prepubertal individuals. The frequency of involvement of the vulva by these types of nevi is uncertain.

Other Benign Pigmented Lesions

Other benign pigmented lesions of the vulva include seborrheic keratosis, postinflammatory (reactive) hyperpigmentation, and dermatofibroma (benign fibrous histiocytoma).

Seborrheic Keratosis Seborrheic keratosis often presents as a macular or papular pigmented lesion that usually feels waxy on palpation (Fig. 33.11). The lesions are usually multiple and may be seen in other sites as well as the vulva in a given patient. In some cases the surface of the lesion can be peeled away to reveal punctate bleeding points at the base. In most cases, however, biopsy is necessary to establish the diagnosis. Biopsy is especially useful to distinguish seborrheic keratosis from vulvar intraepithelial neoplasia, which can also present as pigmented macular or papular lesions.

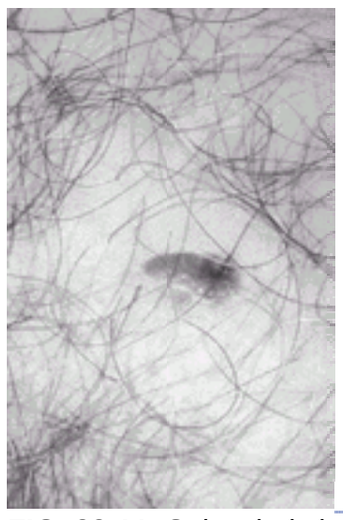

FIG. 33.11. Seborrheic keratosis. Typical appearance of a waxy-appearing, elevated, pigmented lesion. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

On histopathologic examination seborrheic keratosis has a thickened epithelium (acanthosis) with a hyperkeratotic surface. The deeper tips of the rete tend to have uniform length. No significant dermal compression or inflammatory infiltrate is present in most cases. Treatment of seborrheic keratosis is usually local superficial excision or cryotherapy.
Reactive Hyperpigmentation Reactive hyperpigmentation is usually preceded by chronic inflammation (postinflammatory) or injury. Although the skin is pigmented in the involved areas, the surface of the skin maintains its normal character, without surface elevation. Biopsy is usually not necessary to establish the diagnosis although the usual evaluation for the cause of the inflammatory process is necessary. No therapy is needed.
Dermatofibroma/Fibrous Histiocytoma Dermatofibroma is rare on the vulva, however, it may present as a slightly raised, nonpolypoid pale brown to red solitary subcutaneous mass. The term *dermatofibroma* is reserved for those lesions 1.5 cm in diameter or less. Masses larger than this, or that are polypoid in appearance, are referred to as *fibrous histiocytoma.* Biopsy is necessary to establish the diagnosis and to distinguish these benign histiocytic tumors from dermatofibrosarcoma protuberans or malignant fibrous histiocytoma.

Management of Pigmented Lesions

As a general rule, any elevated pigmented lesion of the vulva that is 5 mm or larger in greatest dimension, or otherwise clinically suspicious, should be excised. In these cases, excision, with submission of the specimen for histopathologic examination is both diagnostic and therapeutic. If malignant melanoma is suspected, and outpatient biopsy is considered reasonable, wide and deep excision is needed to properly diagnose and pathologically stage the lesion if it is a melanoma. Three centimeter (3 cm) margins of excision, both wide and deep, can be considered in such cases. Immediate consultation with a specialist familiar with the diagnosis and treatment of melanoma of the vulva may be the best alternative for management of patients with a lesion suspected of being melanoma, rather than attempted excision or biopsy in the outpatient setting.

Depigmentation Disorders

Depigmentation disorder include vitiligo, albinism, and postinflammatory hypopigmentation. Vitiligo is the loss of melanocytes from where they were once present, and is due to an inherited disorder. Albinism is a congenital inability of melanocytes to produce melanin. Postinflammatory hypopigmentation is the loss of melanocytes in the skin secondary to inflammation or injury (Fig. 33.12).

FIG. 33.12. Postinflammatory hypopigmentation. The white area has lost melanocytes and melanin. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) See color figure 33.12.

BENIGN TUMORS OF THE VULVA

Condyloma Acuminatum

HPV infection is the viral cause of vulvar and vaginal condylomata acuminata. HPV is also associated with VIN, a lesion that is a known precursor of certain types of vulvar carcinoma. Condyloma acuminatum (genital wart) is a benign neoplasm that is usually sexually transmitted and can involve the vulva as well as the vagina, cervix, urethra, anus, and perianal skin. HPV-6 and HPV-11 are the usual HPV types associated with genital condyloma acuminatum; HPV-11 is observed in about one-fourth of cases.

On clinical examination condylomata acuminata of the vulva are usually papillary, verrucous, or macular in character and can involve the skin as well as the vulvar vestibule, vagina, and cervix. The lesions are usually multiple. They may be asymptomatic but can be pruritic and may result in the patient coming to the clinic when she observes or palpates the lesion or lesions. Condylomata acuminata of the vulva and vagina may be associated with pregnancy, diabetes mellitus, perineal hygiene problems, immunosuppression, and other related problems. Approximately one-third to one-half of the women with vulvar condyloma acuminatum have associated cervical HPV-related lesions (cervical intraepithelial neoplasia/dysplasia). In children, genital HPV infection may be evidence of sexual abuse.

Magnification of the vulva and vagina with a ring light, or colposcope, and the application of 3% to 5% acetic acid can greatly aid identification of smaller lesions because the HPV-related lesions that involve the mucosa are aceto-white, becoming white in color with the application of the acetic acid. Lesions detectable only by colposcopic examination are considered subclinical HPV infections.

Histopathologic examination of a typical vulvar or vaginal condyloma acuminatum demonstrates epithelial thickening usually associated with acanthosis, koilocytosis, and parakeratosis. Lesions arising in the vulvar skin often have hyperkeratosis and a prominent granular layer. Superficial dermal or submucosal chronic inflammatory cells may be seen beneath the condyloma.

Vulva condyloma acuminatum may persist for years however regression may occur and has been observed following pregnancy. Presentation following pelvic radiation therapy or with immunosuppression has also been observed.

Differential Diagnosis Within the vulva there is an important distinction made between typical condyloma acuminatum and vulvar intraepithelial neoplasia of high grade (VIN 2 or VIN 3/moderate or severe dysplasia or carcinoma in situ). Many pathologists would prefer to refer to macular condyloma acuminatum (condyloma plana) of the vulva as VIN 1, as referenced in leading texts on vulvar pathology, but this is not a uniform practice. Unlike most VIN lesions, typical vulvar or vaginal condylomata are not usually associated with HPV-16 or other high risk HPV types as are VIN 2 or VIN 3 lesions. They are typically DNA-diploid whereas VIN 2 or VIN 3 lesions are usually DNA-aneuploid.
Fibroepithelial Polyp Fibroepithelial polyps may clinically resemble large condylomata, however, the epithelium of a fibroepithelial polyp lacks significant proliferation, unlike the epithelium of typical condyloma acuminatum (Fig. 33.13). This proliferation can be demonstrated immunohistochemically using Ki-67 (MIB-1) immunohistochemistry, where the proliferative cells of condyloma are seen throughout the epithelium, while fibroepithelial polyps only have proliferative cells in the basilar epithelial layers. Condylomata lata or secondary syphilis can suggest condylomata acuminata clinically; however, biopsy demonstrates inflammation and arteritis with many plasma cells. Spirochetes can be demonstrated by immunofluorescence on air-dried scraping of the surface of the lesion, or on Warthin-Starry silver stain of a tissue section. Syphilis serologic studies are appropriate in cases where there is question regarding the differential diagnosis.

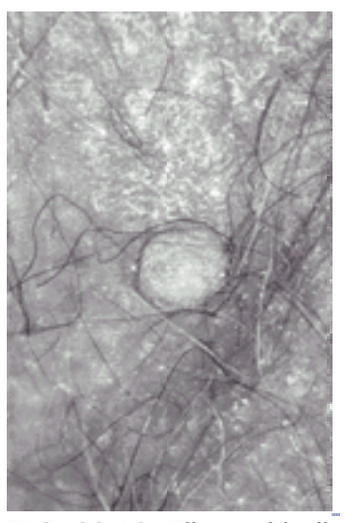

FIG. 33.13. Fibroepithelial polyp (acrochordon) with a pedunculated appearance. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Squamous cell carcinoma can arise in vulvar condyloma acuminatum, and vulvar verrucous carcinoma may resemble a large condyloma. In addition, the so-called giant condyloma of Buschke and Löwenstein is now recognized to be a variant of verrucous carcinoma. The association of vulvar and vaginal condyloma acuminatum with invasive squamous cell carcinoma has been associated with lymphoproliferative disorders, such as Hodgkin disease, as well as chromosomal disorders with immunosuppression related to Fanconi anemia.
Therapy There are many methods to treat vulvar condyloma acuminatum. These include clinician-applied topical concentrated trichloroacetic acid or bichloracetic acid. This treatment method may be effective for small vulvar condylomata. Larger lesions are more commonly treated with surgical excision, electrodesiccation with surface curettage, or electro-loop excision. Cryosurgery and laser ablation have also been used for larger lesions, however these two techniques are usually not the treatments of choice for larger lesions unless the clinician is experienced in their use on the vulva. Topical application by the clinician of a dilute podophyllin toxin preparation is also effective for small lesions, but contraindicated in pregnancy and should not be used in the vagina. These medications inhibit cell proliferation and can be neurotoxic if systemically absorbed through mucosal surfaces. Imiquimod is a topical, immune-enhancing medication that has also been successful in treating small and nonkeratinized condylomata. This medication can be applied by the clinician, or by a well-informed patient who is capable of doing the applications. Approximately 40% to 60% of children with laryngeal papillomatosis are born from mothers with a history of genital condyloma acuminatum. Laryngeal papillomas of infancy and childhood are thought to be acquired at delivery. Although the incidence of HPV infection of the larynx of the newborn from maternal genital papillomavirus infection is unknown, no correlation has been established between the volume of maternal wart tissue and occurrence of infantile laryngeal papillomatosis. Approximately one-half of patients with laryngeal papilloma have HPV-11.

Leiomyoma of the Vulva

Leiomyoma is a benign smooth muscle tumor and is the most common vulvar soft tissue tumor (Fig. 33.14). In children, vulvar leiomyomata may be associated with

esophageal or gastric leiomyomatosis. Histopathologic examination demonstrates that the tumor is composed of smooth muscle cells that can have myxoid change or epithelioid features, both are especially noted in pregnancy. Leiomyoma, in contrast to leiomyosarcoma, has a low mitotic count, lacks significant cytologic atypia, and is not infiltrative or metastatic. Immunohistochemical studies can distinguish these tumors from rhabdomyosarcoma and rhabdomyoma. Therapy is local excision. Gonadotropin inhibition medical therapy may be of value to reduce tumor size before surgery.

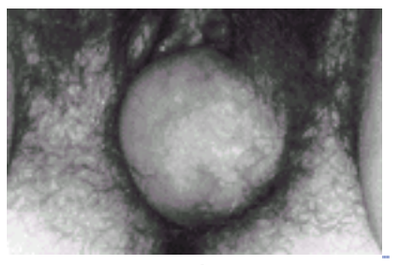

FIG. 33.14. Leiomyoma. Large, firm, and somewhat mobile nontender tumor. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Benign Vulvar Tumors of Sweat Gland Origin

There are several benign epithelial tumors of sweat gland origin that occur in the vulva. The two most important are papillary hidradenoma and syringoma. Other important benign epithelial tumors include mammary-like tumors and clear cell hidradenomas.

Papillary Hidradenoma

Papillary hidradenomas of the vulva may present as a nodule or a papillary mass. They may form a papillary-like mass that bleeds easily if the tumor mass everts from its subepithelial location. These tumors are usually located in the interlabial sulcus and occur after puberty (Fig. 33.15). They are usually under 2 cm in diameter and are not infiltrative. The tumor is currently thought to arise from specialized mammary-like anogenital glands that are found predominately in the interlabial sulcus.

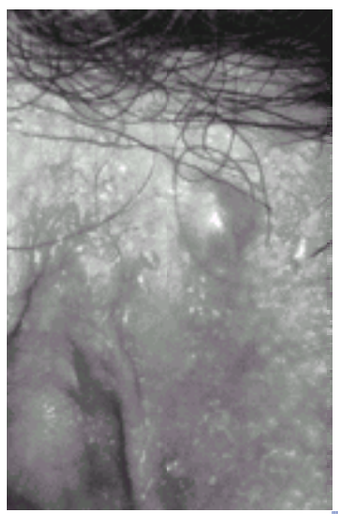

FIG. 33.15. Papillary hidradenoma, asymptomatic, located in the sulcus between the labia minus and majus. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

On histopathologic examination the deep relationship of the tumor with the underlying dermis reveals a circumscribed papillary tumor with a pushing, noninfiltrative boarder. The epithelial component of the tumor is composed of superficial secretory apocrine cells with a second deeper layer of myoepithelial cells below the secretory cells. Local excisional biopsy as a form of treatment is both diagnostic and therapeutic. Excision should be sufficiently deep to encompass the deep portion of the tumor margin. This will provide diagnostic pathologic material as well as be adequate therapy. Superficial biopsies can be somewhat misleading in some cases if the two cell layers of the papillary elements are not apparent and the relationship with the dermis is not seen.

Mammary-like Tissue: Arising from the Specialized Anogenital Glands

Mammary-like tumors were once considered to be from ectopic breast tissue in the vulva, however current evidence supports that the vulva is not in the human milk line and does not contain breast tissue. These tumors may be hidradenoma papilliferum, or resemble benign or malignant breast tumors. Metastatic breast adenocarcinoma is in the differential diagnosis in such cases. For the benign tumors the treatment is as for hidradenoma papilliferum.

Clear Cell Hidradenoma

Clear cell hidradenoma is rare on the vulva, however the histologic appearance, consisting of large regular cells with prominent clear cytoplasm, may present a diagnostic problem for the pathologist. As with the papillary hidradenoma, diagnostic excisional biopsy will be both therapeutic and will greatly aid in the pathologic diagnosis. These tumors, although usually solid, are well defined, with a pushing border at the tumor stromal interface without an infiltrative pattern.

Syringoma

Syringoma usually presents as multiple small, skin-colored papules often occurring bilaterally on the vulva. Pruritus may be a presenting symptom. Syringomas are considered to be benign adenomas of the ducts of the eccrine sweat glands.

The histopathologic diagnosis can be made from a representative biopsy of one of the papules. The comma-shaped, dilated duct elements within the dermis usually contain an inner myoepithelial layer and luminal epithelial cell layer. Syringomas are benign tumors; however, malignant variants of skin appendage tumors that may contain syringoma-like elements (mixed tumors of the vulva) have been reported. Syringoma is usually not treated surgically unless there is a specific mass in question that needs excision for diagnostic purposes. Topical or medical treatment is preferred.

Vascular Lesions

Capillary hemangioma occurs in infants and children. It is a slightly elevated, well-defined, red-to-violet lesion with an irregular surface. Ulceration may occur.

Capillary hemangiomas can be diagnosed clinically without biopsy. They typically regress over time without treatment. On microscopic examination the lesion consists of well-demarcated, clustered, small capillaries in a fibrous tissue.

Cavernous hemangiomas also may occur in children but are rare in the vulva. They are larger, deeper, and more complex than capillary hemangiomas. They can be associated with pelvic hemangiomas. They can involve the clitoris or labia and resemble hypertrophy. Cavernous hemangiomas will usually regress over time and therefore do not require treatment unless they bleed or otherwise become symptomatic.

Acquired hemangioma, also known as senile hemangioma, is common in the vulva in adults. The lesions are usually small, red-to-violet-to-purple papules, and are usually multiple. They do not require therapy but may resemble pigmented lesions and therefore may be biopsied. On microscopic examination acquired hemangiomas

are composed of clustered capillary-like vessels within the dermis, with fibrous tissue about the vessels that may be rich in collagen.

Differential diagnosis of hemangiomas includes hemangiomatous-like changes that may be seen in the vulva after radiation therapy. In addition, angiokeratoma, pyogenic granuloma, bacterial angiomatosis, hemangiopericytoma, angiosarcoma, and Kaposi sarcoma are all vascular lesions that can be included in the differential diagnosis.

Angiokeratoma

Angiokeratoma is a benign vascular tumor that is a variant of hemangioma. They are relatively common on vulva and present as a dark red to purple to black, papular lesion that may have an appearance of a condyloma acuminatum (Fig. 33.16). These vascular lesions are often multiple and usually asymptomatic although they may ulcerate and bleed. They can be associated with Fabry disease. Their elevated and dark appearance may result in them resembling a nevus and this prompts excisional biopsy.

FIG. 33.16. Angiokeratoma. Multiple angiokeratomas in a woman with Fabry disease. White blood cell a-galactosidase of 36 nm per hour per mg (normal = 50–80). (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

On microscopic examination the lesion has a warty appearance with acanthosis and usually some hyperkeratosis. A distinctive feature is that the basal layer of the overlying epithelium is nearly contiguous with the endothelial cells lining the underlying vascular channels of the angiokeratoma. This benign vascular lesion is confined to the superficial dermis and is not infiltrative, as seen with Kaposi sarcoma or angiosarcoma. Angiokeratoma is a benign lesion and does not require treatment unless bleeding or ulceration occurs, or excision is prompted because of its clinical appearance.

Pyogenic Granuloma (Granuloma Pyogenicum)

Pyogenic granuloma typically presents as an elevated, papular, red lesion that in the fully developed state is ulcerated. It is a variant of hemangioma and is analogous to the epulis tumor of pregnancy. Pyogenic granulomas on the vulva occur usually related to pregnancy but may arise in vulvar skin wound infection. The vascular tumor can have rapid growth and can become secondarily infected. Histologically, the findings resemble granulation tissue with inflammation. In fully developed cases at the ulcer edge a “collarette” of elevated dermis and epithelium surrounds the lesion.

Bacillary Angiomatosis

Bacillary angiomatosis clinically presents as a macular and papular red skin lesion or lesions that may resemble Kaposi sarcoma or hemangioma. These lesions are apparently caused by infection with the bacteria *Bartonella henselae* and *B. quintana* (formally, *Rochalimaea henselae*) and *R. quintana*. The bacterial organisms can be detected in tissue with appropriate silver stains.

Kaposi Sarcoma

Kaposi sarcoma is a vascular tumor associated with human immunodeficiency virus (HIV) and herpesvirus (herpesvirus VIII). Neoplastic-appearing, endothelial-appearing cells grow as spindle-shaped cells that form “slit-like” spaces that are filled with red blood cells.

VULVAR CYSTS

Bartholin Cyst and Bartholin Abscess

The Bartholin cyst is a result of distal obstruction of the Bartholin duct. Obstruction results in accumulation of secretion and cystic dilation of the duct (Fig. 33.17). The lining of the Bartholin cyst is epithelium that can be squamous, transitional, low cuboidal mucinous epithelium, or otherwise not classifiable. The Bartholin cyst is filled with mucoid sialomucin that is sterile and stains with mucicarmine, periodic acid-Schiff (PAS) with and without diastase digestion, and Alcian blue at pH 2.5. The cyst epithelium is immunoreactive for carcinoembryonic antigen (CEA).

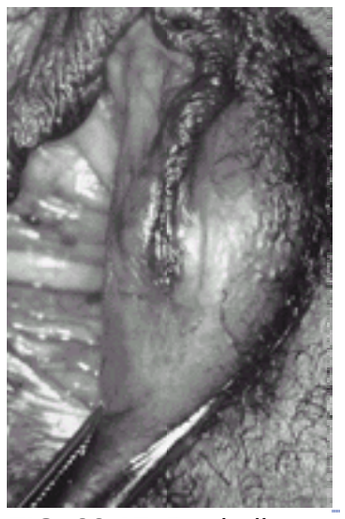

FIG. 33.17. Bartholin cyst. Bartholin duct cyst expanding the left labium majus. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Bartholin cysts are usually treated with marsupialization, using a Word catheter or equivalent to establish a new duct exit to the vestibular surface. In postmenopausal women, a persistent Bartholin mass after drainage or recurrent cysts may require surgical excision to resolve the process and exclude adenocarcinoma of the Bartholin gland.

Bartholin Abscess

Bartholin abscess may be caused by *Neisseria gonorrheae* infection, or related to infection with *Staphylococcus* or anaerobic organisms. The presenting symptoms are pain and sometimes fever. The physical findings demonstrate tenderness, redness, and swelling in the Bartholin gland area.

Microscopically, the Bartholin duct has acute inflammation within the duct as well as within the gland stroma about the duct. The abscess, when fully developed, contains purulent exudate. Treatment of choice is excision and drainage. Antibiotic therapy that the related organism is sensitive to is part of the treatment. In some cases the infection may subside without abscess formation. Persistent chronic inflammation may occur in some cases. Bartholin duct cyst may follow stenosis of the distal Bartholin duct secondary to chronic inflammation of the duct.

Keratinous Cyst (Epithelial Inclusion Cyst)

Keratinous cysts are relatively common on the vulva and can involve the majora, clitoris, perineal body, as well as other vulvar sites (Fig. 33.18). These cysts usually range in size from 2 to 5 mm, but may be larger, and they are typically superficial and can be multiple. They may occur at any age, and can occur in newborns. Milia, a type of multiple keratinous cysts, can occur in the vulva. Keratinous cysts may occur in episiotomy scars and have been observed as a complication of female circumcision. Keratinous cysts contain keratinous material that is white to pale yellow in color and grumous or cheesy in character. Hair is not present in these cysts. Keratinous cysts are not considered premalignant, although carcinoma arising in keratinous cysts may occur.

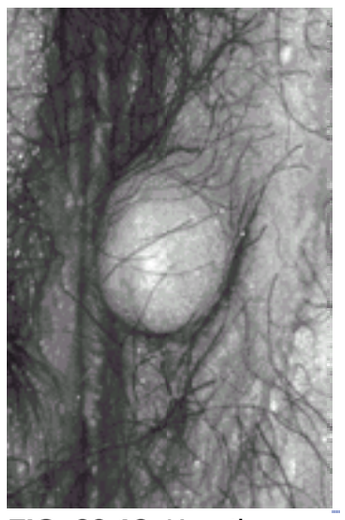

FIG. 33.18. Keratinous cyst (epidermal inclusion cyst). The cyst is firm but compressible. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

On microscopic examination, the cyst lining is flattened, stratified squamous epithelium that is immunoreactive for high-molecular-weight keratin. These cysts may be associated with occluded sebaceous gland ducts that have undergone squamous metaplasia. In the adjacent tissue to the cyst wall, foreign body-type giant cells associated with keratinous material that has leaked into the dermis can be found. Treatment is not necessary if the cysts are asymptomatic. Surgical excision is considered if the diagnosis is in question or if the cysts are enlarging, symptomatic, or become infected.

Mucous Cyst

Mucous cyst occurs primarily in the vulvar vestibule (Fig. 33.19). These cysts apparently arise from occlusion of minor vestibular glands. These cysts are typically simple cysts, superficial, and lined by mucus-secreting, cuboidal-to-columnar epithelium without associated myoepithelial cells. Metaplastic squamous epithelium may be present with the columnar epithelium lining the cyst. The epithelial cyst lining stains with both Alcian blue and Mayer mucicarmine. This distinguishes them from cysts of mesonephric origin that do not stain with these agents.

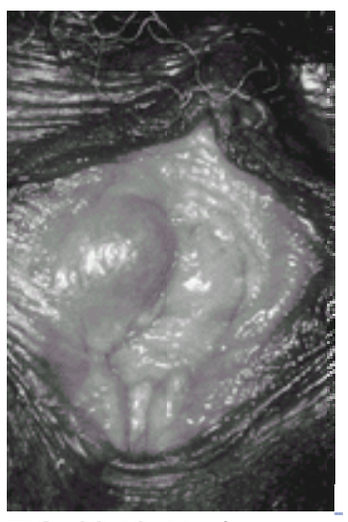

FIG. 33.19. Mucinous cyst of the vulvar vestibule. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.)

Columnar Cell Metaplasia

Columnar cell metaplasia has been described within the vulvar vestibule epithelium, as well as within the vaginal mucosa. Columnar cell metaplasia presents as a solitary flattened red area of the labia minora, or as persistent redness of the upper vagina. In one reported case the process responded to topical estrogen cream. Columnar cell metaplasia of the nonkeratinized squamous epithelium of the vulva vestibule or vagina is a condition where columnar epithelium of mucinous or tubal–epithelial type replaces the squamous epithelium. This has been described after Stevens-Johnson syndrome as well as after laser and 5-FU therapy.

Columnar cell metaplasia appears to be the origin of vulvar ciliated cysts. These cysts are lined with columnar epithelium resembling müllerian epithelium (tubal–endometrial epithelium), consisting of ciliated, secretory, and undifferentiated type cells. The cysts within the vestibule are considered acquired, since the müllerian system does not contribute to the development of the vestibule, which is of urogenital sinus origin. The cysts are distinguished from endometriosis by the absence of associated endometrial stroma or hemosiderin-laden macrophages.

Therapy for these cysts in the vestibule is generally not needed and they can be followed by observation alone. If the cyst or cysts persist, enlarge, or become symptomatic, they can be excised.

Vulvar Endometriosis

Vulvar endometriosis represents ectopic endometrial epithelium. The origin may be from endometrium implanted following vulvar or vaginal tears, or at the time of delivery, or endometrium shed at menstruation. Vascular spread of endometrium to the vulva or vagina may also be a consideration.

On clinical presentation, superficial vulvar or vaginal endometriosis usually presents as a mass that is blue-black to violet in color. In the vulva the mass is often in the posterior fourchette. Deeper endometriosis usually has no associated skin or mucous membrane discoloration. Cyclic pain and enlargement with the menstrual cycle

may be noted.

Diagnosis may be made using fine-needle aspiration cytology or local excision. On histologic examination endometrial glands and stroma are usually identified, often associated with hemosiderin-laden macrophages.

Apocrine Hydrocystoma/Cystadenoma of the Vulva

Apocrine hydrocystoma is a cyst with an epithelial lining with apocrine differentiation. The lining cells are apocrine in character with pink cytoplasm and apical snoutlike secretion. Apocrine cystadenoma is a cyst lined with apocrine-differentiated cells with an epithelial lining that has micropapillary projections. These cysts typically arise in the apocrine gland–bearing areas of the vulva.

Mesonephric-like Cyst (Wolffian-like Duct Cyst)

Mesonephric-like cysts occur on the lateral walls of the vagina, and occasionally within the lateral vulvar vestibule. These cysts are typically thin-walled, translucent in appearance, and contain a clear fluid. The cuboidal to columnar epithelial lining is not ciliated. Using immunohistochemistry for smooth muscle, such as smooth muscle actin, smooth muscle can be seen deep and surrounding these cysts.

Cyst of the Canal of Nuck (Mesothelial Cyst)

Entrapped peritoneum (processus vaginalis) within the round ligament may result in a cyst of the canal of Nuck, causing labial enlargement. These cysts apparently arise from inclusions of the peritoneum at the inferior insertion of the round ligament into the labia majora.

Cysts of the canal of Nuck typically occur in the superior labia majora or inguinal canal. Therefore they are analogous to spermatic cord hydrocele. These mesothelial-lined cysts can achieve substantial size and a concurrent inguinal hernia, which occurs in approximately one-third of cases, and sometimes obscures their diagnosis. These cysts may mimic inguinal hernia on clinical examination.

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Chapter 34

Marc A. Fritz

Amenorrhea

THE NORMAL MENSTRUAL CYCLE
Differential Diagnosis of Amenorrhea
Genital Tract Abnormalities
Ovarian Disorders
Pituitary Disorders
Hypothalamic Disorders
EVALUATION OF AMENORRHEA
Medical History
POLYCYSTIC OVARY SYNDROME
Determination of Estrogen Status
Hypothalamic Amenorrhea
TREATMENT OF AMENORRHEA
Genital Tract Abnormalities
Ovarian Disorders
Hypothalamic Disorders
SUMMARY POINTS

SUGGESTED READINGS
Differential Diagnosis of Amenorrhea
Genital Tract Problems
Gonadal Dysgenesis
Premature Ovarian Failure
Pituitary Disorders (Hyperprolactinemia)
Hypothalamic Amenorrhea
Polycystic Ovarian Syndrome

Amenorrhea is the absence or cessation of menses and may result from a wide variety of pathologic conditions. It is a common symptom of an underlying abnormality in the reproductive system that may be anatomic (developmental or acquired), organic, or endocrinologic in nature. This chapter outlines the differential diagnosis of amenorrhea, discusses the indications and methods for evaluation, and describes options for treatment once a diagnosis and the patient's goals are clearly defined. However, the most common cause of amenorrhea in women of reproductive age is pregnancy and that should be ruled out before considering other etiologies.

THE NORMAL MENSTRUAL CYCLE

Normal menstrual function involves a complex multilevel integration of endocrine signals, local autocrine and paracrine mechanisms, and target cell receptors, all operating at four distinct levels: the genital tract, the ovary, the pituitary gland, and the hypothalamus. First, normal menstrual function requires a normal genital outflow tract. The uterus must have a functional endometrium capable of response to estrogen and progesterone, and be continuous with the cervix, vagina, and introitus. Second, the ovaries must contain follicles responsive to pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) stimulation. Progressive follicular development and ovulation further require the normal operation of local intraovarian regulatory mechanisms that are sensitive to changes in the endocrine milieu. Third, pituitary gonadotrophs must have the capacity to synthesize and secrete gonadotropins in response to hypothalamic gonadotropin-releasing hormone (GnRH) stimulation. The relative amounts of FSH and LH released reflect changes in the pulsatile pattern of GnRH secretion and the feedback modulation of ovarian steroid and peptide hormones. Finally, specialized neurosecretory cells located in the medial basal hypothalamus (arcuate nucleus) must have functional communication with the pituitary gland and be able to synthesize and release GnRH in a pulsatile pattern that varies in response to stimuli from the environment and feedback signals from the periphery.

Amenorrhea may result from congenital or acquired disease or dysfunction at the level of the genital tract, the ovary, the pituitary, or the hypothalamus. In fact, the single most common cause of amenorrhea—chronic hyperandrogenic anovulation (polycystic ovary syndrome; PCOS)—involves a number of interrelated pathophysiologic mechanisms that operate at the ovarian, pituitary, and hypothalamic levels, and does not fall neatly into any one specific category. The wide array of disorders that may be responsible suggests that amenorrhea may present a daunting diagnostic challenge but, in truth, evaluation is relatively straightforward, logical, and requires only tests and procedures with which all gynecologists should be quite familiar. With few exceptions, an accurate diagnosis can be confidently established in very little time and without great expense.

Differential Diagnosis of Amenorrhea

Although the list of potential causes of amenorrhea is long, the majority of cases relate to one of five conditions: pregnancy, PCOS, hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure (Table 34.1). All of the remaining causes are relatively uncommon and only occasionally encountered in a lifetime of clinical practice.

Pregnancy
Genital tract abnormalities
Congenital
Hymeneal obstruction
Congenital absence of all or a portion of the vagina or cervix
Congenital absence of the müllerian duct system
Androgen insensitivity syndrome
Acquired
Cervical obstruction/stenosis
Intrauterine adhesions
Ovarian failure
Gonadal dysgenesis (45X, 46XX, and 46XY)
Premature ovarian failure (postpubertal)
Pituitary disorders
Functional hyperprolactinemia (including hypothyroidism and drug-induced)
Prolactin-secreting and other pituitary tumors (including craniopharyngioma)
Empty sella syndrome and Sheehan syndrome
Hypothalamic disorders
Congenital (Kallmann syndrome)
Stress (weight loss, excercise, emotional)
Polycystic ovary syndrome

TABLE 34.1. *Causes of amenorrhea*

Genital Tract Abnormalities

The embryology of the female genital tract involves the medial migration and midline fusion of the paired müllerian (paramesonephric) ducts to form the uterus, cervix, and upper vagina, and the vertical fusion of that developing ductal system with the invaginating urogenital sinus to form the lower vagina and the introitus. Outflow tract abnormalities that result from failure of müllerian duct development include *vaginal/müllerian agenesis* and *androgen insensitivity syndrome (AIS)*, where the uterus is altogether absent. Abnormalities caused by failure of vertical fusion include *imperforate hymen, transverse vaginal septum*, and *cervical atresia.* These conditions result in an accumulation of menstrual effluent above the level of obstruction (cryptomenorrhea). With two notable exceptions, all outflow tract abnormalities are developmental in origin and therefore cause primary amenorrhea. *Asherman syndrome* and *cervical stenosis/obstruction* are acquired conditions and therefore are causes of secondary, rather than primary, amenorrhea. Asherman syndrome results from intrauterine adhesions that obstruct or obliterate the uterine cavity as a consequence of inflammation (postpartum endometritis, retained products of conception) or trauma (curettage). Severe cervical stenosis with complete outflow

obstruction is a rare complication of cervical conization procedures or other surgical treatments for cervical intraepithelial neoplasia.

Ovarian Disorders

Ovarian failure occurs when few or no follicles remain that are capable of producing estradiol in response to pituitary gonadotropin stimulation. Follicular depletion may occur during embryonic life with no follicles remaining by infancy or early childhood, after puberty has begun but before menarche, or at some later time before menopause would normally be expected. Therefore, depending on when the available supply of ovarian follicles is functionally depleted, puberty may not occur, it may begin normally but stop before the first menses, or it may progress normally to and beyond menarche with secondary amenorrhea having onset at some later point in time.

Gonadal dysgenesis is among the most common of all causes of primary amenorrhea (approximately 30%–40%) and results from an absence of ovarian follicles or accelerated follicular depletion during embryogenesis or the first few years of life. The gonads of affected individuals contain only stroma and appear as fibrous streaks. The most common form of gonadal dysgenesis is Turner syndrome, classically associated with a 45,X karyotype, but also with an assortment of other structural X chromosome abnormalities (deletions, ring, and iso-chromosomes). These X chromosomal anomalies may be present in all or only in some of the cells of the body (mosaicism), depending on the stage of embryonic development at the time that they arise. Although less common, individuals with gonadal dysgenesis also may have a normal 46,XX or a 46,XY karyotype *(Swyer syndrome)* in all cells or in one or more cell lines in mosaic individuals (e.g., 45,X/46,XX; 45,X/46,XY). Most, in the absence of ovarian follicles, have no significant secondary sexual development. A few may have transient normal ovarian function, the extent depending on when the limited supply of ovarian follicles is depleted. Approximately 15% begin but do not complete pubertal development and approximately 5% have sufficient follicles to complete puberty and begin spontaneous menstruation. Spontaneous pregnancies rarely occur and are associated with a relatively high risk for sex chromosome aneuploidy and spontaneous abortion.

Premature ovarian failure (POF) results in secondary amenorrhea at some time after puberty has been completed. It is distinguished from gonadal dysgenesis on the basis of ovarian morphology and histology; instead of streak gonads, the ovaries in POF more closely resemble those of postmenopausal women. Approximately 1% to 5% of women will develop POF before the age of 40 years. The karyotype in individuals with POF is most often normal (46,XX), but also may reveal mosaicism (e.g., 45,X/46,XX). A specific cause for early follicular depletion in POF frequently cannot be determined and is presumed to result from inadequate germ cell migration during embryogenesis or accelerated atresia. POF is frequently associated with *autoimmune disorders* and in some cases (e.g., Addison disease) appears to result from an autoimmune lymphocytic oophoritis. *Radiation* and *chemotherapy* are two other important causes of ovarian failure. The effects of both are dependent upon dose and the age at time of treatment. *Galactosemia* is an autosomal recessive disorder of galactose metabolism caused by a deficiency of the enzyme galactose 1-phosphate uridyltransferase and another, albeit very rare, cause of POF. Affected women have fewer primordial follicles presumably due to the cumulative toxicity of galactose metabolites on germ cell migration and survival.

Other, very rare, ovarian disorders that may cause amenorrhea include *17a-hydroxylase deficiency, aromatase deficiency*, and the *gonadotropin-resistant ovary syndrome.* Unlike in ovarian failure, the ovaries of individuals with these disorders contain follicles and oocytes, but cannot produce estrogen. The enzyme 17 µ-hydroxlase mediates an early step in steroid hormone synthesis, without which progesterones cannot be converted to androgens and subsequently, estrogens. The enzyme aromatase mediates the conversion of androgenic precursors to estrogens; individuals with aromatase deficiency generally exhibit sexual ambiguity at birth, virilization at puberty, and multicystic ovaries. The gonadotropin-resistant ovary syndrome results from genetic mutations in the FSH or LH receptor or post-receptor signaling defects that prevent the ovaries from responding normally to gonadotropin stimulation; although present, ovarian follicles fail to develop beyond the early antral stage and therefore produce little estrogen.

Pituitary Disorders

Pituitary tumors may cause amenorrhea by directly compressing pituitary gonadotrophs or distorting the portal venous network that delivers hypothalamic GnRH stimulation, resulting in decreased FSH and LH secretion. They also may cause inadequate or excessive production of other pituitary hormones, via compression of pituitary tissue, interference with the portal venous circulation, or autonomous secretion (functional pituitary adenomas). Directly or indirectly, these endocrinopathies may disrupt normal ovarian function, thereby causing amenorrhea. Although metastatic lesions may occasionally be seen, malignant pituitary tumors are extremely rare. Virtually all pituitary tumors are benign adenomas that may be functional or nonfunctional; functional tumors may secrete prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), or adrenocorticotropic hormone (ACTH).

Other uncommon pituitary disorders that may cause amenorrhea include the *empty sella syndrome* and *Sheehan syndrome.* The empty sella syndrome results from herniation of the subarachnoid space containing cerebrospinal fluid into the sella turcica with compression of the pituitary gland against the sellar floor, giving the sella an “empty” appearance when viewed by computed tomography (CT) or magnetic resonance imaging (MRI). Sheehan syndrome results from acute infarction and necrosis of the pituitary gland as a rare complication of shock due to obstetric hemorrhage. Depending on the extent of pituitary damage, clinical consequences may be limited to disorders of reproductive function (failed lactation, amenorrhea), or more general, with multisystem failure due to panhypopituitarism.

Hypothalamic Disorders

Absent or abnormal patterns of pulsatile hypothalamic GnRH secretion that fail to stimulate normal levels or patterns of pituitary gonadotropin secretion are the most common cause of amenorrhea. Both *PCOS* and *hypothalamic amenorrhea* that may result from emotional, nutritional, or physical stress are basically hypothalamic disorders, but their pathophysiology and clinical presentations differ considerably. Women with PCOS exhibit an increased frequency of pulsatile GnRH secretion that results in increased LH synthesis, hyperandrogenism, and impaired follicular maturation. In contrast, the inconsistent and generally low frequency pattern of pulsatile GnRH secretion in women with hypothalamic amenorrhea results in low levels of pituitary gonadotropin release that fail to stimulate or sustain progressive follicular development.

Occasionally, a *hypothalamic tumor* (craniopharyngioma, meningioma, hamartoma, chordoma) may distort the tuberoinfundibular tract or portal venous network, thereby interfering with effective delivery of GnRH stimulation, and result in decreased pituitary FSH and LH secretion. Alternatively, interference with hypothalamic dopamine delivery to pituitary lactotrophs may cause *hyperprolactinemia.* In either case, hypothalamic tumors may result in a secondary hypogonadotropic hypogonadism and amenorrhea. In other rare instances, GnRH deficiency is congenital and associated with midline craniofacial defects or with anosmia due to a failure of olfactory axonal and GnRH neuronal migration during embryogenesis *(Kallmann syndrome)*, resulting in primary amenorrhea and sexual infantilism.

EVALUATION OF AMENORRHEA

A detailed medical history and physical examination are always important. In the patient with amenorrhea, elements of particular interest include growth and secondary sexual development (breast and pubic hair), menstrual history (if any), previous surgery or trauma to the pelvis or central nervous system (CNS), family history of hereditary disorders, evidence of physical, psychological or emotional stress, symptoms and signs of hirsutism or galactorrhea, as well as reproductive tract anatomy.

Medical History

The age at which menarche should be expected varies but, in general, the first menses should occur within 2 to 3 years after the initiation of pubertal development. In most young girls (approximately 80%), the first sign of puberty is an acceleration of growth, followed by breast budding (thelarche), and the appearance of pubic hair (adrenarche). In the remainder, adrenarche precedes thelarche by a brief interval, but the two events typically are closely linked. Consequently, menarche should be expected as early as age 10 (when puberty begins at age 8), and rarely later than age 16 (when puberty begins at age 13). On average, in the United States, the mean ages for thelarche, adrenarche, and menarche in black girls are 6 to 12 months earlier than in white girls. When secondary sexual development fails to begin by age 14, or begins but fails to progress at the normally expected pace, evaluation is indicated. Once menstrual cycles have been established, amenorrhea for an interval equivalent to three previous cycles, or 6 months, warrants evaluation.

Questions relating to past medical history, general health, and lifestyle may identify a severe or chronic illness (diabetes, renal failure, inflammatory bowel disease), head trauma, or evidence of physical, psychological, or emotional stress. Weight loss or gain and the frequency and intensity of exercise may be revealing. Headaches, seizures, vomiting, behavioral changes, or visual symptoms may suggest a CNS disorder. Vaginal dryness or hot flushes are evidence of estrogen deficiency and suggest ovarian failure. Progressive hirsutism or virilization is evidence of hyperandrogenism that may result from PCOS, nonclassic (late-onset) congenital adrenal hyperplasia (CAH), or an androgen-producing tumor of the ovary or adrenal gland. Bilateral galactorrhea suggests hyperprolactinemia. Cyclic pelvic or lower abdominal pain or urinary complaints may be caused by developmental anomalies resulting in obstructed menstrual flow, including an imperforate hymen, transverse vaginal septum, or cervical atresia. A previous inguinal hernia repair or curettage suggests the possibility of a developmental anomaly or damage to the reproductive tract. The timing and duration of any treatment with progestational agents (oral contraceptive pills [OCP], depot-medroxyprogesterone acetate), GnRH agonists (leuprolide, goserelin, nafarelin), or other medications (phenothiazines, reserpine derivatives, amphetamines, opiates, benzodiazepines, antidepressants, dopamine antagonists) or drugs (opiates) may provide important diagnostic clues.

Physical Examination Body habitus often provides important clinical information. Height, weight, and body mass index (BMI) should be recorded. Short stature (less than 60 inches) is a hallmark of gonadal dysgenesis; sexual infantilism, webbing of the neck, low set ears and posterior hairline, widely spaced nipples, short fourth metacarpal, and a wide carrying angle of the arms (cubitus valgus) are among the classical stigmata of Turner syndrome. Low body weight is frequently associated with hypothalamic amenorrhea resulting from poor nutrition (eating disorders) or physical, psychological, or emotional stress. Obesity or an increased waist-to-hip ratio (>0.85) is often associated with insulin resistance and chronic anovulation. Examination of the skin may reveal a soft, moist texture as seen in hyperthyroidism; a rapid pulse and classic eye signs (exophthalmos, lid lag), a fine tremor, and hyperreflexia may provide further evidence to suggest a diagnosis of Graves disease. Conversely, dry, thick skin, a slow pulse, diminished reflexes, and thinning of the hair suggest hypothyroidism. Both hypothyroidism and hyperthyroidism may be associated with amenorrhea. Orange discoloration of the skin in the absence of scleral icterus may result from hypercarotinemia associated with excessive ingestion of low-calorie, carotene-containing fruits and vegetables in dieting women. Acanthosis nigricans, velvety hyperpigmented skin most commonly observed at the nape of the neck, in the axillae, and beneath the breasts, strongly suggests severe insulin resistance and the possibility of diabetes. Acne and hirsutism are indications of hyperandrogenism that may result from chronic anovulation (PCOS), nonclassic CAH, or ingestion of androgenic anabolic steroids. When accompanied by any sign of frank virilization (deepening of the voice, frontotemporal balding, decrease in breast size, increased muscle mass, clitoromegaly), the possibility of ovarian hyperthecosis or an ovarian or adrenal neoplasm must be considered. Breast development, as assessed by Tanner staging, is a reliable indicator of estrogen production or exposure to exogenous estrogens. Arrested breast development suggests a disruption of the hypothalamic–pituitary–ovarian (HPO) axis. When menarche has not followed adult breast development, a developmental anomaly of the reproductive tract should also be considered. The breast examination should include gentle compression, beginning at the base and moving toward the nipple. Microscopic examination of any expressed cloudy or white nipple secretions that demonstrate lipid droplets indicate true galactorrhea and suggest hyperprolactinemia. Abdominal examination may rarely reveal a mass as may result from hematometra or an ovarian neoplasm. Growth of hair from the pubic symphysis to the infraumbilical region suggests hyperandrogenism. Abdominal striae raise the possibility of Cushing syndrome, but much more often result from progressive obesity or previous pregnancy. As noted earlier, thelarche and adrenarche typically are closely linked events during puberty and, in general, breast development and growth of pubic hair progress in a symmetric manner. The Tanner stages of breast and pubic hair development should be consistent. Absent or scant growth of pubic hair is a classic sign of AIS when breast development is asymmetrically advanced. Attempts at office examination of the vagina in sexually infantile girls or those with a small hymeneal ring are often difficult and counterproductive, but whenever feasible, speculum examination should be performed. A patent vagina and visible cervix excludes müllerian/vaginal agenesis, AIS, and most obstructive causes of amenorrhea. In those with an absent or infantile vaginal orifice, rectal examination should be performed and may reveal a distended hematocolpos above the obstruction when the uterus is present and functional.

Diagnostic Evaluation A careful history and physical examination will always narrow the range of diagnostic possibilities that must then be differentiated. The subsequent laboratory investigation or imaging should be focused on that differential diagnosis and, with few exceptions a diagnosis can be quickly and easily established. Sexual ambiguity and virilization should be evaluated as separate disorders, mindful that amenorrhea is an important element of their presentation.

Abnormal Genital Tract Anatomy A history of primary amenorrhea accompanied by physical examination that reveals an absent or blind vagina indicates a developmental anomaly of the genital outflow tract. The list of diagnostic possibilities is short and includes an imperforate hymen, a transverse vaginal septum, cervical atresia, müllerian/vaginal agenesis, and androgen insensitivity syndrome (Fig. 34.1). Because each of these disorders has unique features, they generally are not difficult to distinguish.

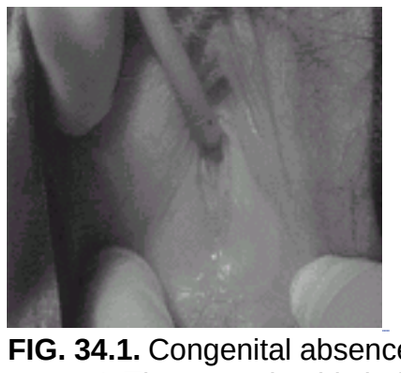

FIG. 34.1. Congenital absence of the vagina. The external genitalia are entirely normal in appearance without any evidence of ambiguity but there is simply no vagina present. The normal pubic hair indicates androgen responsiveness and eliminates the possibility of androgen insensitivity syndrome indicating that this is simply congenital absence of the müllerian duct system.

Patients with an imperforate hymen or transverse vaginal septum/cervical atresia typically present at the expected time of menarche with complaint of cyclic perineal, pelvic, or abdominal pressure or pain and exhibit normal secondary sexual development. In those with an imperforate hymen, genital examination reveals no obvious vaginal orifice, but a thin, often bulging, blue perineal membrane and a fluctuant mass, resulting from the accumulation of mucus and blood in the vagina. In those with a transverse vaginal septum or cervical atresia, examination typically reveals a normal vaginal orifice, a short blind vagina of varying length, and a fluctuant pelvic mass well above to the level of obstruction (hematocolpos, hematometra, hematosalpinx). Differentiation of imperforate hymen and transverse vaginal septum/cervical atresia generally requires no laboratory investigation. Whereas a *transabdominal* or *transperineal ultrasound* examination will reveal the level and volume of sequestered menses, an *abdominalpelvic MRI* provides greater anatomic detail and helps to define the nature of an anomaly (Fig. 34.2). In some instances, laparoscopy may be required to clearly identify the anatomy of a developmental anomaly.

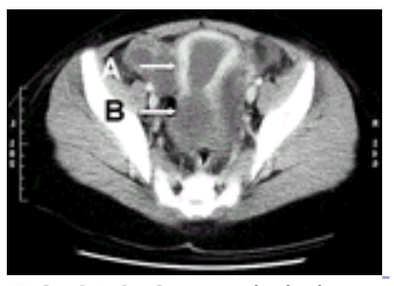

FIG. 34.2. Congenital absence of the lower one third of the vagina. Magnetic resonance imaging demonstrates that a uterus is present (**A**) as well as an upper vaginal pouch (**B**). The upper vagina has formed a hematocolpos which began soon after menarche and presented as a pelvic mass.

In contrast, patients with amenorrhea resulting from müllerian agenesis generally are otherwise entirely asymptomatic. They exhibit normal breast and pubic hair development, an absent vagina, and have no symptoms or signs of cryptomenorrhea because the uterus is altogether absent. The diagnosis is usually self-evident from physical examination alone. Further evaluation to exclude skeletal and urinary tract anomalies is indicated because approximately 12% to 15% of women with müllerian agenesis have skeletal abnormalities (vertebral anomalies are most common) and one third or more have urinary tract anomalies (ectopic kidney, renal agenesis, horseshoe kidney, abnormal collecting system). In girls who have not yet reached the age when menarche (and cryptomenorrhea) would be expected if a uterus was present, imaging must be interpreted cautiously because even abdominal/pelvic MRI can be misleading when the reproductive organs are immature. Remaining alert to the diagnostic possibilities, careful observation over time is preferable to invasive investigations that are otherwise unnecessary. Normal breast development, absent or sparse growth of pubic hair, and a short blind vagina clearly suggest AIS. Although the chromosomal sex is male (46,XY), the phenotype is female. The testes are undescended, often palpable in the inguinal canals (most commonly at the level of the external inguinal ring), and produce normal male levels of testosterone and müllerian inhibitory hormone (MIH). Whereas end-organ insensitivity to androgen action (due to abnormalities of the androgen receptor) prevents normal masculinization of the genitalia, MIH inhibits müllerian development in a normal fashion. Consequently, the external genitalia are those of a female (absent androgen action), the uterus is absent (normal MIH action), and the vagina is short and ends blindly (derived from the invaginating urogenital sinus, absent androgen action). The diagnosis may be suspected when other family members (e.g., aunt, sister) are affected with this X-linked disorder. Incomplete penetrance may result in growth of more pubic hair than might be expected and sometimes can be misleading. However, a serum *testosterone* concentration easily distinguishes androgen insensitivity syndrome (AIS; normal or modestly elevated above the range observed in normal males) from müllerian agenesis (normal range for a female). A *karyotype* firmly establishes the diagnosis. Cervical obstruction/stenosis and Asherman syndrome are abnormalities of genital tract anatomy, but physical examination of the genital tract most often is normal. When cervical stenosis causes symptoms, worsening dysmenorrhea or prolonged light staining or spotting after menses are the most common complaints; amenorrhea is a rare occurrence. In women with a history of previous conization or other cervical surgery or ablative therapy, *uterine sounding* may help to establish a diagnosis. Similarly, most women in whom previous infection or surgical trauma has resulted in intrauterine synechiae present with dysmenorrhea, hypomenorrhea, subfertility, or recurrent early pregnancy loss, rather than amenorrhea. In women whose history clearly suggests the possibility of intrauterine adhesions, *ultrasound* and *hysterosalpingography* can reveal their location and extent, but hysteroscopy is the definitive method for diagnosis.

Normal Genital Tract Anatomy When physical examination reveals normal genital tract anatomy, further evaluation is required to determine the cause of amenorrhea. The possibility of pregnancy should always be considered and excluded. When breast growth is absent or inconsistent with age and associated with primary amenorrhea, the cause of delayed puberty should be determined. The vast majority of these cases have no pathology. In the remainder, evaluation may reveal thyroid disease, chronic illness (malabsorption, renal disease, eating disorders, inflammatory bowel disease), ovarian failure (e.g., gonadal dysgenesis), a pituitary disorder (tumor, empty sella syndrome, hyperprolactinemia), or a hypothalamic cause (Kallmann syndrome; physical, emotional, or psychological stress; tumor). Wrist x-rays for *bone age* and a *GnRH stimulation test* are important components of the evaluation for delayed puberty in children and adolescents, but the diagnostic possibilities and scope of evaluation in adolescents and adults with either primary or secondary amenorrhea are otherwise very much the same.

Thyroid Function Tests Initial evaluation should include a measurement of serum *TSH*. The newest generation of ultrasensitive TSH assays in common use provides the means to detect both primary hypothyroidism (elevated TSH) and primary hyperthyroidism (low TSH). Either may result in chronic anovulation and amenorrhea. Any abnormal value should be confirmed and accompanied by measurement of serum *thyroxine* (tetraiodothyronine; T4) to better define the nature and extent of the

thyroid disorder. When TSH is elevated and the T4 concentration is normal, the diagnosis is subclinical hypothyroidism, best viewed as a compensated state wherein normal levels of T4 are maintained, but only under increased levels of pituitary stimulation. On rare occasions, both TSH and T4 levels may be low, suggesting hypothyroidism of pituitary origin that will require additional evaluation to include hypothalamic/pituitary imaging (MRI) and careful assessment to determine whether other pituitary functions also are affected.

Prolactin A serum *prolactin* determination is another component of the initial evaluation of amenorrhea. Hyperprolactinemia may be associated with a variety of menstrual disturbances—oligomenorrhea and amenorrhea being the most common. In general, prolactin concentrations are higher in amenorrheic than in oligomenorrheic hyperprolactinemic women. Hyperprolactinemia may occasionally result in delayed puberty and primary amenorrhea, if it arises before menarche, and is among the most common causes of secondary amenorrhea. Hyperprolactinemia inhibits pulsatile hypothalamic GnRH secretion, resulting in depressed levels of pituitary FSH and LH secretion. The end result is anovulation or more profound hypogonadotropic hypogonadism, depending on the extent to which gonadotropin secretion is suppressed. One cannot rely on the symptom or finding of galactorrhea to identify individuals whose amenorrhea may result from hyperprolactinemia. Only approximately one third of hyperprolactinemic women will exhibit galactorrhea, probably because breast milk production requires several other hormones, including GH, T4, cortisol, insulin, and most important, estrogen and progesterone. Serum prolactin determinations therefore should be obtained in all amenorrheic women. Hyperprolactinemia has many causes. Among these are:

- prolactin-secreting pituitary adenomas
- other pituitary or hypothalamic tumors that may distort the portal circulation and thereby prevent effective delivery of hypothalamic dopamine (the putative prolactin inhibitory factor or hormone)
- a variety of drugs that lower dopamine levels or inhibit dopamine action (amphetamines, benzodiazepines, butyrophenones, metoclopramide, methyldopa, opiates, phenothiazines, reserpine, and tricyclic antidepressants)
- breast or chest wall surgery, cervical spine lesions, or herpes zoster (activation of the afferent sensory neural pathway that stimulates prolactin secretion, in a manner similar to suckling)
- hypothyroidism (increased hypothalamic thyrotropin-releasing hormone stimulates pituitary prolactin secretion directly)
- pharmacologic estrogens (OCP)
- other rare, nonpituitary sources (lung and renal tumors) or causes of decreased prolactin clearance (renal failure).

All causes must be considered and systematically excluded; a careful history will eliminate many of the possibilities. When medications are the cause, prolactin concentrations are usually only moderately elevated and levels greater than 100 ng/mL generally are uncommon. Although medications may offer an obvious explanation, one cannot confidently assume they are the cause of hyperprolactinemia. If possible, a trial discontinuation or use of an alternative medication should be considered. When that is not possible and hypothyroidism has been excluded, further evaluation to exclude hypothalamic and pituitary tumors and other causes of hyperprolactinemia is appropriate. Imaging of the hypothalamic and pituitary regions to exclude mass lesions in hyperprolactinemic patients can be accomplished with head *CT* or *MRI*. MRI generally is regarded as the superior method because it is more accurate for identification of very small lesions or an empty sella and better defines tumor margins and relationships to surrounding structures. The indications for CT or MRI in the evaluation of hyperprolactinemia remain controversial. Those who advocate liberal use of imaging correctly emphasize that the likelihood of a pituitary tumor does not correlate with the prolactin concentration. Pituitary microadenomas (=10 mm) are very common (10%–30% prevalence in autopsy studies) and even macroadenomas (>10 mm) may be associated with only modest elevations (25–100 ng/mL) of prolactin because they are nonfunctional tumors or may have undergone necrosis. Moreover, imaging may reveal evidence of other hypothalamic disease that may be important (tumor, tuberculosis, sarcoidosis, aqueductal stenosis) and amenable to specific treatment. Those who prefer a more selective approach stress that imaging is costly and has a relatively low yield when performed routinely. They correctly emphasize that pituitary tumors rarely grow (even in pregnancy), are not a contraindication to hormone replacement or OCP, and that their natural course is unaffected by treatment with dopamine agonists (bromocriptine, pergolide, cabergoline). In this view, because diagnosis of a pituitary microadenoma generally has little or no impact on clinical management decisions, MRI should be limited to those with grossly elevated prolactin levels (>100 ng/mL) who are hypoestrogenic, in whom a macroadenoma of greater clinical significance is more likely, and to those with suspicious symptoms (visual disturbances, headaches) or findings (visual field defects, abnormal optic fundi). For asymptomatic patients with moderate hyperprolactinemia (20–100 ng/mL), some advocate a less costly *coned down lateral view of the sella turcica* and reserve MRI for those with an enlarged or abnormal sella (erosion of the sellar floor or clinoid processes) or hypothalamic calcifications that suggest a tumor (e.g., craniopharyngioma). The most prudent approach is to obtain an MRI whenever persistent hyperprolactinemia cannot be confidently attributed to medication or hypothyroidism.

FSH Initial evaluation of amenorrheic women with normal genital tract anatomy should include measurement of serum *FSH* to distinguish ovarian failure (elevated FSH) from hypothalamic/pituitary disease or dysfunction that yields inadequate or ineffective patterns of gonadotropin secretion (low or normal FSH). An elevated FSH level generally is a reliable indicator of ovarian failure, but must be interpreted in the context of the clinical presentation. During the perimenopause, regardless whether it occurs prematurely or at the usual age, FSH levels may rise well before menses have ceased entirely. Those follicles that remain also are relatively insensitive to FSH, but many can and will respond to rising levels of stimulation when the requisite threshold FSH concentration is achieved. Once follicular growth begins and estrogen levels rise, FSH concentrations decline, albeit transiently, before rising again to the levels necessary to stimulate new follicular growth. FSH levels therefore are dynamic, often fluctuate widely during the perimenopause, and must be interpreted cautiously. The FSH level is high in the enigmatic gonadotropin-resistant ovary syndrome that may result from inactivating mutations in the FSH or LH receptor. However, specific efforts to diagnose these rare conditions *(ovarian biopsy, genotyping)* are academic and have no practical clinical value because the prognosis for future fertility is extremely poor and treatment options are no different from those for women with true ovarian failure. Serum FSH concentrations also are elevated in individuals with 17a-hydroxylase or aromatase deficiencies and galactosemia, but these conditions are extremely rare and do not enter into clinical consideration. With few exceptions, a high serum FSH level is an indication of ovarian failure. A history of previous radiation or chemotherapy may provide an obvious explanation. Doses of radiation under approximately 100 rads generally have no significant effect, but risk of ovarian damage rises progressively with higher doses. Individuals treated when young may have only transient amenorrhea with a return of menstrual cycles months or years later, but also are more likely to develop POF. Those treated as adults are at greater risk for immediate and irreversible ovarian failure. Alkylating agents (e.g., cyclophosphamide), used in the treatment of malignancies and other diseases (systemic lupus erythematosus), are extremely toxic to gonadal tissues. As with radiation, the dose required to induce ovarian failure is inversely related to age at the time of treatment. Other chemotherapeutic agents have the potential for ovarian damage, but their effects are less clear; risk increases with the number of agents involved in combination therapies. When ovarian failure occurs before age 30 and cannot be confidently explained, a karyotype should be obtained. An abnormal karyotype may be observed in up to one-half of all women with primary amenorrhea. Classic Turner syndrome (45,X), structural abnormalities of the X chromosome (deletion, ring, iso-chromosome), and mosaicism (e.g., 45,X/46,XX) are the most common abnormalities found. A karyotype also will detect the presence of a Y chromosome that might not otherwise be suspected. The phenotype in Swyer syndrome (46,XY gonadal dysgenesis) and some with Turner mosaicism (45,X/46,XY) is female because the dysgenetic (streak) gonads fail to produce both MIH and androgens. Consequently, the uterus, fallopian tubes, cervix, and vagina develop normally but the genitalia do not masculinize. However, a peripheral leukocyte karyotype alone cannot exclude the presence of occult Y chromosomal material. Further analysis with *fluorescence in situ hybridization (FISH)* using one or more probes that are specific for segments of the Y chromosome is required and should be performed in any individual with a 45,X karyotype or 45,X mosaic cell line. An occult Y chromosome must be identified because affected individuals are at significant risk (approximately 25%) for developing a unique type of germ cell tumor (gonadoblastoma) that may contain malignant elements (dysgerminoma, embryonal cell carcinoma, choriocarcinoma). Virtually all such tumors arise early in life. Over the age of 30, therefore, karyotype is unnecessary and ovarian failure can be confidently regarded as premature menopause. Approximately 25% of patients with gonadal dysgenesis have a normal karyotype (46,XX). As gonadal dysgenesis with a normal karyotype is associated with neurosensory deafness, *audiometry* should be considered. In women with secondary amenorrhea and unexplained POF, further evaluation to exclude autoimmune disease is appropriate as up to 40% may have autoimmune disorders. POF develops in 10% to 60% of women with Addison disease (adrenal insufficiency) and also is more common in women with diabetes mellitus (type 1), myasthenia gravis, and parathyroid disease than in healthy women. However, only those with Addison disease are likely to have a demonstrable autoimmune lymphocytic oophoritis. Ovarian biopsy is not indicated in clinical practice, but because POF may be a component of a polyglandular syndrome, general screening for autoimmune disorders is reasonable. Thyroid abnormalities are the most common and can be identified by measuring *TSH, T4*, and *thyroid autoantibodies (antiperoxidase, antithyroglobulin).* Screening may also include *24-hour urinary free cortisol, fasting blood glucose, serum calcium and phosphorus*, and *antinuclear antibody*. More extensive or specific testing for autoimmune disorders is unnecessary in the absence of other clinical signs and symptoms of disease. Although autoimmune screening is logical and practical, no one or combination of serum markers can confirm a diagnosis of autoimmune ovarian failure. A low normal serum FSH concentration is an indication of hypothalamic or pituitary dysfunction and the most common result observed in clinical practice. PCOS and hypothalamic amenorrhea are the two main diagnostic possibilities and generally are easily distinguished by their clinical presentations.

POLYCYSTIC OVARY SYNDROME

Although there is no universally accepted definition of PCOS, diagnosis generally is based on three criteria—ovulatory dysfunction, clinical evidence of hyperandrogenism (hirsutism, acne, androgenic alopecia) or hyperandrogenemia, and exclusion of other disorders (hyperprolactinemia, thyroid abnormalities, nonclassic CAH). Women with PCOS more commonly exhibit oligomenorrhea (75%) than amenorrhea (25%); irregular and infrequent menses typically begin soon after menarche, but may emerge later, often in association with progressive weight gain. Signs of androgen excess generally do not become evident until years later and progress gradually. Transvaginal ultrasound examination typically reveals ovaries that are modestly enlarged and contain numerous small follicles aligned in the periphery (“string of pearls”), but such findings are not useful for diagnosis because in up to one-third of normal women between the ages of 18 and 25 years, the ovaries have a similar polycystic appearance. Women with PCOS are frequently insulin-resistant (insulin sensitivity is reduced by 30%–40%), exhibit compensatory hyperinsulinemia (up to 80%), and are predisposed to glucose intolerance. Approximately 30% have demonstrable impaired glucose intolerance by glucose tolerance testing; *fasting glucose* is elevated in less than 10%. A *fasting glucose/insulin ratio* less than 4.5 is a fairly specific but somewhat insensitive diagnostic criterion for insulin resistance. Obesity is a common feature of women with PCOS (50%–75%) and exacerbates insulin resistance and the hyperinsulinemia that is associated with elevated androgen levels. Prolactin levels are mildly elevated in 10% to 25% of women with PCOS. Although the ratio of serum LH/FSH is frequently increased (>2.0), measurement of the serum LH level generally is not useful or necessary. The diagnosis of PCOS is not based on findings of ovarian or hormonal abnormalities, but on a history of chronic anovulation and clinical findings of androgen excess or obesity.

When hirsutism is severe or perimenarchial in onset, the possibility of nonclassic CAH also must be considered. Most commonly, nonclassic CAH results from a deficiency of the enzyme 21-hydroxylase which mediates an essential step in cortisol synthesis. Affected individuals cannot efficiently convert 17-hydroxyprogesterone (17-OHP) to 11-deoxycorticosterone (DOC; an intermediate step in cortisol synthesis). A follicular phase 17-OHP level greater than 2 ng/mL merits further evaluation with an *ACTH stimulation test* (serum 17-OHP before and 30–60 minutes after intravenous injection of 250 g ACTH) to confirm the diagnosis (post-stimulation serum 17-OHP concentration >1,000 ng/dL).

Determination of Estrogen Status

Evaluation of estrogen levels would seem logical for differentiating PCOS from hypothalamic amenorrhea and other hypoestrogenic disorders. Unfortunately, available methods cannot easily and reliably define the level of ovarian estrogen production. One cannot rely on symptoms and signs of estrogen deficiency to identify hypogonadal women. Genitourinary atrophy develops only gradually and is uncommonly observed in young women, even when estrogen levels are extremely low, and vasomotor symptoms typically are absent in women with hypothalamic dysfunction. Other methods for assessing the level of ovarian estrogen production include immunoassay of the serum estrogen concentration and “bioassays” based on clinical observation of the amount and character of cervical mucus (“estrogenic” mucus being clear, watery, and relatively abundant) or results of a “progestin challenge test” (presence or absence of withdrawal bleeding after administration of an exogenous progestin). Each of these methods may be useful, but each clearly also has pitfalls.

A serum *estradiol* measurement is easy to perform and relatively inexpensive. One might reasonably expect low estrogen levels in women with hypothalamic amenorrhea and normal levels in women with PCOS. Unfortunately, estradiol concentrations fluctuate erratically and may be normal or low on any given day, and therefore can be misleading. Whereas observations of estrogenic cervical mucus clearly suggest a normal level of ovarian estrogen production, the absence of such findings cannot be confidently interpreted because many women exhibit such mucus only in the late follicular phase of the cycle when estrogen levels are relatively high, or not at all.

The *progestin challenge* is based on the observation that progestin treatment (e.g., medroxyprogesterone acetate 10 mg daily for 5–7 days or progesterone in oil 100 mg i.m.) will induce menses only in those with normal circulating estrogen concentrations. For this purpose, a pure progestational agent must be used; endogenous estrogen status cannot be inferred from the response to an OCP that contains both estrogen and progestin. A positive test (bleeding after completion of progestin treatment) implies normal levels of estrogen production and a negative test (no withdrawal menses) suggests frank hypogonadism. However, withdrawal bleeding correlates poorly with estrogen status; both false-positive (withdrawal bleeding despite generally low levels of estrogen production) and false-negative (absent bleeding despite significant estrogen production) results are common. Up to 20% of women with oligomenorrhea or amenorrhea in whom substantial estrogen is present do not exhibit withdrawal bleeding. Conversely, up to 40% of women whose amenorrhea relates to stress, exercise, weight loss, or hyperprolactinemia, in whom estrogen levels are generally low, exhibit withdrawal bleeding. A false-positive progestin challenge also has been frequently observed in women with POF.

Hypothalamic Amenorrhea

In the absence of obesity or evidence of hyperandrogenism characteristic of PCOS, the most likely cause of amenorrhea in women with a normal or low serum FSH level is a functional disorder of the hypothalamus or higher CNS centers. Women with such “hypothalamic amenorrhea” generally present with secondary amenorrhea that is frequently accompanied by history of emotional stress, weight loss (dieting), poor nutrition (eating disorders, chronic illness), or regular strenuous exercise (endurance training). In contrast to women with PCOS, they typically have normal or low body weight and are poorly estrogenized. In the context of low levels of estrogen production, a low or normal serum FSH has the same implication—a dysfunctional HPO axis—because if that axis were intact and fully functional, the classic negative feedback relationship between estrogen and FSH would stimulate a compensatory increase in FSH secretion and result in an elevated serum FSH concentration. A low or normal serum FSH therefore clearly suggests hypothalamic or pituitary disease or dysfunction. Most women with hypothalamic amenorrhea have a normal FSH concentration; extremely low or undetectable FSH levels are seldom seen except in women with large pituitary tumors or anorexia nervosa.

Amenorrhea associated with weight loss due to dieting is common; anorexia nervosa is fortunately much less common (15/100,000 women/year). In athletic women, the risk of amenorrhea is increased approximately three-fold over that in nonathletic women with the highest prevalence observed in endurance athletes (long-distance running). Chronic debilitating diseases (end-stage renal disease, malignancy, acquired immune deficiency syndrome, malabsorption) also may result in anovulation and amenorrhea. In such cases, hypothalamic amenorrhea represents a functional suppression of the reproductive system that may be viewed as a psychobiologic response to psychological, physical, or nutritional stress. One proposed unifying hypothesis emphasizes the concept of energy balance: When available energy is excessively diverted (exercise), or insufficient (dieting, malnutrition), reproduction is suspended in order to support essential metabolism for survival. The mechanism responsible may involve a stress-induced increase in hypothalamic corticotropin-releasing hormone (CRH) and endogenous opioid secretion that inhibits pituitary gonadotropin release directly, or inhibition of pulsatile hypothalamic GnRH secretion by increased dopamine or opioids.

Hypothalamic–Pituitary Imaging The diagnosis of hypothalamic amenorrhea cannot be established until organic disease of the CNS, hypothalamus, or pituitary gland is excluded with a CNS *MRI.* Imaging is prudent, even when emotional stress, weight loss, poor nutrition, or regular strenuous exercise appear to offer an explanation for hypothalamic dysfunction and amenorrhea. Imaging may reveal a pituitary tumor, an empty sella, or evidence of a hypothalamic tumor, anomaly, or other disease. The vast majority of pituitary tumors are prolactinomas or nonfunctioning adenomas, but other varieties are rarely encountered. Additional evaluation can help to define the nature of a tumor and the extent to which other pituitary functions may be compromised. Grossly elevated prolactin levels clearly suggest a prolactinoma; more modest prolactin elevations may be observed when large tumors infarct or a nonfunctioning adenoma distorts sellar anatomy and disrupts normal dopamine delivery to pituitary lactotrophs. When the clinical presentation suggests Cushing syndrome, screening *(24-hour urinary free cortisol, overnight dexamethasone suppression test)* is indicated; additional evaluation (serum *ACTH, adrenal CT or MRI*) is required when results are abnormal. Physical findings that suggest acromegaly are an indication to measure serum *insulin-like growth factor-1 (IGF-1; somatomedin-C)*; if elevated, an *oral glucose tolerance test with GH levels* should be performed (lack of suppression is diagnostic). Pituitary function testing (TSH, T4, prolactin, 24-hour urinary free cortisol, IGF-1) also is indicated when imaging reveals a macroadenoma or an empty sella to insure that the other trophic pituitary hormones are normal. Dynamic testing is unnecessary in otherwise asymptomatic women with a microadenoma or normal sella. The empty sella syndrome generally is a benign condition and not progressive. However, because of the possibility of an unrecognized coexisting tumor, periodic surveillance with a prolactin determination and MRI are indicated. Anatomic abnormalities of the hypothalamus are distinctly uncommon. Hypothalamic tumors (craniopharyngioma, hamartoma, meningioma) generally are rare and other mass lesions (tuberculosis, sarcoidosis) are even more so. Congenital hypogonadotropic hypogonadism associated with anosmia or hyposmia (Kallmann syndrome) is another rare inheritable disorder associated with a specific anatomic defect: Hypoplastic or absent olfactory sulci. The condition results from a failure of both olfactory axonal and GnRH neuronal migration during development and is genetic in origin (X-linked, autosomal dominant, or autosomal recessive). The most common form (X-linked) derives from mutations in a single gene (*KAL*) on the short arm of the X chromosome that encodes a protein (anosmin-1) necessary for normal neuronal migration. The clinical presentation (primary amenorrhea, sexual infantilism, hypogonadotropic hypogonadism, and anosmia) and common association with other anatomic (cleft lip and palate) and neurologic (hearing loss, cerebellar ataxia, color blindness) abnormalities is not difficult to recognize. Very often, imaging fails to reveal any anatomic abnormality of the pituitary or hypothalamus and in otherwise asymptomatic individuals, the diagnosis is, by exclusion, hypothalamic dysfunction.

TREATMENT OF AMENORRHEA

Treatment of amenorrhea is obviously focused on the specific etiology, when known, and always is tailored to the goals of the patient.

Genital Tract Abnormalities

In women with vaginal/müllerian agenesis, the primary goal of treatment—creation of a functional vagina—can be accomplished with a variety of methods when the time is appropriate. In most cases, progressive vaginal dilation will be successful in the motivated patient. The technique involves application of pressure to the point of moderate discomfort (approximately 20–30 min/d) using commercially available vaginal dilators, first in a posterior direction (to create a pouch), and then in the usual line of the vaginal axis (after about 2 weeks). After the desired depth is achieved, increasingly larger dilators will expand the vaginal diameter and create a functional vagina in approximately 3 to 6 months.

Operative treatment of women with vaginal/müllerian agenesis generally should be reserved for those who refuse or poorly tolerate vaginal dilation. Traditionally, a neovagina has been created by dissection of the rectovaginal space and placement of a skin graft, held in place with a soft mold until the graft was established (McIndoe procedure). Subsequent regular intercourse or vaginal dilation must be maintained to avoid risk of fibrosis and loss of function. More recently, an operation that employs a transabdominal traction device has been described that can create a functional vagina within 7 to 9 days. Where available and applicable, the technique would appear to offer significant advantages over the traditional vaginoplasty procedure. In the rare woman with vaginal/cervical agenesis with a well-formed uterine body, it may be technically possible to create a neovagina continuous with the uterus with the goal of preserving fertility, but the associated long-term infectious morbidity has led most to conclude that the uterus should be removed in most circumstances.

Reassurance and support are important elements of the management of vaginal/müllerian agenesis. Affected women should be counseled that although they are infertile, normal sexual function can be expected and that genetic offspring can be achieved by in vitro fertilization using oocytes retrieved from the normal ovaries and the sperm of the partner, with subsequent transfer of embryos to a gestational surrogate. A growing experience with these techniques has revealed no evidence to

indicate that congenital absence of the vagina and uterus is heritable in a dominant fashion.

AIS presents both similar and different treatment challenges. A functional vagina again can be created by any of the techniques described previously for women with vaginal/müllerian agenesis, but surgical treatment much less often is required as the vagina generally is short but otherwise normal rather than altogether absent. Genetic offspring, of course, are not possible because women with AIS do not have oocytes. They have testes, most commonly located in the inguinal canals at the level of the external inguinal ring but sometimes found within the abdomen. Like women with gonadal dysgenesis whose karyotype contains a Y chromosome (46,XY, 45,X/46,XY), individuals with AIS are at increased risk for development of tumors in their undescended testes. Therefore, the testes should be removed. However, the risk of neoplasia is lower (approximately 5%–10% vs. 25%), tumors are rarely encountered before puberty, and the secondary sexual development that accompanies puberty in women with AIS from the aromatization of testosterone is more natural than can be accomplished pharmacologically. Consequently, removal of the testes and hormone replacement are best delayed until pubertal maturation is complete, generally by age 16 to 18 years.

Initial treatment of women with an imperforate hymen, transverse vaginal septum, or cervical atresia centers on relief of symptoms related to accumulated menstrual fluid and debris. Surgical correction of imperforate hymen is straightforward, requiring only a cruciate incision in the hymen to the base of the hymeneal ring and excision of its central portion to allow drainage of sequestered menstrual fluid and subsequent normal menstruation. Surgical management of a transverse vaginal septum can be very challenging. In its simplest form, the procedure involves excision of the septum or dissection through the atretic segment to connect the margins of the lower and upper vaginal canals with split-thickness skin grafting occasionally required if the distance between the two precludes a primary junction without tension. In rare women with cervical atresia, as in those with vaginal agenesis who have a functional uterine body, the generally poor outcome and high postoperative morbidity associated with heroic efforts to preserve the uterus and fertility suggest that removal of the müllerian remnants is the safest management strategy.

Uterine sounding and gentle cervical dilation often are all that is required to correct a symptomatic cervical obstruction/stenosis. Operative hysteroscopy is the preferred method for treatment of intrauterine synechiae that may be lysed by blunt dissection, scissors, electrodissection, or with a laser; any of these methods achieves results superior to blind curettage. When adhesions are severe or extensive, an intrauterine balloon catheter (left in place for approximately 7–10 days) may be useful to maintain separation between the walls of the uterine cavity. Treatment with a broad-spectrum antibiotic and an inhibitor of prostaglandin synthesis (nonsteroidal antiinflammatory drugs) helps to minimize risk of infection and uterine cramping. High-dose exogenous estrogen treatment (2.5 mg conjugated equine estrogens/day or its equivalent for approximately 4 weeks) also generally is recommended to encourage rapid endometrial reepithelialization and proliferation. Repeated procedures may be required to restore a normal uterine cavity. Approximately 50% to 75% of affected women may be expected to achieve a successful pregnancy, although risks of preterm labor, placenta accreta, placenta previa, and postpartum hemorrhage are increased.

Ovarian Disorders

Women with gonadal dysgenesis and sexual infantilism should be offered growth and sex hormone replacement therapy to promote growth to maximum potential, normal bone density development, and secondary sexual maturation. Treatment with exogenous recombinant human GH (50g/kg/d) stimulates an acceleration of growth that generally can be sustained for 6 years or more and results in an adult height as much as 10 cm over initial predicted height. In those with short stature, sex hormone replacement should be postponed until the bone age reaches 12 or greater to avoid premature epiphyseal closure and allow a longer interval of time for long bone growth. Sex hormone replacement therapy should follow the normal sequence of sex hormone production observed during adolescence and begin with low doses of estrogen alone (0.3 mg conjugated equine estrogens or 0.5 mg micronized estradiol). Dosage should be increased gradually and after approximately 6 to 12 months or first evidence of vaginal bleeding, cyclic treatment with a progestin should be added. To achieve maximum bone and breast development, higher doses (1.25–2.5 mg conjugated equine estrogens or 2–3 mg micronized estradiol) often are required. Once secondary sexual development is completed, longer-term sex hormone replacement should continue to avoid the otherwise inevitable emergence of estrogen deficiency symptoms and bone mineral depletion. Alternatively, a low-dose OCP may be offered, for convenience.

Pregnancy may be achieved in women with gonadal dysgenesis through in vitro fertilization using oocytes provided by a genetically normal oocyte donor. However, pregnancy carries a unique risk for women with 45,X gonadal dysgenesis (Turner syndrome) as numerous cases of aortic dissection, aneurysm, and spontaneous rupture during pregnancy now have been reported. Preconceptional echocardiography may identify patients at risk for whom pregnancy is contraindicated, but catastrophic events may occur despite the absence of abnormal findings. Should they conceive spontaneously or by using donor oocytes, echocardiography should be performed at least once in each trimester, and the practitioner should remain alert to any evidence of progressive dilation of the ascending aorta. Women with 45,XY or 45,X/46,XY gonadal dysgenesis should have their gonads removed soon after diagnosis to avoid the substantial risk of gonadal tumors. Unlike those with AIS whose functional testes produce sex steroids that will promote normal secondary sexual maturation, women with gonadal dysgenesis have nonfunctional streak gonads. Consequently, there is no advantage to delay their removal.

The primary goals of treatment for women with POF that develops after secondary sexual maturation is complete generally are relief from symptoms of estrogen deficiency and prevention of premature bone mineral depletion. Standard regimens of cyclic or combined continuous estrogen/progestin hormone replacement therapy or a low-dose OCP will meet the need, and either is appropriate. In vitro fertilization with use of donor oocytes offers the possibility of pregnancy and the prognosis for success in most such women is excellent. Women in whom POF is diagnosed before age 30 and in whom karyotype reveals a mosaic 45,X cell line must be carefully evaluated and counseled on the potential risks of aortic dissection and rupture during pregnancy, as described earlier. Monitoring or treatment should be offered for any associated autoimmune disorders.

Pituitary Disorders The overwhelming majority of pituitary tumors are prolactin-secreting adenomas or nonfunctioning tumors. TSH-, ACTH-, or GH-secreting adenomas generally are rare. A pituitary tumor often will be discovered when imaging is performed in women with hyperprolactinemia and occasionally in euprolactinemic women with hypogonadotropic hypogonadism that cannot be confidently attributed to weight loss, eating disorders, or regular strenuous exercise (Fig. 34.3). It may be difficult to differentiate a prolactin-secreting adenoma from a nonfunctioning tumor that disrupts normal hypothalamic dopamine delivery, except perhaps when prolactin levels are markedly elevated. However, because treatment options in hyperprolactinemic amenorrheic women with small intrasellar tumors are the same in either case, a specific diagnosis is not critical. The nature of a tumor may become clear only after treatment with a dopamine agonist restores normal prolactin levels; the majority of prolactin-secreting adenomas shrink in size during treatment and those that do not are more likely to be nonfunctioning tumors. In euprolactinemic amenorrheic women, a pituitary tumor also may be only an incidental finding, having no clinical significance.

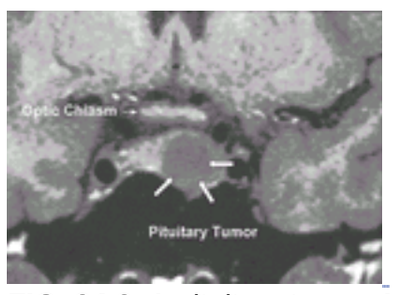

FIG. 34.3. A pituitary tumor. Magnetic resonance imaging of a prolactin-secreting pituitary tumor (*three large arrows*). Note the lateral location and elevation of the diaphragm sella. However, the tumor does not compress the optic chiasm (*single arrow*) and thus no visual disturbances would be anticipated.

Whereas transsphenoidal surgery was commonly performed in the past to remove pituitary tumors, it is now generally reserved for women with rare TSH-, ACTH-, or GH-secreting adenomas, those with large nonfunctioning tumors associated with complaints of headache or visual disturbances, and those in whom medical treatment (described subsequently) fails or is poorly tolerated. Surgery achieves immediate reduction of prolactin levels and restores cyclic menses in approximately 30% of women with prolactin-secreting macroadenomas and in up to 70% with microadenomas. However, residual or recurrent tumors and hyperprolactinemia are common and surgery may be complicated by cerebrospinal fluid leakage, meningitis, diabetes insipidus, or other trophic pituitary hormone deficiencies that require further treatment. Postoperative monitoring involves periodic serum prolactin determinations and repeated imaging. Radiation therapy for pituitary tumors is even less attractive because the response to radiation is slow and such treatment risks development of panhypopituitarism over time. As a result, radiation generally is reserved for postoperative recurrence of large tumors. Dopamine-agonist therapy is the mainstay of treatment for hyperprolactinemia, independent of whether a pituitary tumor is identified. Bromocriptine is highly efficacious but side effects (nausea, headache, orthostatic hypotension, dizziness, nasal congestion) are common. The dose should be titrated incrementally to normalize serum prolactin levels, beginning with a small dose (1.25–2.5 mg) at bedtime, with a second dose taken with breakfast or lunch when required; most patients will require 5.0 mg per day or less. Cabergoline may be an effective alternative when bromocriptine treatment cannot be tolerated, although its lower frequency of side effects and less frequent dosing (0.25–3.0 mg every 3–7 days) also make it an attractive initial therapeutic choice. Vaginal administration of bromocriptine or cabergoline is effective and may help to reduce side effects when oral treatment is poorly tolerated. Dopamine-agonist treatment restores menses and ovulatory function in up to 80% of amenorrheic hyperprolactinemic women, generally within approximately 6 to 8 weeks; reduction or cessation of galactorrhea typically requires somewhat longer-term treatment. Medical treatment with a dopamine agonist (bromocriptine, cabergoline) promotes shrinkage of pituitary macroadenomas in the majority of cases, usually within 6 to 12 weeks. Large tumors that fail to shrink despite effective suppression of excess prolactin secretion generally are nonfunctioning adenomas that cause hyperprolactinemia by interfering with delivery of dopamine from the hypothalamus and require surgery. Regardless of the treatment they receive, women with macroadenomas should be monitored with serum prolactin determinations and imaging every 6 to 12 months for at least 2 years, less often thereafter if tumor size and prolactin levels remain stable, and sooner if prolactin levels rise significantly or symptoms of headache or visual disturbances emerge or recur. Similar monitoring with serial prolactin determinations (every 6 to 12 months) and periodic imaging (annually for 2 years) is

recommended for those with microadenomas. Dopamine-agonist therapy is the best initial choice for persistent or recurrent tumor or hyperprolactinemia. For the few patients who may require radiation therapy, ongoing surveillance must be implemented to detect any evidence of developing panhypopituitarism. Pituitary tumors generally grow slowly or not at all, even during pregnancy. No more than approximately 5% of women with pituitary microadenomas will experience tumor growth during pregnancy, even fewer develop signs or symptoms as a result, and only a rare patient will require surgical intervention. The risk is greater but generally still modest for those with macroadenomas (approximately 15%). Routine serial visual field examinations and serum prolactin determinations therefore are unnecessary, but the patient and her physician must be alert to symptoms that may emerge in any trimester. Headaches generally precede visual disturbances and if either appears, monitoring with serum prolactin measurements, visual field examinations, and imaging should begin. With rare exceptions, dopamine-agonist therapy will arrest and reverse tumor expansion and eliminate associated symptoms and poses no significant risk to mother or fetus. Dopamine-agonist therapy clearly is the treatment of choice for anovulatory hyperprolactinemic women who desire pregnancy or have significant breast tenderness or troublesome galactorrhea, with or without a pituitary adenoma. In the absence of other coexisting causes of infertility, approximately 80% of anovulatory hyperprolactinemic women treated with dopamine agonists may be expected to conceive. In the few who cannot tolerate medical treatment with bromocriptine or cabergoline but desire pregnancy, ovulation induction with exogenous gonadotropins is an effective alternative as prolactin does not alter the effect of the gonadotropins on the ovarian follicles. Women not seeking pregnancy may be offered hormone replacement therapy or even a low-dose OCP that will restore menses and effectively eliminate or prevent the consequences of any associated estrogen deficiency. The uncommonly encountered empty sella syndrome generally is entirely benign and does not progress to pituitary failure. Treatment and subsequent surveillance are the same as in women with a pituitary adenoma. In the rare patient whose amenorrhea results from Sheehan syndrome and its related pituitary insufficiency, more than simple sex steroid replacement therapy may be required. Depending on the extent and scope of pituitary damage, such women also may require glucocorticoid and thyroid hormone replacement. For those affected women who desire a subsequent pregnancy, ovulation induction may be achieved, but only with exogenous gonadotropins.

Hypothalamic Disorders

Chronic anovulation resulting from abnormal patterns of pulsatile hypothalamic GnRH secretion is the cause of amenorrhea most commonly encountered in practice. A hypothalamic etiology can be established only after first excluding other peripheral, ovarian, and pituitary disorders (normal serum TSH and prolactin levels, low or normal serum FSH, negative imaging, where indicated). Most such women are estrogenized and can also be obese or androgenized (PCOS). Some have a more profound hypogonadism with grossly low levels of estrogen production (hypothalamic amenorrhea), often in association with history of emotional, nutritional, or physical stress.

Treatment of women with PCOS is based on whether pregnancy is an immediate goal. Those who desire pregnancy are candidates for ovulation induction. For those not seeking pregnancy, the goals of treatment are to establish regular menses and prevent the consequences of chronic unopposed estrogen stimulation on the endometrium (dysfunctional uterine bleeding, endometrial hyperplasia, endometrial adenocarcinoma), to prevent the emergence or progression of hirsutism, and to reduce the longer-term risks of diabetes and cardiovascular disease associated with the disorder.

The wide range of therapeutic options for ovulation induction in anovulatory women with PCOS who desire pregnancy is only summarized here. When obese, weight loss should always be encouraged and may be all that is required to restore menstrual cyclicity. Even if weight loss does not restore ovulatory function, it may be expected to improve the response to ovulation-inducing agents. The substantial costs, risks, and logistic demands of more aggressive forms of treatment might thus be avoided, but weight loss should never be a prerequisite for treatment.

Clomiphene citrate is the initial treatment of choice as it is safe, inexpensive, and has few serious side effects. Clomiphene is a competitive estrogen receptor antagonist that acts centrally to deplete hypothalamic estrogen receptors, thereby interfering with estrogen-negative feedback and resulting in a compensatory alteration in pulsatile GnRH secretion that stimulates increased pituitary gonadotropin release and, in turn, drives ovarian follicular activity. Treatment should begin with a low dose (50 mg/d cycle days 3–7 or 5–9 after a spontaneous or progestin-induced menses) and subsequently increase in increments (100 mg/d, 150 mg/d) as needed to achieve ovulation. Most women with PCOS will respond to clomiphene, but many prove resistant and ultimately require alternative treatment. Among clomiphene-resistant anovulatory women with PCOS, a significant majority have insulin resistance. Metformin (1,000–2,000 mg/d in divided doses) is an insulin-sensitizing agent that can restore spontaneous menses and cyclic ovulation in many amenorrheic women with PCOS. Consequently, metformin can be used as the first treatment option for ovulation induction, adding clomiphene in those who fail to respond or, as is more commonly done, metformin can be reserved for those who first prove resistant to clomiphene. In either case, many who fail to ovulate in response to either alone will respond when the two are used in combination. Although the safety of metformin treatment in pregnancy has not been established, preliminary evidence suggests that it may reduce the incidence of spontaneous abortion and gestational diabetes in the subset of women with PCOS and insulin resistance.

Those who prove resistant to clomiphene and metformin are candidates for treatment with exogenous gonadotropins. Because such women often are very sensitive to low doses of gonadotropins, unifollicular ovulation can be difficult to achieve and the risk for both multiple pregnancy and ovarian hyperstimulation syndrome is increased. Consequently, treatment must be carefully monitored and is best provided only by clinicians having the necessary training or experience.

Ovarian drilling is a contemporary version of the classic ovarian wedge resection and another treatment option for ovulation induction in clomiphene-resistant, hyperandrogenic, anovulatory women with PCOS (Fig. 34.4). The technique involves laparoscopic cautery, diathermy, or laser vaporization of the ovaries at multiple sites, the objective being to decrease circulating and intraovarian androgen levels by reducing the volume of ovarian stroma. However, the effects of treatment are temporary and postoperative adhesions that may compromise fertility are a distinct possibility. Drilling also has the potential to destroy oocytes and shorten the reproductive lifespan and therefore is best limited to those for whom all other alternatives have been exhausted.

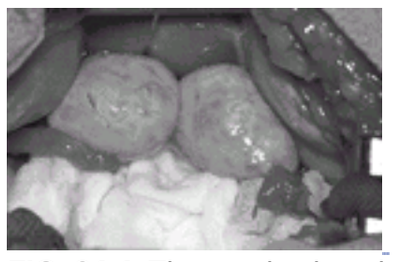

FIG. 34.4. The ovaries in polycystic ovary syndrome shown in a woman with polycystic ovary syndrome at laparotomy. Note the large size of the ovaries, relative to the uterus, with a smooth ovarian capsule without evidence of ovulatory events.

OCPs have long been the mainstay of treatment for amenorrheic women with PCOS who do not desire pregnancy because the combined actions of OCP offer a number of important benefits. Programmed cyclic OCP treatment restores regular, predictable menses, protects the endometrium from the adverse effects of otherwise unopposed estrogen stimulation, and provides effective contraception for the occasional spontaneous ovulation. OCPs decrease circulating androgens by suppressing typically increased serum LH levels that stimulate excess ovarian androgen production and further reduce levels of circulating free androgen by stimulating hepatic production of sex hormone binding globulin. Consequently, within 3 to 6 months after initiation of treatment hair typically grows more slowly, becomes both finer and lighter in color, and therefore is less noticeable and more easily managed.

For those with more severe hirsutism in whom treatment with OCP alone fails to achieve the desired effect, spironolactone can be added (100–200 mg/d in divided doses) to provide more effective control. In the dose range indicated, spironolactone acts as a competitive androgen receptor antagonist and blocks androgen action on the pilosebaceous unit (a hair follicle, sebaceous glands, and arrector pili muscle). The multiple actions of combined treatment with OCP and spironolactone (suppression of excess androgen production, increase in androgen binding, and blockade of androgen action) are complementary and generally quite effective for the management of hirsutism. In extreme cases, a more profound suppression of excess androgen production can be achieved by treatment with a GnRH agonist (e.g., leuprolide acetate) with superimposed cyclic or combined continuous hormone replacement with standard doses of estrogen and progestin to prevent the otherwise inevitable emergence of estrogen deficiency symptoms. Suppression of adrenal androgen production by chronic glucocorticoid treatment risks suppression of the adrenal response to stress, immunosuppression, and progressive bone mineral depletion, should therefore be reserved only for those with documented nonclassic CAH, and must be carefully monitored when offered.

Insulin resistance certainly contributes to the pathophysiology of PCOS by local amplification of ovarian androgen production in response to LH (directly or via IGF-1) and by reducing hepatic synthesis of sex hormone binding globulin (directly). Moreover, hyperandrogenism clearly is associated with an atherogenic lipid profile. There also is evidence that in individuals with glucose intolerance, metformin treatment can reduce the risk of progression to frank diabetes and, presumably, the increased risk of cardiovascular disease associated with that disease. However, these longer-term potential benefits of primary metformin therapy remain unproven. Moreover, the drug is relatively costly and often poorly tolerated (nausea, vomiting, diarrhea). Under such circumstances, whether primary metformin treatment offers sufficient benefits to justify its use as an alternative or complement to other already proven treatment strategies (weight loss, exercise, OCP, statin therapy) remains controversial. Based on the evidence available to date, primary metformin treatment cannot be recommended for all women with PCOS, but may merit serious

consideration in selected individuals.

In the absence of obesity, hirsutism, or other evidence of hyperandrogenism that is characteristic of PCOS, the most likely cause of amenorrhea in women with a normal or low-serum FSH level is a functional disorder of the hypothalamus or higher centers. As for women with PCOS, treatment for women with hypothalamic amenorrhea depends on whether pregnancy is an immediate goal. Those who desire pregnancy clearly are candidates for ovulation induction. For those not seeking pregnancy, the goals of treatment are to establish regular menses, if desired, and to prevent the consequences of chronic estrogen deficiency (genitourinary atrophy, progressive bone demineralization) as most, but not all women with hypothalamic amenorrhea exhibit frankly low levels of endogenous estrogen production.

The range of therapeutic options for ovulation induction for women with hypothalamic amenorrhea (Fig. 34.5) is somewhat narrower than for those with PCOS and again is only summarized here. In women with a low BMI, weight gain should be encouraged but weight gain, like weight loss, can be very difficult to achieve. Women with a low BMI should be educated on the relationship between weight and menstrual function and advised that weight gain may be all that is needed to restore menstrual cyclicity and ovulation. At the least, weight gain may be expected to increase the likelihood of response to more conservative ovulation induction strategies (clomiphene citrate) involving less cost and risk than otherwise may be required. Those in whom symptoms (fasting, purging) or physical findings suggest a potentially serious underlying eating disorder (bulimia, anorexia) should be offered psychiatric evaluation and care before attempting pregnancy as such disorders pose unique risks to both mother and fetus.

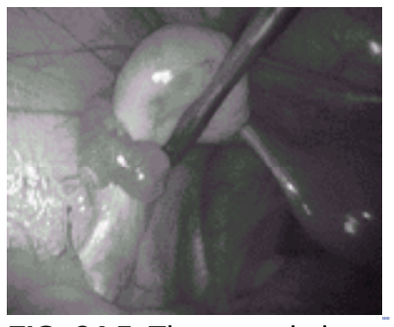

FIG. 34.5. The ovary in hypothalamic amenorrhea. Laparoscopy of the pelvis demonstrates a normal-appearing uterus with the left ovary having a smooth capsule without evidence of follicular activity. This is consistent with the lack of gonadotropin stimulation with a normal but unstimulated ovary.

Similarly, women whose hypothalamic amenorrhea is associated with a high level of regular strenuous exercise should be educated on the pathophysiology involved. Reduced physical activity may restore menstrual cyclicity and ovulation and, at the least, less exercise may improve the probability that conservative methods of ovulation induction will succeed. However, once again, reduced levels of exercise should not be a prerequisite for treatment. For many, high levels of exercise are intrinsic to lifestyle or represent the preferred method for relieving stress and may not be desirable or even feasible.

Ovulation induction should be offered to those who desire pregnancy. Because of its relatively low cost and risk, clomiphene citrate is again the initial drug of choice. However, unlike women with PCOS, those with hypothalamic amenorrhea often fail to respond to clomiphene treatment. Clomiphene response requires an intact and functional HPO axis, something that most women with hypothalamic amenorrhea do not have (as reflected by low or normal serum FSH levels despite frankly low estrogen production). Consequently, one of two alternative approaches to ovulation induction frequently is required. Exogenous synthetic GnRH, administered in a pulsatile fashion via a portable and programmable infusion pump can effectively restore normal levels of pituitary gonadotropin secretion and spontaneous ovulatory function. GnRH pump therapy requires relatively little monitoring once the effective dose has been established, allows ovulation to occur spontaneously, and is associated with only modest risk of a multiple pregnancy. However, many women object to having an indwelling intravenous catheter over an extended interval of time (approximately 3 weeks) and reject this option.

Most often, treatment with exogenous gonadotropins that directly stimulate ovarian follicular development is the preferred method for ovulation induction. Exogenous human chorionic gonadotropin is administered to trigger ovulation when follicular maturation is complete. Treatment requires careful monitoring with serial determination of serum estrogen concentrations and transvaginal ultrasound examinations to determine the size, number, and maturity of developing follicles and to minimize the risks of excessive follicular development, the ovarian hyperstimulation syndrome, and multifetal gestation.

Hormone replacement therapy is indicated for those women with hypothalamic amenorrhea who do not desire pregnancy and in whom weight gain or decreased exercise fails to restore menstrual function. In those who are simply anovulatory and not frankly hypoestrogenic or at risk for unwanted pregnancy, cyclic progestational therapy may be all that is required to restore predictable menses and to prevent the endometrial consequences of chronic unopposed estrogen stimulation. However, the level of estrogen production in such women often fluctuates unpredictably and is difficult to judge confidently on clinical or laboratory criteria. Consequently, treatment with cyclic or combined continuous hormone replacement or OCP is prudent to prevent any prolonged interval of hypoestrogenism and the depletion of bone mineral that may result. Given that spontaneous ovulation may occasionally occur, sexually active women with hypothalamic amenorrhea who do not desire pregnancy are best managed with OCP.

SUMMARY POINTS

- Amenorrhea is a common symptom resulting from an abnormality in the reproductive system that may be anatomic (developmental or acquired), organic, or endocrinologic in nature.
- Congenital anomalies of the müllerian duct system typically present with normal puberty and may be associated with abdominal pain if there is functional endometrium present.
- Gonadal dysgenesis represents the lack of any ovarian function prior to puberty leading to sexual infantilism.
- Premature ovarian failure presents as amenorrhea associated with an elevated FSH level and, if occurring prior to age 30, may be associated with the presence of a Y chromosome.
- Pituitary tumors are very common, with the majority secreting prolactin and associated with hypoestrogenic amenorrhea and galactorrhea.
- Hypothalamic amenorrhea is the general term used to describe hypoestrogenic amenorrhea when no anatomic abnormality is identified. It is commonly associated with weight loss or athletic stress.
- Polycystic ovarian syndrome is a very common clinical problem which may present with amenorrhea but is associated with excess androgen production. A significant majority of these women have insulin resistance.
- The most common cause of amenorrhea in women of reproductive age is pregnancy.

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Chapter 35

Steve N. London

Abnormal Uterine Bleeding

DIAGNOSIS
Pregnancy
Hormones
Iatrogenic
Mechanical
Infection
Cancer
IMAGING AND SPECIAL STUDIES IN THE MANAGEMENT OF ABNORMAL UTERINE BLEEDING
TVS and SIS in the Evaluation of Abnormal Uterine Bleeding
The Role of MRI in the Evaluation of Women with Abnormal Uterine Bleeding
MANAGEMENT OF SPECIAL SITUATIONS
Acute Hemorrhage
Menorrhagia
Abnormal Bleeding on Oral Contraceptives
Abnormal Bleeding in Perimenopause
SUMMARY POINTS

SUGGESTED READINGS
Diagnosis
Pregnancy
Hormones
Iatrogenic
Mechanical
Infection
Cancer
Imaging and Special Studies in the Management of Abnormal Uterine Bleeding
Management of Special Situations

This chapter presents a simplified diagnostic and therapeutic approach to the woman with abnormal uterine bleeding, discusses imaging studies that facilitate accurate diagnosis and management, and presents therapeutic plans for management of acute hemorrhage, menorrhagia, bleeding on oral contraceptives, and the dysfunctional bleeding associated with perimenopause. This chapter does not address abnormal bleeding in the postmenopausal woman either on or off hormone replacement.

This chapter is divided into three sections: the first is a simplified diagnostic approach with discussion about the differential diagnosis and therapeutic options for each condition. This is followed by section on imaging modalities available to aid in the diagnosis of abnormal uterine bleeding. Special emphasis is placed on the role of pelvic ultrasound, saline infusion sonogram, and magnetic resonance imaging (MRI). The third section presents a therapeutic approach in special clinical situations, including the patient presenting with acute hemorrhage, bleeding on oral contraceptives, menorrhagia, and perimenopause.

DIAGNOSIS

The differential diagnosis for all women presenting with abnormal uterine bleeding can be encompassed by the mnemonic PHIMIC (pregnancy, hormones, iatrogenic, mechanical, infection, and cancer) (Table 35.1). The use of this mnemonic simplifies the approach and allows the clinician to cover a vast array of possibilities in the most efficient and treatment focused manner. This category/group approach provides for patient safety by assuring that serious conditions such as pregnancy, cancer, or unrecognized infections are not overlooked.

P—Pregnancy
H—Hormones
I—Iatrogenic
M—Mechanical
I—Infection
C—Cancer

TABLE 35.1. *PHIMIC—differential diagnosis for abnormal uterine bleeding*

Before evaluating what is abnormal uterine bleeding, we must begin with a definition of what is normal uterine bleeding. Normal menstrual flow is the result of a withdrawal of an estrogen-primed endometrium. This should occur at regular intervals that vary by no more than 3 days from the woman's mean menstrual interval. Typically, normal ovulatory menses occur every 24 to 35 days with most women experiencing a predictable interval. Ovulatory women will set their own mean cycle length, which is defined as from the first day of bleeding, cycle day 1, to the next first day of bleeding in the subsequent cycle and will not vary more than 3 days. For example, if a woman's mean cycle interval is 26 days; her menstrual calendar should reflect menses varying from between 23 and 29 days. A variation greater than 3 days is suggestive of either oligoovulation or estrogenized anovulation and is classified as abnormal. The mean duration of normal menstrual flow is 3 to 7 days. Bleeding that persists longer than 7 days or decreases hemoglobin levels is considered, by definition, excessive. Unfortunately, there is no simple clinical way to quantitate the amount of blood lost during a menstrual period. Counting the number of sanitary protectives used in a menstrual cycle has proven to be inaccurate based on differences in personal hygiene and cultural backgrounds. When accurately quantitated, blood loss during an entire normal ovulatory menstrual cycle is approximately 60 to 80 mL. This amount of blood loss will not cause a decrease in hemoglobin in women consuming a normal balanced diet.

Traditionally, aberrations in menses have been classified as either *menorrhagia*, defined as an excessive amount of menstrual blood loss, *metrorrhagia*, defined as intermenstrual, irregular or otherwise noncyclic bleeding, or *menometrorrhagia*, which combines both menorrhagia and metrorrhagia leading to heavy irregular uterine bleeding (Table 35.2). While these terms are traditionally used they require that the clinician make a cognitive decision based on the patient's description of her symptomatology. This has the potential to alter the ability to make an accurate diagnosis, as the differential diagnosis of a woman with menorrhagia is different than that of metrorrhagia. Since menstrual histories are sometimes difficult to obtain due to the frequent miscommunication between the patient and her physician, limiting the description of the symptomatology to abnormal uterine bleeding without narrowing it to the more scientific term is encouraged. By approaching every woman, irrespective of whether she has menorrhagia, metrorrhagia, or menometrorrhagia with a generalized mnemonic such as PHIMIC, the clinician avoids narrowing the differential diagnosis too quickly, thus assuring that all possibilities are considered. Therefore, when a patient presents with abnormal uterine bleeding, its etiology will be found within one of six broad diagnostic categories: pregnancy, hormonal, iatrogenic, mechanical, infection, or cancer. This allows the same diagnostic approach for every woman, regardless of her age.

Menorrhagia—excessive blood loss at regular intervals
Metrorrhagia—irregular or frequent menses that are not excessive
Menometrorrhagia—excessive irregular bleeding
Polymenorrhea—menses more frequent than 21 days
Hypermenorrhea—excessive menstrual flow
Oligomenorrhea—menses greater than every 34 days

TABLE 35.2. *Definitions*

Pregnancy

Pregnancy should be considered in any woman who presents with abnormal uterine bleeding unless she has had a hysterectomy or is over the age of 60. Even women who have had tubal ligations as well as women who are in their 50s and have not menstruated in 1 to 2 years may have the occasional pregnancy. It is safe, on a clinical basis, to say that a physician will never regret ordering too many pregnancy tests, but may regret not ordering enough.

Screening for pregnancy is typically accomplished by using a highly accurate urinary pregnancy test. It is not necessary to do a serum quantitative human chorionic gonadotropin (hCG) evaluation on every woman who presents with abnormal uterine bleeding. Currently available urinary pregnancy tests are immunometric or “sandwich” assays that use antibodies directed to the intact hCG molecule. This makes the urine pregnancy test extremely sensitive and specific. It is important that every clinician know what the limits are in sensitivity of the pregnancy test and the reference preparation that their practice uses. The two reference preparations currently in use are the First and the Third International Reference preparations. The original reference preparation was the Second International Reference Preparation (2nd-IRP) which measured intact and free ß-hCG subunits. One unit of the 2nd-IRP is approximately equivalent to two units of the first or third IRP.

If the woman with abnormal uterine bleeding is found to have a positive urinary pregnancy test, a serum quantitative ß-hCG assay should be obtained. While this result is pending, it is appropriate to perform a pelvic sonogram to determine whether there is an identifiable intrauterine pregnancy, an adnexal mass, or a negative exam (no pregnancy within the uterus and no adnexal masses). If the ß-hCG returns above the discriminatory zone, then the finding of an empty uterus is suggestive of an ectopic pregnancy and management of ectopic pregnancy can be instituted. If the ß-hCG is below the discriminatory zone and the patient is asymptomatic and reliable, she can return in 48 hours for a repeat ß-hCG assay to determine the probability of a viable intrauterine pregnancy. Upon return, the patient can be rescanned if her ß-hCG is expected to be over the discriminatory zone or a repeat ultrasound can be scheduled based upon the projected time period interval when the level will be anticipated to exceed the discriminatory zone maximum. It is important to remember that 10% to 15% of all ectopic pregnancies have normal ß-hCG doubling times and that rupture of ectopic pregnancies has occurred with falling ß-hCG values. If the level has remained constant or is falling this is suggestive of a nonviable pregnancy, whether in the uterus or in an ectopic location, this can be followed for another 48 hours.

Many pregnancies are lost without being able to determine if it was an early intrauterine loss or a nonviable ectopic pregnancy which resolved without becoming clinically symptomatic.

Hormones

Hormonal disorders that can cause abnormal bleeding can be grouped under four broad categories: coagulation disorders, prolactin disorders, thyroid disorders, and chronic anovulation (Table 35.3). Coagulation disorders are relatively rare. Coagulation disorders are most commonly found in girls who are within 1 year of their first menstrual cycle and have a falling hemoglobin level. Von Willebrand disease needs to be excluded in every adolescent presenting with excessive menstruation (menorrhagia). Women with coagulopathies may present with acute hemorrhage and hypovolemic symptoms. These women almost invariably present with anemia or frank hemorrhage to the emergency department within a short interval after the onset of menstruation. They also need to be evaluated for conditions associated with abnormal bone marrow function or rapid turnover of platelets such as leukemia, idiopathic thrombocytopenic purpura, or aplastic anemia.

1. Coagulation—Von Willibrand, leukemia, idiopathic thrombocytopenic purpura, aplastic anemia
2. Hyperprolactinemia
3. Thyroid disorders
4. Chronic anovulation—hypothalamic, adrenal, polycystic ovarian syndrome (hyperandrogenic anovulation), perimenopause

TABLE 35.3. *Hormonal causes: disorders to consider*

While hyperprolactinemia is a significant cause of abnormal bleeding in women, the prolactin itself is not the direct cause of the abnormal bleeding. The high prolactin levels are the result of alterations in neurotransmitters within the hypothalamus and prolactin down-regulates gonadotropin-releasing hormone (GnRH) secretion resulting in altered gonadotropin release, ovarian dysfunction, and subsequent abnormal uterine bleeding. A prolactin-secreting pituitary adenoma is the most common pituitary tumor in women and should be the first concern of a health care provider when evaluating a patient with an elevated prolactin level. It is reasonable to perform an MRI of the sella turcica in all women with a prolactin level greater than 60 ng/mL. In general, prolactin excess should be treated with bromocriptine if pregnancy is desired. If pregnancy is not desired and the patient has enough endogenous estrogen to prevent osteoporosis, then the prolactin level can simply be followed. Whether or not the woman has enough estrogen to prevent osteoporosis can be determined by the patient's response to progestin administration. If the patient fails to menstruate in response to this progestin challenge then consideration of estrogen replacement or other drug for prevention of osteoporosis is necessary. However, the abnormal bleeding will not resolve unless the prolactin level is returned to normal by treatment with a dopamine agonist such as bromocriptine. Even after the prolactin level has returned to normal there may be enough hypothalamic dysfunction that ovulation induction by other means may be required in women desirous of pregnancy. If the patient has a small microadenoma and desires contraception then oral contraceptives are the treatment of choice. If the patient does not need or desire contraception, cyclic progestin therapy with medroxyprogesterone acetate 10 mg for 14 days every other month can be used.

A woman's lifetime risk of developing thyroid disease is approximately 15% and excess or a deficiency of thyroid hormone can affect a woman's menstrual cycle. The most common disorder is hypothyroidism and approximately two-thirds of women with hypothyroidism will develop an aberration of menses. Any woman who develops abnormal uterine bleeding, postpartum depression, premenstrual syndrome, or depression should be screened for thyroid disease (Table 35.4). The principal screening test for thyroid disease is a measurement of serum thyroid-stimulating hormone (TSH). No further testing is required if the TSH is within normal limits. If the TSH is low this suggests hyperthyroidism and measurement of free thyroxine (T4) and free triiodothyronine (T3) should be performed. If either one is elevated the diagnosis of hyperthyroidism is made. After diagnosing hyperthyroidism, a radioactive iodine uptake scan is performed. If the T4 and T3 are normal a diagnosis of subclinical hyperthyroidism may be entertained. If the TSH is high then a free T4 should be obtained. If the free T4 is low, replacement with synthetic thyroxine is begun. A dose of 25 µg per day of synthetic thyroxine is given and increased every 4 weeks by 25 µg per day until the patient's TSH normalizes and her clinical symptoms have resolved. Menstruation will usually return to normal 8 to 10 weeks after the patient has achieved a euthyroid state.

1. Abnormal uterine bleeding
2. Postpartum blues/depression
3. Premenstrual syndrome
4. Depression

TABLE 35.4. *Thyroid dysfunction: when to screen*

The most common hormonal disorder causing abnormal uterine bleeding is estrogenized anovulation (World Health Organization type II anovulation). Anovulatory bleeding in the past has been described as dysfunctional uterine bleeding. Dysfunctional uterine bleeding refers to bleeding unrelated to mechanical factors, iatrogenic causes, infectious agents, cancer, or pregnancy. There is no one particular pattern of bleeding that unequivocally defines dysfunctional uterine bleeding. A woman may present with anything from complete secondary amenorrhea to frank hemorrhage. Therefore, characterizing the menstrual flow is of no diagnostic advantage.

Syndromes of chronic anovulation can be grouped etiologically as either hypothalamic (central nervous system), adrenal (adrenal androgen production), ovarian (polycystic ovarian syndrome; PCOS), or perimenopausal in origin. None of these groups have a clear-cut laboratory profile and a precise classification often proves difficult. PCOS is one of the more confusing causes of chronic anovulation. The exact etiology of this syndrome remains elusive, although a large percentage of women with PCOS have been noted to have hyperinsulinemia secondary to insulin resistance. The National Institutes of Health (NIH) consensus conference has defined PCOS as amenorrhea or oligoovulation with clinical or biochemical evidence of hyperandrogenemia. While many authorities have frequently found insulin resistance in women with PCOS, there currently is no practical and reliable method to clinically diagnose insulin resistance. The use of insulin sensitizers in this group, despite being somewhat controversial, is enjoying widespread use, primarily for women desirous of pregnancy. Because of the controversy in the use of insulin sensitizers in the treatment of the abnormal uterine bleeding associated with PCOS, it is best to treat these patients with cyclic progestin, oral contraceptives, or clomiphene citrate if pregnancy is desired and reserve insulin sensitizers for those women in whom clomiphene citrate has failed and who want to become pregnant.

Another common hormonal cause of anovulatory uterine bleeding is the perimenopausal transition. Most women experience a 5- to 8-year transition from regular menstrual cycles to frank amenorrhea with an interval of abnormal uterine bleeding in between. This interval is marked by intervals of hypoestrogenism with symptoms such as hot flashes, irritability, and some vaginal atrophy, alternating with intervals of estrogenized anovulation. Usually the first sign of the perimenopausal transition is a shortening of the menstrual cycle accompanied by an increase in premenstrual symptomatology. Women over the age of 35 who present with a change in their mean menstrual cycle interval irrespective of other symptomatology who desire future childbearing should be screened for impending ovarian failure with a day 3 follicle-stimulating hormone (FSH) level. There are two therapeutic options for women with abnormal bleeding in the perimenopausal transition. The first is the cyclic administration of progestins. Typically, this is accomplished by the administration of 10 mg of medroxyprogesterone acetate for 14 days each month or every other

month. This therapy may be associated with intermenstrual bleeding and occasionally may precipitate premenstrual symptoms. There is no place for the use of injectable progestins in the management of perimenopausal bleeding. The best choice to control abnormal bleeding in the perimenopausal transition, if the patient is a healthy nonsmoking woman, is the use of continuous combined oral contraceptives. The use of oral contraceptives in perimenopause will ease the transition by enforcing regular menstrual shedding, decrease blood loss, reduce premenstrual symptoms, preserve bone mass, and reduce the lifetime risks of endometrial and ovarian cancers without increasing the risk of breast cancer. The use of hormone replacement therapy, as used in frankly menopausal women, is to be discouraged as this provides additional estrogen and progestin without suppressing the endogenous production and thus increases the total amount of sex steroid exposure to the uterus.

Iatrogenic

Iatrogenic causes of abnormal uterine bleeding appear to be increasing as many drugs used for cancer, renal disease, and transplantation either mimic or modify endogenous hormones and cause abnormal uterine bleeding. Every woman presenting with a change in her menstrual cycle requires that a careful history be taken with respect to her general health as well as use of any prescription or over-the-counter medications. The physician should inquire about drugs prescribed within the past 6 months even if the patient is not currently taking any medications (Table 35.5). Drugs that can effect the menstrual cycle include prednisone, tamoxifen, coumadin, heparin, and Depo-Provera.

1. Prednisone
2. Tamoxifen
3. Coumadin
4. Heparin
5. Depo-Provera

TABLE 35.5. *Drugs associated with abnormal uterine bleeding*

Mechanical

Uterine leiomyomata are one of the most common causes of abnormal uterine bleeding and one of the leading causes of hysterectomy in the United States. Approximately one fourth of all women have uterine leiomyomata, but fortunately only a small fraction of that number will be clinically symptomatic and come to medical attention. Submucous or intracavitary myomas most commonly cause abnormal uterine bleeding. Submucous myomas may cause bleeding by frank erosion and ulceration of the endometrial surface, and intracavitary myomas prevent the normal hemostatic mechanisms required to stop normal menstruation. An intramural myoma may cause bleeding by creating large venous lakes and preventing the uterus from appropriately constricting blood vessels supplying the endometrium at the time of menstruation (Fig. 35.1). Bleeding from a myoma can vary from frank hemorrhage to slight intermenstrual spotting. Uterine leiomyomata are estrogen-dependent. Therefore, any agent that blocks estrogen's biosynthesis or action could theoretically cause regression of myoma. Currently, there is no medical therapy that truly causes regression of leiomyomata. GnRH agonists block gonadotropin secretion resulting in hypoestrogenism and, hence, cause a reduction in the size of the estrogen-dependent muscle cells within the myoma. However, there is rapid return of myoma volume and symptomatology once the GnRH agonist is discontinued and estrogen production by the ovary resumes. RU-486 and other antiprogesterone drugs have been shown to shrink myomas in clinical trials. The long-term effect of these agents on leiomyomata however is unknown. Depo-Provera is often effective in reducing the amount of abnormal bleeding and may even cause some regression in myoma size. Oral contraceptive agents do not cause regression of the myoma but they may stabilize the endometrium enough to effectively control the abnormal bleeding associated with uterine myoma. It is very reasonable to make an attempt to control abnormal uterine bleeding with a trial of oral contraceptive agents in women with leiomyomata before attempting more expensive and hazardous therapies. Despite the use of oral contraceptives, the abnormal bleeding in many women will not be controlled or they may not want to take oral contraceptives on a continuous basis. It is reasonable to consider a hysterectomy or a uterus-sparing operation such as myomectomy when more conservative medical methods have proven unsuccessful. There is not enough outcome evidence in the literature to recommend one surgical approach over the other. Until more data are available, management of uterine leiomyomata will remain empirical.

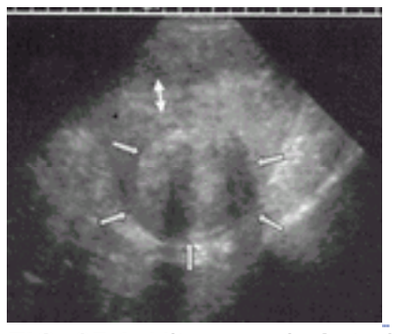

FIG. 35.1. Ultrasound of uterine leiomyoma. This is a transvaginal ultrasound in a woman who has an intramural myoma (*arrows*). The myoma clearly does not impinge on the endometrial cavity with intervening myometrium. The endometrial stripe is defined by a *double arrow.*

Endometrial polyps are found in up to 50% of women presenting with abnormal uterine bleeding. There is no precise etiology for the formation of these polyps but they clearly originate from the endometrium. Detecting polyps can often be difficult. Endometrial polyps are best diagnosed by either hysteroscopy (Fig. 35.2) or saline infusion sonogram (SIS). The SIS is extremely sensitive but may overdiagnose the polyps. It is not uncommon at the time of hysteroscopy and dilation and curettage (D&C) for removal of the polyps diagnosed by SIS to find none present. Additionally, many small polyps will regress spontaneously. Since small polyps are found in asymptomatic women, the role of small endometrial polyps in a woman complaining of abnormal uterine bleeding is unknown.

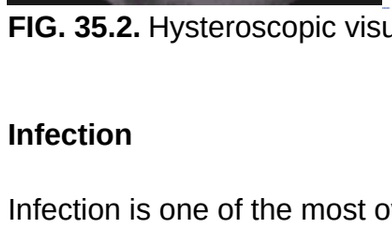

FIG. 35.2. Hysteroscopic visualization of an endometrial polyp. An endometrial polyp is present on the anterior fundal aspect of the endometrial cavity (*arrow*).

Infection

Infection is one of the most overlooked causes of abnormal uterine bleeding. Historically, endometritis has been considered a cause of abnormal uterine bleeding, despite a paucity of evidence in the literature. Endometritis is diagnosed by the finding of an increased number of plasma cells on endometrial biopsy. Culture of the endometrial cavity is not clinically useful and is complicated by the high rate of contamination by vaginal organisms. Studies have failed to show any significant endometrial infection associated with abnormal uterine bleeding. The absence of culture-positive studies and the subjective diagnostic criteria used casts doubt whether chronic endometritis truly causes abnormal uterine bleeding. However, endocervicitis is a known cause of abnormal bleeding, particularly intermenstrual and postcoital bleeding. It is appropriate for women with abnormal bleeding to have cultures or DNA probe tests performed for chlamydia and gonorrhea to rule out those organisms as a cause. Due to the false-negative rate of these diagnostic procedures it is often prudent to treat empirically for chlamydia, if no other cause is found.

Cancer

Endometrial and cervical cancers are uncommon yet important causes of abnormal uterine bleeding. Cervical cancer often presents with postcoital bleeding or irregular menstruation. Even if the patient has a normal Pap smear within the previous year it is prudent to repeat the smear, particularly if the patient has other risk factors for cervical cancer. Endometrial cancer remains a possibility in any woman presenting with abnormal uterine bleeding and endometrial biopsy should be performed in all

women over the age of 35, the age at which the incidence begins to rise. Therapy will depend upon the staging of the disease. Complex endometrial hyperplasia with atypia is usually managed by simple hysterectomy. Other forms of hyperplasia may be safely managed with cyclic or continuous high-dose progestin therapy. If cyclic progestin is chosen, the minimum effective dose is 10 mg of medroxyprogesterone acetate for 14 days each month. Continuous progestin therapy is usually 20 to 40 mg of medroxyprogesterone acetate daily for 90 days. The use of a test-of-cure endometrial biopsy or hysteroscopy with curettage is controversial. However, it is reassuring to the patient and physician to document regression and uncover the rare progesterone receptor–negative hyperplasia.

IMAGING AND SPECIAL STUDIES IN THE MANAGEMENT OF ABNORMAL UTERINE BLEEDING

A transvaginal sonogram (TVS) has become an integral component of the evaluation of women with abnormal uterine bleeding. This is true even if the patient has a normal pelvic exam as the sonogram is focusing on the internal architecture of the uterus not necessarily the overall size. The use of TVS identifies small myoma, adenomyosis, and excessive endometrial thickness. The presence of these factors requires further evaluation with either biopsy or SIS. While TVS is necessary even if the patient has a normal pelvic exam, the TVS does not replace the health care provider performing a thorough and careful pelvic exam.

TVS and SIS in the Evaluation of Abnormal Uterine Bleeding

Hysteroscopy and D&C are not often used as primary diagnostic and therapeutic modalities. While office hysteroscopy does not require anesthesia, the procedure is expensive and requires an experienced operator as compared to TVS and endometrial biopsy. TVS allows acoustic visualization of the endometrium, ovaries, and the myometrium, which is more information than obtained by hysteroscopy. TVS is very sensitive for identification of leiomyomata that are greater 2 cm in diameter. TVS also has the ability to identify adenomyosis and endometrial polyps but its sensitivity and specificity for these conditions is lower. TVS has a 60% sensitivity and a 93% specificity for identifying pathology within the endometrial cavity. Still, TVS should be the first- line diagnostic modality when evaluating disorders of the myometrium and endometrium because of its simplicity and lack of risk. The sensitivity and specificity of TVS can be enhanced with the infusion of saline creating an SIS. Many other names have been used for this procedure including hydrosonogram, sonohysterosalpingography, and saline hysterosonography. No consensus for the appropriate terminology has been reached, but “saline infusion sonography” appears to be gaining acceptance due to its acronym SIS, which avoids confusion with old acronyms of HSG for hysterosalpingogram.

The endometrial thickness in women of reproductive age varies greatly. Still, it should be measured to enhance the sensitivity of TVS in predicting intrauterine pathology. When the endometrial thickness is greater than 8 mm consideration should be given to SIS. The accuracy and precision of SIS can be further enhanced with the addition of an endometrial biopsy. One study has suggested the sensitivity and specificity for the detection of intrauterine pathology at 97% and 70%, respectively, and a positive and negative predictive value of 82% and 94% compared with hysteroscopy/D&C or hysterectomy. Therefore, the use of endometrial biopsy and SIS to identify intrauterine pathology has displaced hysteroscopy and D&C as the primary procedure in the evaluation of abnormal uterine bleeding. Even though surgical evaluation is now a second-line procedure, the health care provider must still remember that hysteoscopy with curettage is more accurate than the less invasive office-based procedures and still has a place in the diagnosis and management of the patient with abnormal uterine bleeding.

The Role of MRI in the Evaluation of Women with Abnormal Uterine Bleeding

With the development of new high-field strength magnets the evaluation of the uterus by MRI has become much quicker and accurate. MRI has the advantage over computed tomography (CT) by not being limited by the surrounding bony structures. Compared to TVS, the MRI is less dependent on operator experience, uterine position, and size. The uterus on MRI is best seen on the T2 weighted sequence. Three regions within the uterus are normally identified: a central bright area that corresponds to the endometrium, another area of intermediate signal intensity that corresponds to the myometrium, and a third layer between the endometrium and myometrium that is hormonally sensitive and termed the *junctional zone.* The thickness signal characteristics of these three areas are evaluated independently when looking for uterine pathology. The greatest advantage of MRI is its ability to distinguish between adenomyosis and uterine leiomyomata. While both of these conditions can cause pelvic pain, typically increasing dysmenorrhea as well as abnormal bleeding, there are patients who desire future fertility or for other reasons desire to preserve their uterus and the conservative operations are different for each condition. The MRI image has a sensitivity of 86% and a positive predictive value of 65% in detecting the presence of adenomyosis when junctional zone thickening is greater than 12 mm. The MRI can also be used to determine whether the adenomyosis is diffuse or superficial. If the adenomyosis is superficial it can successfully be treated with roller-ball endometrial ablation, whereas deep adenomyosis is best treated by hysterectomy. Additionally, the MRI has the ability to accurately define myoma less than 2 cm, the limit of TVS. This is important for women undergoing in vitro fertilization. MRI is becoming an efficient and cost-effective complementary tool and may soon supplant hysteroscopy as the second-line diagnostic modality in abnormal uterine bleeding.

MANAGEMENT OF SPECIAL SITUATIONS

Acute Hemorrhage

It is not uncommon for women with chronic anovulation or uterine leiomyomata to present to the emergency department with acute hemorrhage and symptoms of hypovolemia. These patients need rapid control of their hemorrhage and a clinical decision has to be made quickly as to whether to proceed to the operating room or to make an attempt at medical control. If the patient is hemodynamically unstable, a D&C is indicated as it will result in immediate cessation of the bleeding and allow time for transfusion and correction of the underlying pathology. If the patient is stable enough to attempt medical management, fluid resuscitation is begun. Blood products are then given as necessary and high-dose parenteral estrogen therapy initiated. The high dose of estrogen will initiate endometrial proliferation and increase fibrinogen as well as factors V and IX, but most important, it promotes platelet aggregation and clotting at the capillary level. It is appropriate to use i.v. estrogen even when the patient has uterine leiomyomata. Both i.v. and p.o. estrogen work equally as well but the parenteral route is usually chosen if the clinical situation requires rapid cessation of the blood loss. Intravenous conjugated estrogen is given 25 mg every 4 hours until the bleeding stops. The oral regimen is equally efficacious and consists of 2.5 mg conjugated estrogen or 2 mg of micronized estradiol every 4 hours for 24 hours followed by a single daily dose for 7 to 10 days. If the bleeding persists for more than 12 to 24 hours with either one of these regimens, a D&C is indicated. Whether the estrogen is given i.v. or p.o., a progestin should be started at the same time and continued for 5 to 7 days at which time the patient should expect a withdraw bleed. If the patient is not having acute hemorrhage but rather is having heavy menstrual flow and becoming anemic then the use of high-dose oral contraceptives may be considered. In these cases the patient is given 4 pills containing 30 to 35 µg of ethinyl estradiol for 4 days followed by 3 pills for 7 days followed by 2 pills for 11 days then 1 pill a day thereafter. Hysterectomy should be considered in women who have completed childbearing and when medical management has failed.

Menorrhagia

Menorrhagia affects approximately 15% to 20% of women presenting with abnormal uterine bleeding and causes significant social inconvenience as well as the potential for significant anemia. The first line of therapy for the treatment of women with menorrhagia is antiprostaglandin agents, the cyclooxygenase inhibitors or nonsteroidal antiinflammatory drugs (NSAIDs). Women with menorrhagia have significantly higher levels of prostaglandin E (PGE) when compared to prostaglandin F_{2a}. The antiprostaglandin agents affect the balance between PGE and thromboxane. Many prospective trials have shown use of NSAIDs beginning on the day of menstruation and continued throughout menses significantly decrease blood loss. The use of the cyclooxygenase-1 (COX-1) class of agents is contraindicated in women with peptic ulcer disease, asthma, and allergy to aspirin. Numerous regimens have been used all with similar efficacy: mefenamic acid 500 mg t.i.d., ibuprofen 400 mg t.i.d., and naproxen sodium 275 mg q6h after a loading dose of 550 mg. All these regimens have demonstrated a significant decrease in blood loss. The newer COX-2 inhibitors have markedly fewer problems and inhibit the same COX enzyme, but have not been tested in clinical trials. They may improve the overall success of this approach with fewer side effects.

Another strategy, using the levonorgestrel intrauterine device (IUD), has recently been introduced. Several controlled trials have shown that its use significantly decreases the amount of menstrual blood lost per cycle by causing an intense atrophy of the endometrium. The levonorgestrel IUD should be considered in any woman who needs contraception and who is experiencing menorrhagia. If these therapies fail to control the problem, oral contraceptives can also be considered. Surgical therapy should be considered when medical management has failed or is medically contraindicated. Surgical therapy consists of either endometrial ablation or hysterectomy. Endometrial ablation by any technique is reported to provide 90% to 95% patient satisfaction, with amenorrhea being achieved in approximately 50% of patients. Unfortunately, the long-term problems associated with endometrial ablation are not known. With regard to hormone therapy after menopause, the patient having endometrial ablation must be regarded as having fully responsive endometrium. There is a theoretical risk of concealed endometrial cancer, but this has not been reported to date. Hysterectomy results in amenorrhea 100% of the time and has a higher patient satisfaction rate than endometrial resection 2 years after the procedure.

Abnormal Bleeding on Oral Contraceptives

Abnormal bleeding on oral contraceptives is usually due to an insufficient amount of estrogen in a particular pill to stabilize the endometrium. Strategies to control the bleeding involve increasing the estrogen content of the pill, changing to a different birth control pill which increases the estrogen/progestin ratio, or giving supplemental estrogen. Since most noncompliance with oral contraceptives is related to the progestin content and if a patient is comfortable with the side effects in her particular pill, an attempt should be made to continue with that level of progestin and add supplemental estrogen, either 1.25 mg conjugated estrogen or 2 mg of estradiol starting at

the time the patient bleeds and continuing for 7 days. This regimen is repeated at the same time for two consecutive months whether or not the patient has spotting in the two subsequent cycles.

Alternatively, the patient can simply use a pill with a higher estrogen/progestin ratio or a higher-dose estrogen pill to determine if that will be sufficient to control the bleeding. If the patient fails to respond to these regimens then other factors need to be assessed. Abnormal bleeding on pills is significantly increased in women who smoke, due to enhanced estrogen clearance, and when taking antibiotics because of alterations in absorption. All efforts should be made to have the patient stop smoking. Additionally, cultures or DNA probe for chlamydia should be obtained as endocervicitis-related chlamydia is a significant cause of abnormal bleeding in women on birth control pills.

Abnormal Bleeding in Perimenopause

The most common cause of abnormal uterine bleeding in the perimenopausal woman is estrogenized anovulation. Still, every woman in this category needs a complete evaluation as detailed earlier in this chapter, particularly as they are now in the age range where the incidence of endometrial cancer is beginning to be significant. Attributing the abnormal uterine bleeding to the perimenopausal transition is a diagnosis of exclusion and can only be made after a through evaluation. Therapy with oral contraceptives should be initiated provided the patient has no contraindication to their use, primarily smoking. Oral contraceptives have been shown to decrease the amount of blood loss associated with menstruation providing cycle regulation and relief from menorrhagia. Additionally, oral contraceptive agents preserve bone mass during a time when occult bone loss may be occurring. Most significantly, oral contraceptive agents provide reduction in the risk of endometrial and ovarian cancer for 10 to 15 years following their discontinuation. Every effort should be made to encourage the use of oral contraceptives in all perimenopausal woman.

SUMMARY POINTS

- Use of the mnemonic PHIMIC (pregnancy, hormones, iatrogenic, mechanical, infection, and cancer) offers a simplified yet complete approach to the evaluation of abnormal uterine bleeding. Patients presenting with abnormal uterine bleeding should have a pregnancy test, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, Pap smear, DNA probe for gonorrhea and chlamydia, and a transvaginal ultrasound.
- Estrogenized anovulation is the most common cause of abnormal uterine bleeding. Anovulation may be caused by a variety of conditions, including elevated prolactin, hyper- or hypothyroidism, adrenal disorders, and polycystic ovarian syndrome (hyperandrogenic anovulation).
- Von Willebrand disease should be considered in any young woman experiencing menorrhagia within 1 year of menarche.
- No therapeutic advantage of intravenous estrogen over oral estrogen in the control of acute hemorrhage is known.
- Saline infusion sonography and endometrial biopsy, when performed together, have a 97% sensitivity and 70% specificity in determining intrauterine pathology.
- MRI can reliably differentiate between deep and superficial adenomyosis. MRI can accurately identify leiomyomata less that 2 cm in size and determine their location.

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Chapter 36

Robert L. Reid

Premenstrual Syndrome

MOLIMINA, PREMENSTRUAL SYNDROME (PMS), AND PREMENSTRUAL DYSPHORIC DISORDER (PMDD)
Diagnosis
Etiology
Therapy
Medical Interventions

SUGGESTED READINGS
Introduction, Diagnosis, and Etiology
Therapy: Education, Counseling, and Lifestyle Modification
Antidepressant Therapy
Medical Ovarian Suppression
Surgical Therapy

MOLIMINA, PREMENSTRUAL SYNDROME (PMS), AND PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

During the reproductive years, up to 80% to 90% of menstruating women will experience symptoms (breast pain, bloating, acne, constipation) that forewarn them of impending menstruation, so-called *molimina*. Available data suggest that as many as 30% to 40% of these women are sufficiently bothered by such molimina that they would seek relief if it were readily accessible, simple, and safe. Since the term *premenstrual syndrome*, or *PMS*, has become so ingrained in lay culture most women describe the symptoms of molimina as PMS. However moliminal symptoms show a variable association with the more severe psychological symptoms typically required to meet research diagnostic criteria for PMS.

Researchers in the field have argued that the term *PMS* should be reserved for a more severe constellation of symptoms that affects closer to 5% of women during their reproductive years. To capture the true severity of PMS in this population, the definition describes not only the symptoms but also their functional impact. PMS has been defined as “the cyclic recurrence in the luteal phase of the menstrual cycle of a combination of distressing physical, psychological, and/or behavioral changes of sufficient severity to result in deterioration of interpersonal relationships and/or interference with normal activities.”

The American Psychiatric Association, following years of debate about whether to include PMS in their *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, included as an appendix (meaning that the subject requires further study) a condition labeled *premenstrual dysphoric disorder (PMDD)* (Table 36.1). Such a designation was intended to alert physicians to a combination of specific severe symptoms (mostly psychiatric in nature) that could mimic other psychiatric disorders with the exception that the symptoms recurred in the premenstrual phase of the menstrual cycle.

1. Timing of symptoms
   Symptoms are present during the last week of the luteal phase, remit within the first few days of menses, and are absent during the week following menses. The symptoms occur during most, if not all, menstrual cycles.
2. Symptoms
   At least five symptoms are required, including at least one of the first four symptoms:
   - Markedly depressed mood
   - Marked anxiety
   - Marked affective lability
   - Persistent and marked anger
   - Decreased interest in usual activities
   - Lethargy
   - Marked change in appetite
   - Hypersomnia or insomnia
   - A sense of being overwhelmed or out of control
   - Physical symptoms
3. Severity
   The symptoms markedly interfere with work, school, social activities, and relationships with others.
4. Other disorders
   Rule out that the disorder is not merely an exacerbation of a major affective, panic dysthmic, or personality disorder, although PMDD can be superimposed upon any of these disorders.
5. Confirmation of the disorder
   The above criteria must be confirmed by prospective daily self ratings for two consecutive menstrual cycles.

Source: Adapted from American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV). Washington, DC, 1994.

TABLE 36.1. *Diagnostic criteria for premenstrual dysphoric disorder (PMDD)*

Diagnosis

History and Charting A typical woman suffering from PMS may describe herself as a well-adjusted person for most of the month who is productive at work and in other endeavors, and, if she has children, a good mother. However starting 7 to 10 days prior to menstruation she awakes in the morning with feelings of anger, anxiety, or sadness. At work she may have difficulty concentrating on the tasks at hand and she may overreact to otherwise typical actions of co-workers, friends, partner, or children. She feels depressed but she cannot understand why because she typically enjoys life and is happy with most of its aspects. Occasionally depression, anger and aggression, or anxiety may be extreme and result in concerns for the welfare of the affected woman or those around her. A “black and white” diagnostic cutoff for determining if someone suffers from PMS is not presently possible. Although many women report feeling bloated and irritable before menstruation, further questioning usually reveals that these symptoms have little substantive impact on their lives. In part, the distinction between troublesome premenstrual moliminal symptoms and PMS may have to do with the duration and severity of symptoms. Particularly in the first few years after symptoms appear, the severity of PMS may vary dramatically from month to month. The nature of symptoms and their functional impact is best established by self-report using a prospective calendar record. Any calendar used for this purpose must obtain information on four key areas: specific symptoms, severity, timing in relation to the menstrual cycle, and baseline level of symptoms in the follicular phase. Retrospective accounts about symptoms often fail to provide critical information on timing of symptoms or baseline level of symptoms during the follicular phase of the cycle. For example, many individuals with underlying psychiatric disease will experience premenstrual exacerbation of their symptoms. They will recall the severe symptoms prior to menstruation and may give a history that sounds typical for PMS. However when they complete a 2-month calendar record it usually becomes apparent that symptoms are present all the time and are at their worst premenstrually. This has been termed “premenstrual magnification” of an underlying psychiatric disorder. Typically PMS symptoms appear after ovulation, worsen progressively leading up to menstruation, and are relieved at varying rates after onset of menstruation. In some women there is almost immediate relief from psychiatric symptoms with the onset of bleeding while for others the return to normal is more gradual. The most severely affected women report symptoms beginning shortly after ovulation (2 weeks before menstruation) and resolving at the end of menstruation. Such individuals typically report having only one “good week” per month. If this pattern is longstanding then it becomes increasingly difficult for interpersonal relationships to rebound during the good week with the result that symptoms may start to take on the appearance of a chronic mood disorder. (Whenever charting leaves the diagnosis in doubt, a 3-month trial of medical ovarian suppression [discussed later in the chapter] will usually provide a definitive answer.) About 5% to 10% of women who suffer from PMS experience a brief burst of symptoms (coincident with the midcycle fall in estradiol that accompanies ovulation) with a return to normal until later in the luteal phase when symptoms recur (Fig. 36.1). The different patterns of PMS symptoms are shown in Figure 36.2.

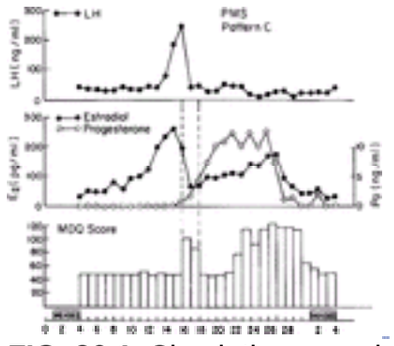

FIG. 36.1. Circulating gonadotropin, estradiol, and progesterone concentrations correlated to symptom severity in a woman with midcycle and premenstrual syndrome (PMS) symptoms—so-called pattern C PMS. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Female Reproductive Endocrinology. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

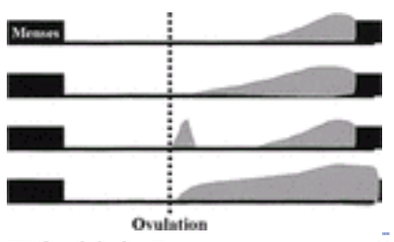

FIG. 36.2. Four common patterns of premenstrual syndrome symptomatology in relation to the menstrual cycle. Note that in every case symptoms commence after ovulation. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

Information should be sought about stresses related to the woman's occupation and personal life as these may tend to exacerbate PMS. Past medical and psychiatric diagnoses may be relevant in that a variety of medical and psychiatric disorders may show premenstrual exacerbation. A prospective symptom record should usually be maintained for a minimum of two complete cycles prior to establishing a diagnosis since an unfavorable life event occurring during the follicular phase of a single month could give the erroneous impression that symptoms were continuously present. Key components of a prospective symptom record are listed in Table 36.2.

1. Daily listing of symptoms
2. Ratings of symptom severity throughout the month
3. Timing of symptoms in relation to menstruation
4. Rating of baseline symptom severity during the follicular phase

TABLE 36.2. *Key elements of a prospective symptom record used for the diagnosis of premenstrual syndrome*

One example of such a calendar record, the PRISM calendar (prospective record of the impact and severity of menstrual symptoms) (Fig. 36.3) allows rapid visual confirmation of the nature, timing, and severity of menstrual cycle–related symptomatology and at the same time provides information on life stressors and use of PMS therapies. Although symptoms are rated in severity on a scale from 1 to 3, the actual interpretation of the calendar requires no mathematical calculations. An arm's length assessment of the month-long calendar usually allows a rapid distinction to be made between PMS and other more chronic conditions (Fig. 36.4).

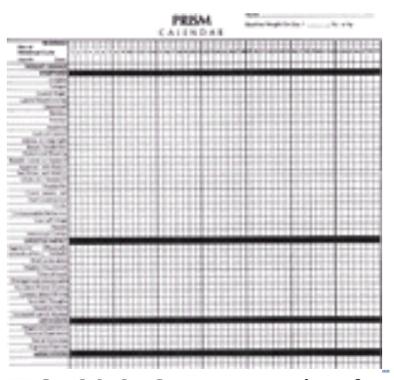

FIG. 36.3. One example of a prospective record of the impact and severity of menstrual symptoms—the PRISM calendar. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

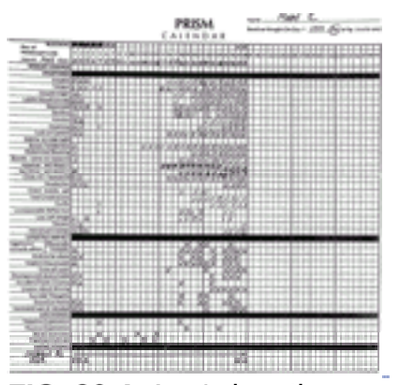

FIG. 36.4. Arm's length assessment of a completed PRISM (prospective record of the impact and severity of menstrual symptoms) calendar reveals a pattern of symptoms consistent with premenstrual syndrome. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

Physical Findings History should usually be accompanied by physical and gynecologic exam since many women with apparent PMS may have coexisting medical conditions. The summation of premenstrual and menstrual symptoms often determines the overall experience of women who suffer from PMS and therapy directed at gynecologic disorders such as dysmenorrhea (associated with endometriosis) or heavy flow (associated with fibroids) can dramatically reduce the perceived severity of PMS. Organic causes of PMS-like symptoms must be ruled out. Marked fatigue may result from anemia, leukemia, hypothyroidism, or diuretic-induced potassium deficiency. Headaches may be due to intracranial lesions. Women attending PMS clinics have been found to have brain tumors, anemia, leukemia, thyroid dysfunction, gastrointestinal disorders, pelvic tumors including endometriosis, and other recurrent premenstrual phenomena such as arthritis, asthma, epilepsy, and pneumothorax. Efforts to rule out such causes for premenstrual distress are important before choosing any PMS therapy.
Blood Tests Contrary to some claims there is no blood test that will establish a diagnosis of PMS. Blood work is only helpful to rule out conditions such as anemia, leukemia, or thyroid dysfunction.

Etiology

Many theories have attempted to explain the diverse manifestations of PMS but until recently no single theory has received widespread acceptance. Many of the early theories lacked biologic plausibility and appeared to have emerged as a means to market specific therapeutic products (Table 36.3). More recently a theory that links gonadal steroid levels and central serotonergic activity has started to emerge.

TABLE 36.3. *List of proposed etiologies for premenstrual syndrome*

The current consensus seems to be that in some predisposed women normal fluctuations in the gonadal hormones estrogen and progesterone trigger central biochemical events related to PMS symptomatology. Of all the neurotransmitters studied to date, serotonin seems to be the most promising central target. It is likely that serotonin levels dip premenstrually in most women and that susceptible individuals will show varying degrees of psychiatric symptomatology. Many women report a menstrual or immediate postmenstrual state of mental well-being (sometimes bordering on euphoria) that may reflect a rebound surge of serotonin activity. The theoretic effects of gonadal hormones on serotonin activity (Fig. 36.5) form the basis for most of the current interventions for PMS and PMDD.

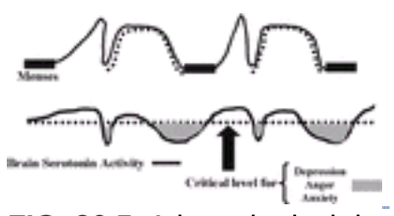

FIG. 36.5. A hypothetical depiction of the interrelationship between gonadal steroid fluctuations and central changes in serotonin activity to explain the timing of symptoms in premenstrual syndrome. When serotonin levels or activity fall below an arbitrary level (that may be influenced by stress, heredity, or other factors) symptoms of anger, anxiety, or depression may emerge. (From Reid RL. Premenstrual syndrome. Solid line, estrogen; dotted line, progesterone. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

Several lines of evidence from clinical medicine support this interrelationship between estrogen or lack of estrogen effect (perhaps mediated by progestin-induced depletion of estrogen receptors) and central serotonergic activity. The midcycle appearance of PMS symptoms in women with pattern C PMS coincides with the periovulatory fall in estradiol, whereas the reappearance and ever-increasing severity of symptoms in the late luteal phase may result from progesterone-induced depletion of central estrogen receptors coincident with the decline of estradiol leading up to menstruation (see Fig. 36.1). Estrogen has been shown to alleviate clinical depression in hypoestrogenic perimenopausal women in double-blind clinical trials. The addition of sequential progestin therapy to estrogen replacement triggers characteristic PMS-like mood disturbance in some susceptible postmenopausal women. Anti-estrogens given for ovulation induction may, at times, provoke profound mood disruption. Women with premenstrual syndrome show a surprisingly high frequency of premenstrual and menstrual hot flashes (85% of those with PMS vs. 15% of non-PMS controls) that are typical of those experienced by menopausal women. Selective serotonin reuptake inhibitors (SSRIs) have been shown to relieve hot flashes in breast cancer survivors made menopausal by chemotherapy. In each of these circumstances, a decrease in exposure to estrogen has been linked to mood disturbance and in each case a decrease in serotonin activity (inferred from the response to SSRIs) appears to be the proximate cause.

Therapy

Education and Counseling Women who present with severe premenstrual complaints often benefit from reassurance that they are not “losing their minds” and that PMS is a real condition that affects many women of reproductive age. Reassurance that, although we do not yet have all the answers about PMS, we have available a range of very effective therapies is equally important information. The prospective documentation of symptoms is as much a part of therapy as it is the key to diagnosis (see Table 36.1). The very use of a calendar record (listing the range of PMS symptoms) may provide much needed reassurance that other women experience similar symptoms. The completed chart may demonstrate to the patient for the first time the cyclicity of her symptoms supporting a clear link to hormonal shifts of the menstrual cycle. While it is useful for women with PMS to learn to anticipate times in the month when vulnerability to emotional upset and confrontation may be greatest, the strategy of making important decisions “only on the good days,” as espoused in some PMS clinics, falls apart if premenstrual symptoms last for more than just a few days per month. For some women premenstrual symptoms may last for a full 3 weeks and advising them to restrict their important activities to the remaining days of the month is neither helpful nor warranted. Interventions aimed at reducing symptoms are more appropriate in this circumstance.

Lifestyle Modification

Communication Strategies When an individual is suffering to a degree that requires more than simple counseling and reassurance, measures aimed at lifestyle modification should first be explored. Women with such symptoms should be encouraged to discuss the problem with those individuals who are central to their life including partner, other family members, or friends. Often confrontations can be avoided if an understanding partner or friend recognizes the cause for a woman's upset and defers discussion of the controversial subject until another time. Strategies for stress reduction can be helpful. Communication skills and assertiveness may be improved with counseling. Group counseling in a program supervised by a clinical psychologist may be invaluable.

Diet While there have been many books written describing specific “PMS diets” few of the recommendations contained therein are based on scientific fact. Several simple dietary measures may afford relief for women with PMS. Reduction of the intake of salt and refined carbohydrates may help prevent edema and swelling in some women. Although a link between methylxanthine intake and premenstrual breast pain has been suggested, available data are not convincing. Nevertheless, a reduction in the intake of caffeine may prove useful in women where tension, anxiety, and insomnia predominate. Anecdotal evidence suggests that small, more frequent meals may occasionally alleviate mood swings. Based on evidence that cellular uptake of glucose may be impaired premenstrually, there is, at least, some theoretic basis for this dietary recommendation. Several lines of evidence indicate that there is a tendency toward increased consumption of alcohol premenstrually and women should be cautioned that excessive use of alcohol is frequently an antecedent factor in relationship discord. Calcium supplementation to reduce symptoms has been shown to be marginally superior to placebo in a randomized placebo-controlled trial.

Exercise Exercise is reported to reduce premenstrual molimina in women running in excess of 50 km per cycle. The effects of exercise in women with well-characterized PMS have not been rigorously evaluated. As part of an overall program of lifestyle modification, exercise may reduce stress by providing a time away from the home and by providing a useful outlet for any anger or aggression. Some women who suffer from PMS report that exercise promotes relaxation and helps them sleep at night.

Medical Interventions

The primary factor directing the selection of therapy should be the intensity and impact of premenstrual symptoms. Symptoms that are causing major disruption to quality of life rarely respond to lifestyle modification alone and efforts to push this approach often do nothing more than delay effective therapy. Conversely, minor symptoms or symptoms that are short-lived each month seldom justify major medical interventions.

Attention should always initially be directed to symptoms for which simple, established treatments exist. For example, dysmenorrhea or menorrhagia may be satisfactorily relieved with prostaglandin synthetase inhibitors or oral contraceptives.

Mefenamic acid (500 mg t.i.d.) in the premenstrual and menstrual weeks has outperformed placebo for the treatment of PMS in some, but not all, clinical trials. It is likely that many of the end-stage mediators of PMS symptomatology are prostaglandins, which indicates this prostaglandin synthetase inhibitor may be working through a general inhibition of prostaglandin activity. Based on this, mefenamic acid is an ideal adjunct for any woman with coexisting dysmenorrhea and menorrhagia. In practice however, its effectiveness for premenstrual symptomatology, particularly psychological symptoms, seems quite variable. Mefenamic acid is contraindicated in women with known sensitivity to aspirin or those at risk for peptic ulcers.

Trials comparing oral contraceptive therapy to placebo have not shown a beneficial effect on mood in most circumstances. However, when contraception is required in a woman with PMS and coexisting dysmenorrhea or menorrhagia, the net effect of an oral contraceptive pill may be positive. Although oral contraceptives by no means guarantee relief from PMS they may afford sufficient relief from associated physical symptoms, so that for some women, the remaining premenstrual manifestations become tolerable. When an oral contraceptive user presents with PMS it is common to find that symptoms begin earlier in the cycle. This effect may result from exposure to progestin in the oral contraceptive 3 weeks before onset of menstruation rather than progesterone exposure 2 weeks before menses as occurs in natural cycles. In the woman presenting with distressing PMS while on an oral contraceptive, a switch to an alternate means of contraception is often attended by a substantial reduction in symptoms.

Published data in regard to the efficacy of pyridoxine (vitamin B_6) have been contradictory, however, this medication in proper doses (100 mg daily) is, at worst, a safe placebo that becomes one part of an overall management plan for women with distressing molimina that should include lifestyle modification and changes in diet. Patients should be cautioned that these medications do not work for all women and that increasing the dose of pyridoxine in an effort to achieve complete relief of symptoms may lead to peripheral neuropathy. Pyridoxine should be discontinued if there is evidence of tingling or numbness of the extremities.

Neither progestin therapy nor oil of evening primrose has been shown to be efficacious for PMS in controlled clinical trials.

Premenstrual mastalgia which affects up to 10% of women in reproductive age may occur in isolation from other PMS symptoms and, as such, should be considered a moliminal symptom. Low-dose danazol (100 mg OD) or luteal phase–only danazol (200 mg OD) can bring about dramatic relief of mastalgia in most women, however higher doses (400 mg OD) may be required to relieve other PMS symptoms. Mastalgia may also respond to tamoxifen (10 mg daily), but has not been shown to

respond to diuretics, medroxyprogesterone acetate, or pyridoxine.

The routine use of diuretics in the treatment of PMS should be abandoned. Most women show only random weight fluctuations during the menstrual cycle despite the common sensation of bloating. In the absence of demonstrable weight gain it is likely that this symptom may result from constipation or bowel wall edema rather than from an overall fluid accumulation. In rare cases, ingestion of salt and refined carbohydrates has been shown to result in true fluid retention. In cases where a consistent increase in weight can be documented or where edema is demonstrable, limitation of salt and refined carbohydrate intake should be attempted first. If such dietary restrictions fail to relieve premenstrual fluid accumulation, use of a potassium-sparing diuretic, such as spironolactone, may be considered. Continued use of a diuretic activates the renin–angiotensin–aldosterone system resulting in rapid rebound fluid accumulation as soon as the diuretic is discontinued. Weight takes approximately 2 to 3 weeks to return to normal after discontinuation of a diuretic in some people. Unfortunately this leaves the affected woman with the impression that she has to have a diuretic to maintain normal fluid balance.

Some women report overriding symptoms of anxiety, tension, and insomnia in the premenstrual week. New short-acting anxiolytics or hypnotics such as alprazolam or triazolam, respectively, may be prescribed sparingly for such individuals. Buspirone has also proven useful in preliminary trials.

Estrogen withdrawal has been implicated in menstrually-related migraines and evidence indicates that estrogen supplementation commencing in the late luteal phase and continued through menstruation may alleviate headaches in some women. As discussed subsequently, if headaches are severe and are unrelieved by short-term estrogen supplementation they can often be controlled by intramuscular or oral sumatriptan therapy or by medical ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists and continuous combined hormone replacement therapy.

Antidepressant Therapy A range of newer antidepressant medications that augment central serotonin activity (SSRIs or selective serotonin and norepinephrine reuptake inhibitors [SNRIs]) have been shown to alleviate severe premenstrual syndrome. The theoretic effect of these agents on serotonin levels throughout the menstrual cycle is depicted in schematic fashion in Figure 36.6. Since these agents will also relieve endogenous depression, a pretreatment diagnosis, achieved by prospective charting, is very important. Practically speaking, many women who attend a gynecology clinic to seek relief from premenstrual symptoms express reservations about taking an antidepressant, particularly if a short-term end point (3–6 months away) is not likely. Long-term therapy may be required to control symptoms of PMS for women in their 30s until menopause. Rapid reappearance of PMS has been reported after cessation of SSRI therapy by premenopausal women.

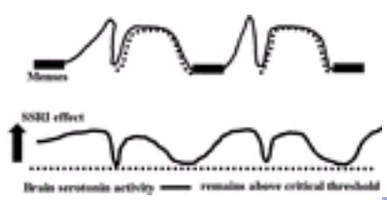

FIG. 36.6. Hypothetical depiction of how drugs that elevate serotonin activity can alleviate premenstrual syndrome. Solid line, estrogen; dotted line, progesterone. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

For patients in whom PMS psychiatric symptoms predominate, antidepressant therapy may provide excellent results. SSRIs, such as fluoxetine, sertraline, paroxetine, fluvoxamine, and velafaxine (an SNRI) have all been successfully employed. Symptom profiles may help in selecting the most appropriate agent (i.e., fluoxetine in patients where fatigue and depression predominate; sertraline if insomnia, irritability, and anxiety are paramount). SSRIs have been associated with loss of libido and anorgasmia, which are particularly distressing to this patient population. Appropriate pretreatment counseling is essential. Tricyclic antidepressants (TCAs) have not generally been effective with the exception of clomipramine, a TCA with strong serotonergic activity. Intolerance to the side effects of TCAs is common. Most women who suffer from PMS would prefer to medicate themselves only during the symptomatic phase of the menstrual cycle. Studies have demonstrated that luteal phase therapy may be effective for many women with PMS. Practically speaking, a trial of SSRI therapy should be commenced with continuous use. After a woman has determined the optimal dosage to achieve the desired response it is reasonable to test luteal phase–only therapy to determine if the benefit is maintained.
Medical Ovarian Suppression Suppression of cyclic ovarian function may afford dramatic relief for the woman with severe and long-lasting symptoms (Fig. 36.7). In each case therapy should be directed to the suppression of cyclic ovarian activity while ensuring a constant low level of estrogen sufficient to prevent menopausal symptomatology and side effects.

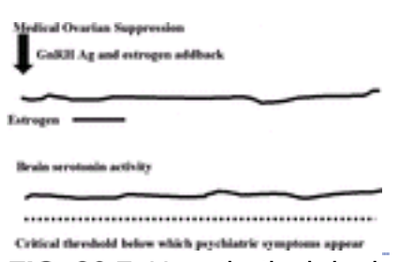

FIG. 36.7. Hypothetical depiction of how medical or surgical elimination of ovarian steroid fluctuations can stabilize central serotonin activity and eliminate premenstrual syndrome. (From Reid RL. Premenstrual syndrome. In: DeGroot L, ed. Endotext.com. Available at: http://www.endotext.com/. Accessed January 16, 2003, with permission.)

As a rule, although oral contraceptives suppress ovulation they seldom relieve the psychiatric symptoms of PMS, perhaps because ovarian steroidogenesis is replaced by exogenous synthetic steroids. Danazol 200 mg b.i.d. will effect ovarian suppression in approximately 80% of women with prompt relief from symptoms. Higher doses up to 200 mg q.i.d. may be required in the remaining women in order to achieve complete menstrual suppression. Danazol, at a dose of 200 mg b.i.d., has relatively few side effects; these may include hot flashes, muscle cramps, and occasional cases of epigastric pain, fine tremor, or insomnia. In the woman without preexisting hair growth, hirsutism is rarely a problem at these dosages when treatment is limited to 1 year or less. In the individual with preexisting acne or increased body hair, alternative interventions should be considered. The use of danazol causes a shift to a more unfavorable lipid profile which is likely to have little impact when danazol is used on a short-term basis. In the patient who tolerates danazol well, and in whom symptomatic relief is dramatic, this effect is the primary concern that will influence decision making about long-term treatment. GnRH agonists effect rapid medical ovarian suppression thereby inducing a pseudomenopause and affording relief from PMS. This approach is unsatisfactory in the long term not only because of the troublesome menopausal symptoms it evokes but also because if creates an increased risk for osteoporosis and ischemic heart disease. When combined with continuous combined hormone replacement therapy, GnRH agonists afford excellent relief from premenstrual symptomatology without the attendant risks and symptoms resulting from hypoestrogenism. The major drawback to this therapeutic approach is the expense of medication and the need for the patient to take multiple medications on a long-term basis. A simpler and less expensive approach involves the use of depo-medroxyprogesterone acetate (DMPA). This approach results in rapid suppression of cyclic ovarian function without attendant menopausal symptomatology. The major drawback to this approach is that a substantial percentage of women will experience irregular bleeding and gradual weight gain. The ideal situation, in which DMPA induces amenorrhea, may be problematic for the woman who wishes future fertility. Patients should always be counseled about the potential for protracted anovulation following use of this medication.
Surgical Therapy The fact that medical approaches to PMS should be exhausted prior to considering surgery (hysterectomy and oophorectomy) for debilitating PMS has been emphasized in an American College of Obstetricians and Gynecologists' committee opinion on premenstrual syndrome (No. 155, April 1995). Clinical trials, however, have clearly shown this therapy to be effective. For the woman in whom there is unequivocal documentation that premenstrual symptoms are severe and disruptive to lifestyle and relationships, and in whom conservative medical therapies have failed (either due to lack of response, intolerable side effects, or prohibitive cost), the effect of medical ovarian suppression should be tested. At times this therapeutic approach (a GnRH agonist and continuous combined hormone replacement therapy) can be maintained until menopause with satisfactory symptom control. Some women, despite complete relief of symptoms, cannot afford or choose not to take this combination of medications for prolonged intervals (as long as 10–15 years from diagnosis until menopause in some cases). In these specific circumstances a surgical option may be considered. In the circumstance where family is complete and permanent contraception is desired, the pros and cons of oophorectomy for lasting relief from premenstrual symptomatology should be discussed with the patient. In many women the progestin component of hormone replacement therapy, when given sequentially, may induce an apparent recrudescence of PMS-like symptoms and, when given continuously, may result in unwanted irregular bleeding. Accordingly, hysterectomy at the time of oophorectomy is a consideration that allows subsequent hormone replacement with low-dose estrogen alone.

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Chapter 37

Richard S. Legro and Ricardo Azziz

Androgen Excess Disorders

NORMAL ANDROGEN PRODUCTION AND METABOLISM
Androgen Production and Action
Androgen Clearance
Bioavailability of Androgens
Androgens, Age, and Menopause
Androgens and Obesity
SIGNS AND SYMPTOMS OF ANDROGEN EXCESS
Androgen Excess and the Pilosebaceous Unit
Androgens and Hypothalamic–Pituitary–Ovarian Axis Dysfunction
Androgens and Hypothalamic–Pituitary–Adrenal Axis Dysfunction
Virilization and Masculinization
THE POLYCYSTIC OVARY SYNDROME
Clinical, Biochemical, and Metabolic Features of PCOS
Sequelae of PCOS
OTHER ANDROGEN EXCESS DISORDERS
The HAIRAN Syndrome
Nonclassic Adrenal Hyperplasia
Androgen-Secreting Tumors
Rare Causes of Androgen Excess
IDIOPATHIC HIRSUTISM
EVALUATION OF ANDROGEN EXCESS
Laboratory Evaluation of Androgen Excess
Laboratory Assessment for Metabolic Abnormalities
Radiologic Imaging in the Evaluation of the Patient with Androgen Excess
TREATMENT OF ANDROGEN EXCESS
Regulation of Uterine Bleeding
Treatment of Hirsutism, or Androgen Excess-Associated Acne or Alopecia
Treatment of Associated Metabolic Abnormalities
Treatment of Hyperandrogenic Oligoovulatory Infertility
SUMMARY POINTS

SUGGESTED READINGS
Normal Androgen Metabolism
The Polycystic Ovary Syndrome
Other Androgen Excess Disorders
Evaluation of Androgen Excess
Treatment of Androgen Excess

Androgen excess (i.e., hyperandrogenism) is a common, albeit heterogeneous, endocrine disorder of women. The clinical presentation of androgen excess may range from mild hirsutism, acne, or subtle ovulatory dysfunction, to the rare patient with frank virilization and masculinization. Androgen excess disorders include the polycystic ovary syndrome (PCOS), nonclassic adrenal hyperplasia (NCAH), the hyperandrogenic–insulin resistant–acanthosis nigricans (HAIRAN) syndrome, and androgen-secreting neoplasms. Although the most recognizable clinical feature of androgen excess is hirsutism, it should be noted that not all patients with hirsutism have evidence of androgen excess, as in the patient with idiopathic hirsutism (IH). Likewise, not all patients with an androgen excess disorder have clinically evident hirsutism, as in the Asian patient with PCOS. Because of its frequent association with PCOS, clinically evident androgen excess (e.g., hirsutism) is a useful marker for the presence of metabolic abnormalities in these women, including insulin resistance and glucose intolerance resulting in an increased risk for type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). With these new insights, the burden of care for the treating physician has increased beyond that of solely treating the presenting complaint to include the detection and, if possible, prevention of these metabolic consequences.

NORMAL ANDROGEN PRODUCTION AND METABOLISM

Androgen Production and Action

Androgens are C19 steroids (that is they contain 19 carbons) produced from circulating low-density lipoprotein (LDL) cholesterol (a C27 molecule). As in most metabolic pathways, the first step is rate limiting (i.e., the conversion of cholesterol to the weak progestogen pregnenolone, a C21 steroid) by cytochrome P450scc (Fig. 37.1). The zona reticularis of the adrenal cortex, and the theca and stroma of the ovaries, secrete androgens produced through de novo synthesis from cholesterol. In addition, circulating steroid precursors can be metabolized further in these organs or in peripheral tissues, including the liver, adipose tissue stroma, and the pilosebaceous unit (PSU) in skin, to more potent androgens (e.g., the conversion of testosterone to dihydrotestosterone [DHT]), to estrogens via the action of aromatase, or they can be inactivated and readied for excretion (Fig. 37.2). The origins of the principal circulating plasma androgens in pre- and postmenopausal women are summarized in Table 37.1. Androstenedione is the most important precursor of testosterone and DHT, while dehydroepiandrosterone (DHEA) accounts for only 5% to 13% of circulating testosterone in normal women.

FIG. 37.1. Pathways of androgen synthesis. The ovary, the testis, and the adrenal gland produce six common core steroids. The core d5 steroids are pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone. The core d4 steroids are progesterone, 17-hydroxyprogesterone, and androstenedione (androstene-3,17-dione). The core steroids are important precursors for the production of sex steroids, glucocorticoids, and mineralocorticoids.

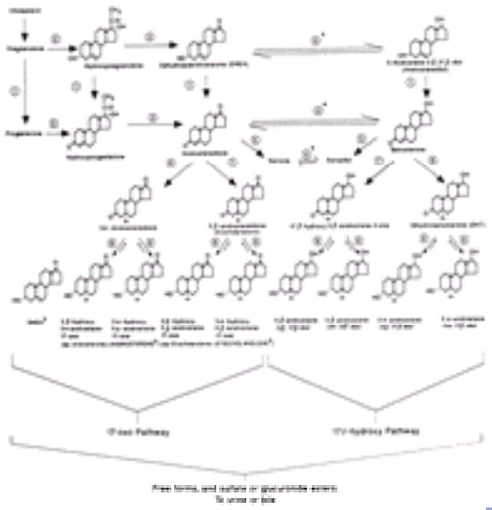

FIG. 37.2. Principal pathways of androgen metabolism. Enzymes: *1*, 3ß-hydroxysteroid dehydrogenase; *2*, 17ß-hydroxylase; *3*, 17,20-lyase (17,20-desmolase); *4*, 17ß-hydroxysteroid dehydrogenase (17-keto reductase); *5*, aromatase; *6*, 5a-reductase; *7*, 5ß-reductase; *8*, 3ß-oxoreductase; and *9*, 3a-oxoreductase. **a:** In the gonads the 17ß-hydroxysteroid dehydrogenase reaction predominantly produces 17ß-dehydrogenated products (androstenediol and testosterone), while the reverse is true in peripheral tissues. **b:** Aldosterone, etiocholanolone, and dehydroepiandrosterone are the principal urinary metabolites of androgens. (From Azziz R. Reproductive endocrinologic alterations in female asymptomatic obesity. *Fertil Steril* 1989;52:703–725, with permission.)

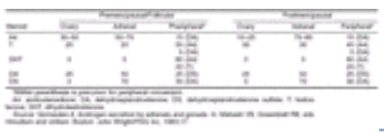

TABLE 37.1. *Percent origin of androgens in women*

Androgens, either directly or through metabolites, can act systemically in a classic endocrine fashion, or locally in a paracrine and intracrine fashion (e.g., in the PSU). Androgens exert their genomic effects through interaction with the androgen receptor, a member of the nuclear receptor superfamily. The unbound androgen receptor is a cytoplasmic protein and, upon ligand binding, it translocates into the nucleus. In the nucleus it influences the transcription of target genes through a complex process which includes interactions with other transcription factors and coactivators. As noted, androgens can also exert their effects indirectly, though metabolites such as the aromatization to estrogens.

Androgen Clearance

The clearance of androgens is accomplished by hepatic extraction and peripheral metabolism, which are highly dependent on the unbound portion of circulating steroid. Approximately 10% of testosterone and 50% of androstenedione are metabolized peripherally in women. Clearance of androgens by the hepatic splanchnic circulation involves mainly catabolism via 5a- and 5ß-reductase. Androgen metabolites are further conjugated by the liver (95% glucuronic and 5% sulfuric), facilitating their urinary excretion (see Fig. 37.2). Some 15% of androgen sulfates are excreted in bile, of which 80% are reabsorbed in the gut. Peripheral metabolism of androgens also occurs in the various target tissues including skin, muscle, brain, and adipose tissue. A-ring (aromatization), 17ß-hydroxysteroid dehydrogenization, 5a- and 5ß- A-ring reduction, and 3a- and 3ß-oxo-reduction give rise to potent androgens such as DHT, or to weaker metabolites such as 5a-androstane-3a,17ß-diol, androsterone, and etiocholanolone. These are subsequently conjugated by the liver and excreted in the urine and bile. Measurement of these metabolites (e.g., 3a-androstanediol glucuronide) was proposed as a circulating marker of peripheral androgen excess, but its clinical use currently is negligible.

Bioavailability of Androgens

Androgens circulate in the body bound by a variety of proteins, including albumin, cortisol-binding globulin, acid a2-glycoprotein and, most important, sex hormone binding globulin (SHBG, formerly known as testosterone or testosterone-estradiol binding globulin [TeBG]). Because of its much higher concentration and total amount, albumin has a much greater overall binding capacity for androgens than SHBG, but the affinity of androgens for SHBG is several orders of magnitude higher, thus binding the largest portion of circulating testosterone. Androgens bound to SHBG are essentially not bioavailable, although those complexed with albumin are more readily available for tissue interaction due to the much lower affinity of this protein for these steroids. The liver produces SHBG, and production is stimulated by estrogen, particularly oral forms; and inhibited by androgens, and most importantly, insulin. These factors lead to lower levels of SHBG and higher bioavailable androgens in men and in women with androgen excess disorders compared to healthy women.

As noted in the following sections, the production, metabolism, and circulating levels of androgens are affected by age, menopausal status, and the presence of obesity, among other factors.

Androgens, Age, and Menopause

Androgen metabolism and circulating levels can be significantly altered by age. Most notably, adrenal androgen production clearly decreases with age in premenopausal and postmenopausal women. Serum dehydroepiandrosterone sulfate (DHEA-S) concentrations decrease linearly with age beginning at about 20 years, independent of menopause. An impaired secretion of 17 a-hydroxyprogesterone, 17 a-hydroxypregnenolone, DHEA, and androstenedione has also been observed in postmenopausal women following acute adrenal stimulation. In normal postmenopausal women plasma concentrations of androstenedione are about half that observed in premenopausal women, although there is no observable difference in the clearance rate of this steroid between premenopausal and postmenopausal women. After menopause androstenedione levels continue to gradually decrease with age. Testosterone levels are less affected by age and menopause, and it is clear that the ovary continues to produce a significant amount of testosterone in postmenopause. Most of the decrease in circulating testosterone with age and menopause is explained by the lower androstenedione levels.

Androgens and Obesity

In eumenorrheic obesity the production rate and metabolic clearance rate (MCR) of ovarian and adrenal-secreted androgens are increased while circulating levels remain normal. The increased MCR may be due to an obesity-related decrease in the plasma concentration of the carrier protein SHBG. Steroid sequestration by fat may also increase steroid clearance, leading to an extremely large pool of sex hormones in obese individuals. Adipose tissue metabolism of steroids, including aromatization and 17ß-hydroxysteroid dehydrogenation, also contributes to the increased MCR of androgens while alterations in hepatic conjugation and extraction can also be a contributing factor. The increased ovarian and adrenal production noted in obesity may reflect changes in the intraglandular or circulating concentration of androgens, estrogens, prolactin, growth hormone and other growth factors, and most importantly, insulin. Although weight reduction corrects any abnormality noted in steroid levels, it is not known whether the elevated production and MCRs of androgens also normalize following weight reduction.

The degree of androgen excess that can result in the appearance of clinical features most commonly has its source in the increased production (or intake) of androgens, which can be altered by age and degree of obesity. However, other factors such as the potency of the androgen produced (DHT>testosterone>androstenedione>DHEA), the amount of androgen that is free or weakly bound in serum (i.e., the amount bioavailable), and the degree and type of central and peripheral metabolism also play a role in determining and modifying the phenotype of androgen excess.

SIGNS AND SYMPTOMS OF ANDROGEN EXCESS

Androgen excess results in various clinical signs and symptoms, including abnormalities of the PSU (hirsutism, acne, and androgenic alopecia), the hypothalamic–pituitary–ovarian axis (i.e., ovulatory and menstrual dysfunction), and the hypothalamic–pituitary–adrenal axis (adrenal androgen excess). If the androgen excess is very severe, virilization or masculinization can also be apparent.

Androgen Excess and the Pilosebaceous Unit

The pilosebaceous unit (PSU) is the common skin structure that gives rise to both hair follicles and sebaceous glands, which are found everywhere on the body except

the palms, soles, and lips. The density is greatest on the face and scalp (400–800 glands/cm ^{2}) and lowest on the extremities (50 glands/cm ^{2}). The number of PSUs does not increase after birth (about 5 million), but they can become more prominent through activation and differentiation. Generally, three phases of the hair growth cycle can be considered. The period of active growth is termed anagen, after which the hair follicle enters a resting or catagen phase of varying length of time (Fig. 37.3). During this transition the hair shaft separates from the dermal papillae at the base. The separated hair is then shed during the telogen phase. The period of anagen varies from 3 years on the scalp to 4 months on the face. For corresponding parts of the skin, men have longer anagen phases than women do, which may be partially due to their higher circulating androgen levels.

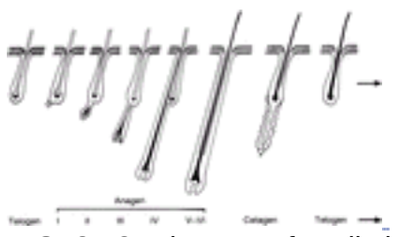

FIG. 37.3. Diagram of cyclic hair follicles, a club hair (white) in old telogen and early anagen (I–IV) follicles, and a new hair (black) in new anagen (V–VI) follicles. (From: Uno H. *Seminars in reproductive endocrinology.* Vol 4. New York: Thieme, 1986, with permission.)

The effects of androgens are most visible on the PSU. Androgens stimulate the transformation of fine, unpigmented vellus hairs to coarse, pigmented, thickened terminal hairs, a process known as *terminalization*, in skin areas sensitive to the effects of androgens. The peripheral effects of androgens are determined primarily by the intracellular actions of the enzymes 17ß-ketosteroid reductase (converting androstenedione to testosterone) and 5a-reductase (converting testosterone to the more potent androgen, DHT), and the androgen receptor content. Before puberty body hair is primarily composed of fine, short unpigmented vellus hairs. The increase in androgen production observed with pubertal development transforms some of these, mainly in androgen-sensitive areas of skin such as the axilla and the genital triangle, into the coarser, longer, pigmented terminal hairs. It should be noted that not all skin areas are androgen-sensitive. For example, the development of terminal hairs in body areas such as the eyebrows, eyelashes, and the temporal and occipital scalp is relatively androgen-independent.

Excess androgen-dependent hair growth present in women can result in clinically evident hirsutism (see the following section). Paradoxically, androgens can exert opposite effects on the hair follicles of the scalp, causing conversion of terminal follicles to vellus-like follicles, a process termed *miniaturization.* This effect may lead to the development of androgenic alopecia in women (see " Androgenic Alopecia") or male-pattern baldness characterized by frontal and sagittal scalp hair loss. Androgens can also cause increased sebum production and abnormal keratinization of the PSU, contributing to the development of seborrhea and acne evident at puberty and in women with androgen excess. Ethnic and genetic differences can modify the effects of androgens on skin, as demonstrated by the lesser degree of hirsutism present in Asian women with PCOS (Fig. 37.4).

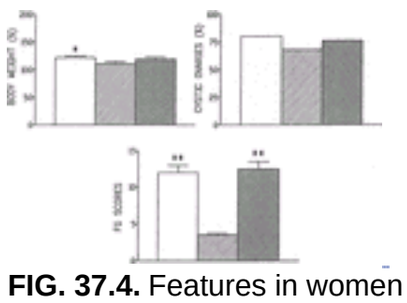

FIG. 37.4. Features in women with polycystic ovary syndrome (75 women, 25 each from the United States, Italy, and Japan). Note the much lower prevalence of hirsutism among Japanese women. (From Carmina et al, *Am J Obstet Gynecol* 1992;167:1807–1812, with permission.)

Hirsutism Hirsutism is the presence of terminal (coarse) hairs in females in a male-like pattern. Excessive growth of coarse hairs of the lower forearms and lower legs alone does not constitute hirsutism, although women suffering from hirsutism may note an increase in the pigmentation and growth rate of hairs on these body areas. Hirsutism should be viewed much as polycystic ovaries, as a sign rather than a diagnosis. Most commonly hirsutism is associated with androgen excess. Although the term "idiopathic hirsutism" was coined to identify the presence of hirsutism without other identifiable cause or abnormality, this may actually reflect our limited ability to assess androgen action in the peripheral compartment or even in the circulation (see Evaluation of Androgen Excess).
Acne The PSU, in addition to the hair follicle, also contains a sebaceous gland that produces an oily protective secretion, sebum. The excessive production of sebum, in response to androgen action, may lead to oily skin, clogged hair follicles, folliculitis, and the development of acne. Elevations in serum androgen levels have been noted in patients with acne, particularly in those with concurrent hirsutism, although not all investigators agree. Although the persistence or appearance of acne in adulthood has been suggested to be more frequently associated with androgen excess, we observed evidence of hyperandrogenemia in the majority of 30 consecutive nonhirsute, acneic patients regardless of age. Some investigators have observed that while serum androgen levels may be relatively normal in acneic patients, the conversion of androgens to DHT via 5a-reductase was increased in the affected skin. These data suggest that androgen suppression may be useful in treating acne in many of these patients, and it is clear that acne frequently improves following treatment with antiandrogens, oral contraceptives, or glucocorticoid suppression. Thus, empirical treatment with oral contraceptives, or even glucocorticoids, may be justified in acneic patients without other evidence of overt androgen excess.
Androgenic Alopecia Scalp hair loss as a consequence of androgen excess can take two forms. In severe cases, where massive androgen excess and virilization/masculinization are present, patients can demonstrate the typical pattern of balding found in men (i.e., premature male-pattern balding). More common, however, is the so-called androgenic (also termed *androgenetic*, as an inherited etiology is often suspected) alopecia of women (i.e., female-pattern balding). In female androgenic alopecia a diffuse thinning of hair throughout the sagittal scalp is primarily noted and approximately 40% of women with androgenic alopecia have some form of hyperandrogenemia. However, if only nonhirsute women with androgenic alopecia are considered, then only 20% of these patients are found to be hyperandrogenemic.

Androgens and Hypothalamic–Pituitary–Ovarian Axis Dysfunction

Androgens, indirectly, through conversion to estrogens, and directly may alter the secretion of gonadotropins in women. However in most patients without severe forms of androgen excess, the direct effect of androgens on the hypothalamic–pituitary–ovarian axis, independent of their aromatization to estrogens, appears to be limited. Excessive androgen levels may also directly inhibit follicular development at the ovarian level, which may result in the accumulation of multiple small cysts within the ovarian cortex, the so-called "polycystic" ovary.

Androgens and Hypothalamic–Pituitary–Adrenal Axis Dysfunction

Adrenal androgen excess (i.e., elevated levels of DHEA and DHEA-S, and of the adrenal fraction of androstenedione) is a concomitant finding in many women with androgen excess. However, it is also possible that extraadrenal androgens (e.g., ovarian) may alter adrenocortical steroidogenesis and androgen secretion. For example, a 20% to 25% decrease in mean DHEA-S levels follows long-acting gonadotropin-releasing hormone-a (GnRH-a) suppression in women with PCOS with elevated levels of this adrenal androgen, although elevated adrenal androgen levels in these women rarely normalize with GnRH-a suppression. Thus, it appears that the secretion of adrenal androgen can be increased by extraadrenal hyperandrogenemia, although the clinical relevance of such an effect is unclear.

Virilization and Masculinization

Virilization includes the appearance of sagittal and frontal balding, clitoromegaly, and severe hirsutism. Furthermore, if androgen levels are extremely elevated for a substantial period of time the features of virilization may be accompanied by masculinization of the body habitus, with atrophy of the breasts, an increase in muscle mass, a redistribution of body fat, and a deepening of the voice. Premenopausal patients with virilization or masculinization are almost always amenorrheic. In general, virilization or masculinization should raise the suspicion of an androgen-secreting neoplasm or classic (but not nonclassic, as discussed later) adrenal hyperplasia. Occasionally girls suffering from severe insulin-resistance syndrome (discussed later in the chapter) may exhibit a moderate degree of virilization.

THE POLYCYSTIC OVARY SYNDROME

By far the most common, although the least understood, cause of androgen excess is polycystic ovary syndrome (PCOS), accounting for a vast majority of patients seen. PCOS affects 4% to 6% of women in the developed world. There is no firm consensus as to the definition of PCOS; criteria arising from a 1990 National

Institutes of Health conference on the subject have proven clinically and investigationally useful. These criteria note that PCOS should include the presence of:

- clinical or biochemical evidence of hyperandrogenism
- ovulatory dysfunction
- the exclusion of other causes of androgen excess or ovulatory dysfunction, such as including adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, and androgen-secreting neoplasms.

Thus, PCOS represents unexplained functional hyperandrogenic chronic anovulation and is a diagnosis of exclusion.

Other diagnostic criteria for PCOS have been proposed, including the finding of a polycystic ovary morphology on ultrasound, with multiple 2-to 8-mm subcapsular preantral follicles forming a “black pearl necklace” sign (Fig. 37.5). However, it should be noted that “polycystic ovaries” on sonography or at pathology are simply a sign of androgen excess and possibly PCOS. For example, this ovarian morphology is frequently seen in patients with adrenal hyperplasia (Table 37.2), and up to 25% of unselected women have polycystic ovaries on ultrasound, many of which are normoandrogenic with regular menstrual cycles. Hence, we consider the appearance of polycystic ovaries, particularly on sonographic exam, to be a sign, albeit nondiagnostic, of androgen excess and PCOS.

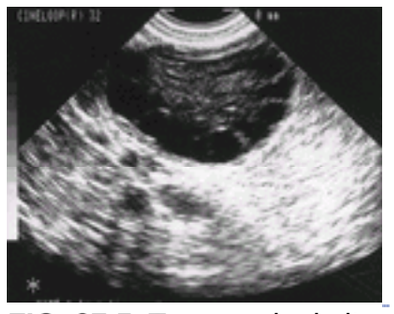

FIG. 37.5. Transvaginal ultrasound visualization of a polycystic ovary. Note the string of subcapsular follicles measuring 2 to 8 mm in diameter, with increased central stromal mass.

Hyperandrogenism without insulin resistance
Steroidogenic enzyme deficiencies
Congenital adrenal hyperplasia
Aromatase deficiency
Androgen-secreting tumors
Ovarian
Adrenal
Exogenous androgens
Anabolic steroids
Transsexual hormone replacement
Other
Acne
Idiopathic hirsutism
Hyperandrogenism and insulin resistance
Congenital
Type A syndrome
Type B syndrome
Leprechaunism
Lipoatrophic diabetes
Rabson-Mendenall syndrome
Polycystic ovary syndrome
Acquired
Cushing’s syndrome
Insulin resistance
Glycogen storage diseases
Type 2 diabetes
Other
Central nervous system
Trauma/lesions
Hyperprolactinemia
Nonhormonal medications
Valproate
Hereditary angioedema
Bulimia
Idiopathic (includes normoandrogenic women with cyclic menses)

TABLE 37.2. *Syndromes or diseases entities associated with polycystic ovaries*

Clinical, Biochemical, and Metabolic Features of PCOS

Approximately 70% to 80% of women with PCOS demonstrate frank elevations in circulating androgens, particularly free testosterone, and 25% to 50% will have elevated levels of the adrenal androgen metabolite, DHEA-S. Prolactin levels are usually normal, although they may be slightly elevated (generally <40 ng/mL) in a small fraction of patients. The luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio is greater than 2 or 3 to 1 in approximately 60% of these patients. As noted, the ovaries of about 70% of patients with PCOS usually contain intermediate and atretic follicles measuring 2 to 8 mm in diameter, resulting in a “polycystic appearance” at sonography (see Fig. 37.4, Fig. 37.5). About 60% of patients with PCOS are obese, although significant fractions are nonobese.

While not part of the diagnostic criterion, many women with PCOS appear to be uniquely insulin-resistant. Approximately 50% to 70% of patients with PCOS demonstrate profound insulin resistance and secondary hyperinsulinemia, independent of body weight. In PCOS, insulin resistance usually refers to the impaired action of insulin in stimulating glucose transport and in inhibiting lipolysis in adipocytes. Insulin resistance in PCOS appears to be due to an intracellular defect of insulin signaling.

The compensatory hyperinsulinemia, resulting from the underlying insulin resistance, augments the stimulatory action of LH on the growth and androgen secretion of ovarian thecal cells, while inhibiting the hepatic production of SHBG. Treatment of patients with PCOS with insulin sensitizers may result in lower circulating levels of LH suggesting that insulin resistance, or more likely hyperinsulinemia, is in part responsible for the gonadotropic abnormalities observed in many women with PCOS. Since insulin is also a mitogenic hormone, the extremely elevated insulin levels may lead to hyperplasia of the basal layers of the epidermis, resulting in the development of acanthosis nigricans (a velvety, hyperpigmented change of the crease areas of the skin) (Fig. 37.6), and acrochordons. Overall, insulin resistance and secondary hyperinsulinemia affects a large fraction of patients with PCOS, and may cause or augment the androgen excess of these patients.

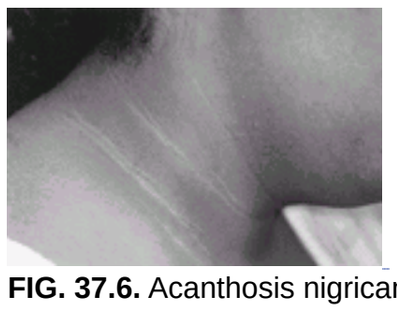

FIG. 37.6. Acanthosis nigricans on the nape of the neck: a sign of hyperinsulinemia.

Sequelae of PCOS

Clinically evident PCOS tends to develop shortly after menarche and persists through most of the reproductive life. Nonetheless, some patients may present initially in the prepuberty with premature adrenarche, with affected girls displaying hyperinsulinemia, elevated DHEA-S levels, and postmenarche oligomenorrhea. At the other end of the reproductive spectrum, both menstrual irregularity and hyperandrogenemia appear to normalize as women with PCOS approach perimenopause. Although the endocrine and reproductive features of the disorder may improve with age, the associated metabolic abnormalities, particularly glucose intolerance, may actually worsen with age.

Infertility-Chronic Anovulation One of the most common reasons that women with PCOS present to the gynecologist is due to infertility secondary to chronic anovulation. These women are not sterile, but subfertile due to the infrequency and unpredictability of their ovulation. As a general rule, women with PCOS represent one of the most difficult groups in which to safely induce ovulation. Many women with PCOS are unresponsive or resistant to ovulation induction with clomiphene citrate and may have an inappropriate or exaggerated response to the administration of human menopausal gonadotropins (menotropins). In part, the abnormal response to

ovulatory agents of patients with PCOS relates to their degree of hyperinsulinemia and obesity, and to abnormalities of the intraovarian hormonal milieu and the increased number of preantral follicles. Women with PCOS are especially at increased risk for multiple gestation and developing the hyperstimulation syndrome—a syndrome of massive enlargement of the ovaries, development of rapid and symptomatic ascites, intravascular contraction, hypercoagulability, and systemic organ dysfunction. These complications generally occur following treatment with gonadootropins, although ovarian hyperstimulation has even been reported in women with PCOS conceiving a singleton pregnancy spontaneously, or after clomiphene citrate or pulsatile GnRH use.

Gynecologic Cancers Many gynecologic cancers have been reported to be more common in women with PCOS including ovarian, breast, and endometrial carcinomas. However, the best case of an association between PCOS and cancer can be made for endometrial cancer, as many risk factors for this cancer, including obesity, chronic anovulation, and hyperinsulinemia, are present in the patient with PCOS. Patients with endometrial cancer have significantly higher body mass index (BMI) and frequency of diabetes hypertension, hirsutism, nulliparity, and infertility than controls.

Type II Diabetes Mellitus The inherent insulin resistance present in many with PCOS, aggravated by the high prevalence of obesity in these individuals, places these women at increased risk for impaired glucose tolerance and type 2 DM. About 30% to 40% of obese women of reproductive age with PCOS have been found to have impaired glucose tolerance (IGT), and about 10% have frank type 2 DM based on a 2-hour glucose level greater than 200 mg/dL. Of note is that only a small fraction of women with PCOS with either IGT or type 2 DM display fasting hyperglycemia consistent with diabetes by the 1997 American Diabetes Association criterion (fasting glucose =126 mg/dL) (Fig. 37.7). The conversion rate to glucose intolerance over time is unknown, which makes recommendations for frequency of screening for glucose intolerance difficult. However, the level of insulin resistance found in women with PCOS based on dynamic measures of insulin action has in other populations (i.e., children of parents with diabetes) been associated with a marked increased risk of developing type 2 DM.

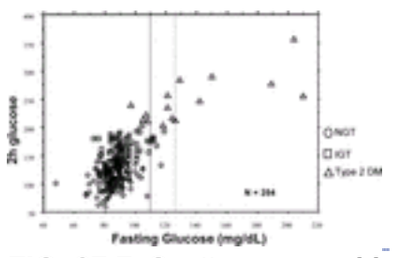

FIG. 37.7. Scatterogram of fasting blood glucose levels versus 2-hour postchallenge glucose levels in 254 women with polycystic ovary syndrome (PCOS). Points on the graph are coded to reflect the World Health Organization status based on postchallenge glucose levels. *A*, 140 to 199 mg/dL = impaired glucose tolerance. The *dashed vertical line* is the threshold (110 mg/dL) for the diagnosis of impaired fasting glucose according to the 1997 American Diabetes Association criteria. The *solid vertical line* (126 mg/dL) is the threshold for the diagnosis of type 2 diabetes mellitus by the same criteria. (From Legro RS, Kunselman AR, Dodson WC, et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–169, with permission.)

Cardiovascular Disease Many women with PCOS appear to form a subset of the metabolic syndrome first described by Reaven (i.e., syndrome X or insulin-resistance syndrome) consisting of insulin resistance, hypertension, dyslipidemia, glucose intolerance, and CVD. The mechanisms underlying the relationship between the insulin resistance/hyperinsulinemia and hypertension are unclear, but may include sodium retention, overactivity of the sympathetic nervous system, impairment of membrane transport, and stimulation of vascular smooth muscle cells. Other effects of hyperinsulinemia and insulin resistance include the development of an atherogenic plasma lipid profile due to insulin enhancement of synthesis of very-low-density lipoproteins and hypertriglyceridemia. Insulin also causes the proliferation of smooth muscle cells and stimulation of collagen synthesis in small arterioles. These effects, in combination with insulin-induced growth factor elaboration and inhibition of regression of lipid plaques, contribute to the development of atherosclerosis and the resultant CVD. Many women with PCOS have significant dyslipidemia, with lower high-density lipoprotein (HDL), and higher triglyceride and low-density lipoprotein (LDL) levels than age, sex, and weight-matched controls. Studies have documented other interim risk factors, such as increased carotid artery intimal thickness, to suggest that these women have evidence of atherosclerotic disease earlier and at a more advanced stage than control women. However, an increase in actual cardiovascular events in women with PCOS, such as myocardial infarction, has not been observed, although a higher number of nonfatal cerebrovascular disease events have been noted. We should note that there are a number of features of PCOS that do not fully fit the definition of the metabolic syndrome. For example, although dyslipidemia is part of the metabolic syndrome, the elevation in LDL levels noted in PCOS is not one of the characteristic findings. Additionally, although the risk of developing hypertension later in life appears to be higher in patients with PCOS, hypertension has not been associated with PCOS in women of reproductive age.

OTHER ANDROGEN EXCESS DISORDERS

Other major androgen excess disorders include the HAIRAN syndrome, 21-hydroxylase (21-OH) deficient NCAH, and very rarely, ovarian or adrenal androgen-secreting neoplasms.

The HAIRAN Syndrome

The HAIRAN (hyperandrogenic-insulin resistant-acanthosis nigricans) syndrome is an inherited disorder of severe insulin resistance, distinct from PCOS, and which actually includes many different genetic syndromes. Although single-point mutations of the insulin receptor are rare among these patients, some patients with this syndrome may actually suffer from a form of the familial lipodystrophy syndrome. Approximately 3% of hyperandrogenic women suffer from these disorders. These patients are diagnosed by having extremely high circulating levels of basal (>80 µU/mL) or glucose-stimulated (>300–500 µU/mL) insulin levels, although exact diagnostic criteria are lacking, in part due to the heterogeneity of the syndrome. Patients can be severely hyperandrogenemic, with testosterone levels reminiscent of patients with androgen-secreting neoplasms, resulting in the development of severe hirsutism and even virilization. In addition to significant hirsutism, patients also develop the characteristic dermatologic finding of acanthosis nigricans (see Fig. 37.6). Because of their high androgen levels, gonadotropin levels in these patients may be somewhat suppressed resulting in persistent endometrial atrophy and amenorrhea in spite of the administration of a cyclic progestogen or an oral contraceptive.

Because of the mitogenic effect of insulin on ovarian theca cells, the ovaries of many patients with the HAIRAN syndrome will become hyperthecotic. On ultrasound and histology the ovaries morphologically have a paucity of cortical cysts, and demonstrate a thickened and enlarged theca/stroma compartment. In addition, these patients are at significant risk for dyslipidemia, type 2 DM, hypertension, and CVD. These patients can be particularly difficult to treat although the selected use of long-acting GnRH analogs has been promising. Some patients may necessitate surgery, either ovarian wedge resection or oophorectomy.

Nonclassic Adrenal Hyperplasia

Nonclassic adrenal hyperplasia (NCAH), also referred to as late-onset congenital adrenal hyperplasia, is a homozygous recessive disorder due to mutations in the *CYP21* gene which results in an abnormal (or absent) cytochrome P450c21 with relatively deficient 21-OH activity. Overall, between 1% and 8% of women with androgen excess have 21-OH–deficient NCAH depending on ethnicity, with the highest rates reported among Ashkenazi Jews. Due to the lack of 21-hydroxylation the progestogenic precursors to cortisol, 17 a-hydroxyprogesterone (17 a-HP) and to a certain degree 17 a-hydroxypregnenolone, accumulate in excess. These steroids are then metabolized to C19 products, principally androstenedione and testosterone (see Fig. 37.1, Fig. 37.2). However, clinically and biochemically these patients are very difficult to distinguish from other hyperandrogenic patients, particularly patients with PCOS. Patients with NCAH may present only with persistent acne or may have moderate degrees of hirsutism and oligoamenorrhea. Frank virilization or even severe hirsutism is relatively rare. The levels of the exclusive adrenal androgen metabolite DHEA-S are not any higher than that of other hyperandrogenic women.

Although the frequency is relatively low, all patients with unexplained androgen excess should be screened for NCAH due to *CYP21* mutations, as this diagnosis has a different prognosis, a different treatment regimen, and requires genetic counseling regarding the risks of congenital transmission. The measurement of a basal 17 a-HP in the follicular phase and in the morning can be used to screen for this disorder. In addition, these patients can be treated with corticosteroid replacement, although many of the patients who are diagnosed in adulthood tend to also demonstrate a PCOS-like pattern requiring additional ovarian suppression.

While it is theoretically possible that NCAH may be due to mutations in other genes determining steroidogenic enzymes, such CYP11B1 (encoding for P450c11a and 11ß-hydroxylase (CYP11B1) or HSD3B (for 3ß-hydroxysteroid dehydrogenase), mutations in the genes coding for these enzymes are rarely noted in adult women presenting with androgen excess.

Androgen-Secreting Tumors

Androgen-secreting neoplasms are relatively rare, affecting between 1 of 300 and 1 of 1,000 hirsute patients. These tumors usually originate in the ovary, and rarely the adrenal cortex. The most common androgen-producing tumor in a premenopausal woman is a Sertoli-Leydig cell tumor, with thecomas and hilus cell tumors being less frequent. Hilus cell tumors are often small, and can be less than 1 cm in diameter, theoretically below the range of ultrasound visualization. Another rare neoplasm may be a granulosa cell tumor, 10% of which primarily secrete androgens instead of estrogens. Also, any large tumor within the body of the ovary (i.e., benign cystic teratomas, dysgerminomas, epithelial tumors) can produce androgens indirectly by causing hyperplasia of the surrounding normal stroma. Fortunately, the vast majority of ovarian androgen-secreting neoplasms are benign.

Alternatively, adrenal androgen-secreting tumors are generally malignant (i.e., adrenocortical carcinoma) and associated with a high mortality rate, although androgen-secreting adrenal adenomas have also been reported. Fortunately, adrenal androgen-secreting neoplasms are rare with an estimated incidence of two cases per one million persons per year. The age of onset in adults peaks in the fifth decade. Virilization can accompany both tumors primarily producing androgens and tumors primarily producing cortisol (Cushing syndrome). A long history of symptoms, as in the case with an ovarian tumor does not exclude the presence of an adrenocortical neoplasm.

The presence of androgen-secreting neoplasms should be suspected when the onset of androgenic symptoms is rapid and sudden, when androgen excess initially presents in late life, when they lead to virilization and masculinization, or are associated with cushingoid features. Nonetheless, it should be remembered that some of younger patients with virilization suspected of having an androgen-secreting neoplasm actually suffer from the HAIRAN syndrome (discussed earlier). Suppression and stimulation tests can be misleading and are not encouraged for the diagnosis of these neoplasias. Overall, the single best predictor of an androgen-producing tumor is clinical presentation, and not biochemical markers. For example, in one study we noted that the positive predictive value of a repeat total testosterone above 250 ng/dL was only 9%, as most women with total testosterone levels above this cutoff have other abnormalities, such as the HAIRAN syndrome or PCOS.

Rare Causes of Androgen Excess

Clinical signs of androgen excess may also result from the presence a corticotropin-secreting tumor, due to either a pituitary adenoma (i.e., Cushing's disease) or an extrapituitary (ectopic) source, although patients are usually also cushingoid. In one study of young women with Cushing's syndrome all had stigmata of hyperandrogenism (hirsutism, acne, or balding), but only 70% had oligomenorrhea. However, as Cushing's syndrome has an extremely low prevalence in the population (1 in a million) and screening tests do not have 100% sensitivity/specificity, routine screening of all women with androgen excess for Cushing's syndrome is not indicated. Nonetheless, clinical signs more commonly found in Cushing's syndrome, such as ecchymoses, proximal muscle weakness, centripetal reddened striae, facial rubor and swelling, and perhaps hypertension and glucose intolerance should signal screening tests. Screening for cortisol excess can be conducted with a 24-hour urine collection for free cortisol.

The use of exogenous androgens, often found among body builders, or the excessive use of androgens among postmenopausal women should also figure in the differential diagnosis. Severe hirsutism, and even virilization, that begins during pregnancy has its own unique differential including benign ovarian sources such as hyperreactio luteinalis (i.e., gestational ovarian theca–lutein cysts) or luteomas, and extremely rare fetoplacental sources, such as aromatase deficiency resulting in androgen excess due to the placental inability to convert precursor androgens into estrogens. Finally, gonadal dysgenesis associated with an abnormal Y chromosome can initially present as peripubertal androgenization.

IDIOPATHIC HIRSUTISM

Although idiopathic hirsutism (IH) is not actually an androgen excess disorder, it is included among them and should be considered in the differential diagnosis of androgen excess. Overall, approximately 5% to 15% of hirsute women will have the diagnosis of “idiopathic” hirsutism. The diagnosis of IH is, by exclusion, made in a patient who is obviously hirsute, but in whom the circulating androgens and ovulatory function appear to be normal, and no other disorders can be identified. While some clinicians use regular menses as diagnostic of normal ovulatory function, we should note that approximately 40% of eumenorrheic hirsute women are actually anovulatory, and hence do not suffer from IH. Although biochemically these patients do not have an obvious elevation in circulating androgen levels, it also is likely that many of these patients simply demonstrate degrees of hyperandrogenemia that may not be detectable with routine clinical androgen assays. Nonetheless, in some of these women the 5a-reductase activity in the skin and hair follicles is probably overactive and leads to hirsutism in spite of normal circulating androgen levels.

EVALUATION OF ANDROGEN EXCESS

The history and physical examination are essential to making a diagnosis of the underlying cause of androgen excess. History taking should focus on the onset and duration of the various stigmata of androgen excess, should include a thorough menstrual history, and a discussion of concomitant medications. The physical examination should carefully assess the patient for cushingoid features, acanthosis nigricans, balding, acne, and degree and type of body hair distribution. One commonly used scale to score the degree of excess hair growth is based on a modification of the Ferriman-Gallwey scale (Fig. 37.8). Signs of virilization and masculinization should be sought, although their recognition is usually obvious. Clitoromegaly is usually defined as a clitoral index greater than 35 mm^2, where the clitoral index is the product of the sagittal and transverse diameters of the glans of the clitoris in millimeters. In normal women these diameters are in the range of 5 mm.

FIG. 37.8. Modified Ferriman-Gallwey scale for assessing hirsutism. (Modified from Hatch, et al. Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 1981;140:815–830.)

Evidence and risk factors for insulin resistance should be sought out as they are critical to the long-term health of the women affected. Family history of diabetes and CVD, especially of first-degree relatives with premature-onset heart disease (males <55 years and females <65 years), is an important part of the assessment. Lifestyle factors such as smoking, alcohol consumption, and diet and exercise histories should be recorded. Signs of insulin resistance on physical exam such as obesity, particularly with a centripetal fat distribution, and the presence of acanthosis nigricans and acrochordons should be recorded. Acanthosis nigricans is principally noted in most crural areas of the body, including the back of the neck, the axilla, underneath the breasts, and even on the vulva.

Weight should be corrected for height by using the BMI (divide weight in kilograms by the square of the height in meters, i.e., kg/m^2). However, the pattern of fat distribution rather than BMI seems to be most predictive of morbidity and mortality. In women a central or abdominal distribution of adiposity fat (the so-called apple-shaped or android obesity) has been associated with an increased risk for CVD and with an increased index of death from all causes. Fat distribution is most easily assessed using the waist-to-hip ratio (WHR), obtained by measuring the circumferences at the narrowest point of the abdomen (i.e., the abdominal measure), generally immediately above the umbilicus, and the widest part of the hips (i.e., the hip measures). Values greater than 0.72 (primarily android fat distribution) are considered abnormal but increased morbidity and mortality becomes more noticeable at values greater than 1.0. In women, the android pattern of obesity has been associated with abnormal lipid profiles and increased insulin resistance compared to the gynecoid pattern.

The laboratory evaluation should have the objective of excluding related and specific disorders and, if necessary, providing confirmation of androgen excess. As well, the presence of metabolic abnormalities, particularly in patients with PCOS or the HAIRAN syndrome, should be sought out.

Laboratory Evaluation of Androgen Excess

Specific related disorders that should be excluded prior to diagnosis of androgen excess are thyroid dysfunction, hyperprolactinemia, NCAH, the HAIRAN syndrome, and androgen-secreting tumors. Thyroid dysfunction and NCAH are ruled out by measuring a third generation thyroid-stimulating hormone (TSH) and a basal 17- aHP level, the latter measured in the follicular phase of the menstrual cycle. If the 17-HP level is greater than 2 ng/mL, the patient should undergo an acute adrenal stimulation test to exclude 21-hydroxylase deficient NCAH. If the 17-HP level 60 minutes following corticotropin administration is greater than 10 ng/mL, the diagnosis of 21-OH–deficient NCAH is established.

As noted previously, hirsute women claiming to have regular menstrual cycles should be evaluated for ovulatory dysfunction, most simply by obtaining a basal body temperature chart and a serum progesterone in the luteal phase (days 20–24) of the menstrual cycle. If the patient has ovulatory dysfunction, as evidenced by either a luteal progesterone level less than 4 ng/mL in a eumenorrheic patient, or because she has overt menstrual abnormalities, the diagnosis of PCOS should be entertained. In women with ovulatory dysfunction, serum prolactin and fasting insulin levels should also be obtained to exclude hyperprolactinemia and the HAIRAN syndrome, respectively. Androgen-secreting neoplasms are generally excluded by the history and physical exam. Rarely, a 24-hour urine free cortisol is required in a

patient with features suggestive of Cushing's syndrome.

The measurement of circulating androgen levels, including total and free testosterone, and DHEA-S is useful, primarily in the minimally or nonhirsute oligoovulatory patient, to exclude the presence of androgen excess as the cause of the ovulatory dysfunction. However, these measurements have limited diagnostic use in the patient who is frankly hirsute, and have a low positive predictive value for adrenal or ovarian androgen-secreting neoplasms.

Inappropriate gonadotropin secretion has been one of the characteristic signs of PCOS, and many clinicians have used elevated LH/FSH ratios of 2:1 or 3:1 as diagnostic criteria for PCOS. Nonetheless, because up to 50% of patients with PCOS may have a normal ratio, the LH and FSH are episodically secreted, and the LH/FSH ratios tend to normalize with increasing BMI, or alternatively with insulin-sensitizer therapy. Measuring gonadotropins is an insensitive marker of PCOS.

Laboratory Assessment for Metabolic Abnormalities

Metabolic abnormalities are common among women with PCOS, and occur in all patients with the HAIRAN syndrome. In patients with the HAIRAN syndrome the presence of insulin resistance is obvious, although this may not be the case in women with PCOS. Unfortunately, there are no accurate, inexpensive, or reproducible tests for clinically assessing insulin sensitivity. The standards are dynamic tests such as the euglycemic clamp and the frequently sampled intravenous glucose tolerance test (FSIVGTT). These assessments primarily determine insulin-mediated glucose uptake in the skeletal muscle, the primary tissue using circulating insulin. Insulin-mediated glucose uptake, however, is just one aspect of insulin's protean actions. While these methods are the most accurate for determining decreased sensitivity to insulin (or insulin resistance), they are too laborious and expensive to use for the routine clinical evaluation of insulin resistance.

A fasting glucose-to-insulin ratio of less than 4.5 may be a good marker of insulin resistance in obese women with PCOS. Although a fasting insulin level alone is often clinically useful in other non-PCOS populations, insulin levels, either fasting or postprandial, have only a moderate correlation with more detailed studies of insulin action, and are less useful in patients with impaired glucose tolerance or frank diabetes, due to deficiencies in insulin secretion. Most important, it is key to understand that there is a wide range of insulin sensitivities in normal populations, and that substantial overlap of even the most precise measure of insulin action between insulin-resistant and control populations is always present. As such, about 50% of obese women with PCOS may not have clinically recognizable insulin resistance on the basis of either fasting values or more dynamic test results. On an individual basis, therefore, it is often not possible to diagnose insulin resistance and a diagnostic trial with an insulin sensitizer should be considered.

Given the high prevalence of abnormalities in glucose tolerance, patients with PCOS or HAIRAN syndrome should be screened for IGT or frank diabetes with an oral glucose tolerance test (oGTT) using a 75-g glucose load. Considering the World Health Organization criteria, IGT is diagnosed by a 2-hour glucose of between 140 mg/dL and 199 mg/dL, while frank diabetes is diagnosed by 2-hour glucose during the oGTT =200 mg/dL. Abnormal oGTT results need to be repeated for confirmation. The development of glucose intolerance heralds ß-cell dysfunction with inadequate insulin secretion for the degree of reduced peripheral insulin sensitivity. The development of IGT is a clear risk factor for developing type 2 DM and may also be an independent risk factor for CVD, such as myocardial infarction and stroke.

Although no firm guidelines exist, obtaining a plasma lipid profile in patients with PCOS or the HAIRAN syndrome should be considered, particularly in women over the age of 35, those with a strong family history of diabetes or CVD, and those with significant insulin resistance.

Radiologic Imaging in the Evaluation of the Patient with Androgen Excess

Routine ultrasound of the pelvis in patients with androgen excess is probably not indicated. Polycystic ovaries can be noted with many of the androgen excess disorders and remain nonspecific (see Fig. 37.8). Nonetheless, the appearance of polycystic ovaries may be useful as a potential predictor for the development of ovarian hyperstimulation syndrome during ovulation induction. Furthermore, a transvaginal sonogram in obese individuals to properly examine the ovaries for pathologic masses may be appropriate. In cases where an androgen-secreting tumor is suspected, a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the adrenals should be considered to exclude adrenal masses as small as 5 mm in diameter and detect bilateral adrenal hyperplasia in the event of a corticotropin-secreting tumor. However, about 2% of the population harbor a clinically insignificant adrenal adenoma (i.e., incidentaloma) making the finding of such an adrenal mass not diagnostic for an androgen-secreting adrenal tumor. Functional radiologic techniques such as selective venous catheterization or scintigraphy with iodomethyl-norcholesterol are rarely used for the localization of such tumors.

TREATMENT OF ANDROGEN EXCESS

Treatment of androgen excess tends to be symptom-based. In general, we can consider four different reasons for treatment including:

1. regulation of uterine bleeding, reducing the risk of endometrial hyperplasia and cancer, dysfunctional uterine bleeding (DUB), and secondary anemia
2. improvement of dermatologic abnormalities such as hirsutism, acne, or alopecia
3. amelioration and prevention of associated metabolic abnormalities, particularly insulin resistance and hyperinsulinemia
4. treatment of the associated anovulatory infertility.

Overall, avenues of treatment include the suppression of androgen production, the blockade of peripheral androgen action, the improvement of any associated insulin resistance and dyslipidemia, and topical, mechanical, or cosmetic measures for improving the dermatologic manifestations of these disorders (Fig. 37.9). The vast majority of patients with androgen excess will require, and benefit the most from, combination therapy.

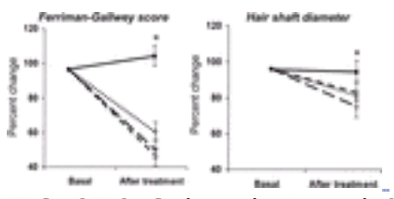

FIG. 37.9. Spironolactone (100 mg/d), flutamide (250 mg/d), and finasteride (5 mg/d) were compared for the treatment of hirsutism in a randomized, double-blind, placebo-controlled trial including 40 affected women. (Modified from Moghetti P, Tosi F, Tosti A, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000;85:89–94, with permission.)

Regulation of Uterine Bleeding

In general, the regulation of uterine bleeding can be achieved with oral contraceptives, cyclic or continuous progestogens, and in some patients with PCOS, with insulin-sensitizing agents, and rarely surgery.

Oral Contraceptives Oral contraceptive medications generally act by suppressing circulating LH and FSH leading to a decrease in ovarian androgen production. In addition, the estrogen in the birth control pill increases SHBG, decreasing free testosterone levels. Furthermore, the progestin in the birth control pill can lead to a beneficial antagonism of 5a-reductase activity and androgen binding to the androgen receptor. Finally, these medications may also decrease adrenal androgen production by a mechanism not yet clear. Oral contraceptives are very effective at regulating uterine bleeding and decreasing the associated risk of endometrial hyperplasia or carcinoma in the hyperandrogenic patient, regardless of etiology. It is preferable, although not critical, to select a pill containing a progestin with low androgenic activity (e.g., norethindrone acetate, ethynodiol diacetate, desogesterol, gestodene, or norgestimate). There is some evidence that oral contraceptives can worsen insulin resistance and glucose tolerance in women with PCOS. However, there is no evidence that these effects of the oral contraceptive pill on glucose metabolism result in an increased risk for developing type 2 DM in the general population, and their use in patients with androgen excess patients not be limited by this concern.

Cyclic or Continuous Progestogens Cyclic progestogen administration is also useful to regulate uterine bleeding in patients with androgen excess, particularly in amenorrheic women. It is not known how many progestin-induced withdrawal bleeds per year are necessary to adequately prevent the development of endometrial cancer in women with PCOS, although extrapolating from the postmenopausal hormone replacement literature, monthly treatment for a minimum of 12 days or longer is optimal. Because progestogen administration can occasionally stimulate an ovulatory event, and because not all these patients are completely anovulatory, it may be preferable to treat sexually active at risk for pregnancy women with continuous oral micronized progesterone, 100 to 200 mg twice daily.

Glucocorticoids Glucocorticoid therapy may be beneficial in regulating menstrual bleeding in the patient with NCAH. However, we have found that NCAH monotherapy is effective primarily in those women whose treatment is initiated in adolescence and that many older patients will require combination therapy. The lowest effective dose of glucocorticoids should be used (e.g., dexamethasone 0.25 mg daily or every other day). Glucocorticoids should be administered with caution

as they have the potential of producing weight gain and cushingoid features, and worsening existing insulin resistance.
Insulin-Sensitizing Agents Drugs developed initially to treat type 2 DM have now also been used to treat PCOS. These include metformin and thiazolidinediones. Other drugs such as acarbose have also been studied in PCOS, and beneficial effects have been reported. However, we should note that none of these agents are currently approved by the Food and Drug Administration (FDA) for the treatment of PCOS or for related symptoms such as anovulation, hirsutism, or acne.
Metformin Metformin was approved for the treatment of type 2 DM by the FDA in 1994, but was used clinically for close to 20 years before that in other parts of the world. Metformin is a biguanide that works primarily by suppressing hepatic gluconeogenesis, but it also improves insulin sensitivity peripherally. Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin, occurring in about 30% of treated women. There is a small risk of lactic acidosis among women taking this medication, which may be triggered by exposure to intravenous iodinated radiocontrast agents in susceptible individuals, although this adverse effect occurs primarily in patients with poorly controlled diabetes and impaired renal function. Metformin therapy has also been found to improve uterine bleeding and menstrual function.
Thiazolidinediones Thiazolidinediones are peroxisome proliferator activating receptor ?-agonists, and are thought to improve insulin sensitivity through a postreceptor mechanism. In a large multicenter trial, troglitazone has been shown to have a dose-response effect in improving ovulation and menstrual dysfunction in women with PCOS. This appears to be mediated through decreases in hyperinsulinemia and decreases in free testosterone levels. Troglitazone has subsequently been removed from the worldwide market due to its potential for inducing hepatotoxicity. Newer thiazolidinediones such as rosiglitazone and pioglitazone appear to be safer in terms of hepatotoxicity, but have also been associated with embryotoxicity in animal studies (both are pregnancy category C). Furthermore, there are limited studies on their effectiveness in PCOS. When using these drugs, liver function tests should be monitored on a regular basis. Combination treatment with other insulin sensitizers, primarily metformin, has been shown to further improve insulin sensitivity and glycemic control in type 2 DM, although the effect of such combination therapy in women with PCOS is not yet clearly delineated.
Surgery In patients with intractable uterine bleeding who have completed their childbearing, consideration may be given to a hysterectomy and bilateral salpingo-oophorectomy. In addition, ovulatory function may also improve following ovarian wedge or laparoscopic ovarian drilling procedures, although the long-term effect of these therapies on menstrual function is unclear.
Weight Loss Multiple studies in hyperandrogenic or women with PCOS have shown that weight loss can lower circulating androgen levels and cause spontaneous resumption of menses. These changes have been reported with a weight loss as small as 5% of the initial weight. In patients with massive obesity, consideration may be given to surgical means of inducing weight loss, such as laparoscopic gastric bypass.

Treatment of Hirsutism, or Androgen Excess-Associated Acne or Alopecia

The treatment of hirsutism can be complex, and has recently been reviewed. Optimum therapy usually requires a combination of approaches, including suppression of circulating androgens (with oral contraceptives, insulin sensitizers, or even long-acting GnRH analogs or glucocorticoids), peripheral androgen blockade (with spironolactone, flutamide, cyproterone acetate, or finasteride); and the use of a topical hair growth inhibitor (eflornithine hydrochloride) or mechanical methods of hair reduction or destruction (electrology or lasers), and appropriate cosmetic measures (bleaching or chemical depilating). Acne in patients with androgen excess can usually be treated with oral contraceptives, accompanied by topical or antibiotic therapies. The treatment of androgenic alopecia may require the use of androgen suppression in combination with androgen blockade and topical means of stimulating hair regrowth (e.g., minoxidil).

Most medical methods alone, while improving hirsutism do not produce the dramatic results that many patients desire. In general, combination therapies appear to produce better results than single agent approaches. Response with medical therapies often take 3 to 6 months to notice improvement, and adjunctive mechanical removal methods are often necessary. However, the majority of women appear to experience improvement in their hirsutism. Unfortunately, there are no universally accepted techniques for assessing the response of hirsutism to treatment. Some of the depilatory treatments used by patients are so effective that it is difficult to ever determine baseline hirsutism and response to treatment such that the patient's subjective assessment guides therapy.

Androgen Suppression Women with documented hyperandrogenemia would theoretically benefit most from androgen-suppression therapy, although in actual practice, the clinical response to this type of therapy does not correlate with androgen levels. Suppression of ovarian androgen secretion has been achieved with oral contraceptives, progestins, or GnRH analog treatment. Oral contraceptives improve hirsutism, although the response of hirsutism to this therapy alone is generally modest. Treatment with a long-acting GnRH agonist may result in a greater lowering of circulating androgens, and theoretically a greater degree of hair growth suppression, although comparative trials against other agents and combined agent trials have yielded mixed results. It should be noted that a long-acting GnRH agonist given alone results in unacceptable bone loss. Glucocorticoid suppression of the adrenal glands also offers theoretical benefits, but deterioration in glucose tolerance is problematic for women with PCOS, and long-term effects such as osteoporosis are a significant concern. Furthermore, glucocorticoid suppression produces only minimal improvements in hair growth in hirsute women.
Androgen Receptor Antagonists Androgen receptor antagonists antagonize the binding of testosterone and other androgens to the androgen receptor. As a class therefore, they are teratogenic, and pose risk of feminization of the external genitalia in a male fetus, should the patient conceive. Spironolactone, a diuretic and aldosterone antagonist, binds to the androgen receptor with 67% of the affinity of DHT. It has other mechanisms of action, including inhibition of ovarian and adrenal steroidogenesis, and direct inhibition of 5-a-reductase activity. Hirsutism and acne have been successfully treated with spironolactone. The usual dose for the treatment of hirsutism is 25 to 100 mg twice a day, and the dose should be titrated to minimize the potential for side effects. About 20% of women given spironolactone will experience increased menstrual frequency, a reason for combining this therapy with oral contraceptive. Other side effects include polyuria, orthostatic hypotension, nausea, dyspepsia, and fatigue. Because spironolactone can cause and exacerbate hyperkalemia, it should be used cautiously in patients with renal impairment, and should not be combined with other potassium-sparing diuretics. The medication also has potential teratogenicity as an anti-androgen, although exposure has rarely resulted in ambiguous genitalia in male infants. Flutamide is another nonsteroidal anti-androgen that has been shown to be effective against hirsutism. The most common side effect is dry skin, but its use has rarely been associated with hepatitis. A dose of 250 mg per day is generally used. Because there is greater risk of teratogenicity with this compound, contraception should be used.
5a-Reductase Inhibitors There are two forms of the enzyme 5a-reductase: type 1, predominantly found in the skin and type II, predominantly found in the prostate and reproductive tissues. However, both forms are found in the pilosebaceous unit (PSU) and may contribute to the development of hirsutism, acne, and alopecia. Finasteride inhibits both forms of 5a-reductase, and is available as a 5-mg tablet for the treatment of prostate cancer and a 1-mg tablet for the treatment of male alopecia. It has been found to be effective for the treatment of hirsutism in women. Finasteride is better tolerated than other antiandrogens, but has the highest and clearest risk for teratogenicity in a male fetus and adequate contraception must be used. Overall, randomized trials have found that spironolactone, flutamide, and finasteride have similar efficacy in improving hirsutism (see Fig. 37.9).
Insulin-Sensitizing Agents and Lifestyle Modification It is difficult to separate the effects of an improvement in insulin sensitivity from that of androgen suppression, as any improvement in insulin sensitivity can raise SHBG and thus lower bioavailable androgen. Given the long onset of action for improving hirsutism and acne, longer periods of observation are needed. In the largest and longest randomized trial to date of these agents, troglitazone, in a dose-response fashion, was found to significantly improve hirsutism in women with PCOS without lowering total testosterone, a benefit presumably achieved through the decrease in free testosterone. Weight loss in the obese patient may also benefit hirsutism and acne, albeit modestly. Increases in SHBG through improved insulin sensitivity from weight loss may lower bioavailable androgen levels. About 50% of the women who lose weight experience an improvement in their hirsutism.
Topical Hair Growth Suppression—Ornithine Decarboxylase Inhibitors Ornithine decarboxylase is necessary for the production of polyamines, and is also a sensitive and specific marker of androgen action in the prostate. Inhibition of this enzyme limits cell division and function, including that of the PSU. A potent inhibitor of this enzyme, eflornithine, has been found to be effective as a facial cream for the treatment of unwanted facial hair. It is available as a 13.9% cream of eflornithine hydrochloride, and is applied to affected areas twice daily. In clinical trials, 32% of patients had marked improvement after 24 weeks compared to 8% of women given placebo, and the benefit was first noted at 8 weeks. It is pregnancy category C. The cream appears to be well tolerated, with only about 2% of patients developing skin irritation or other adverse reactions.
Mechanical and Cosmetic Means of Hair Reduction and Destruction Mechanical hair removal methods (shaving, plucking, waxing, depilatory creams, electrolysis, and laser vaporization) can assist in controlling hirsutism, and often are the front line of treatment used by women. Shaving, bleaching, or chemical depilation may be useful temporary treatments for unwanted hairs. Although shaving can lead to a blunt hair end that may feel “stubble-like,” it does not lead to a worsening of hirsutism. Depilating agents, while useful, can result in chronic skin irritation and worsening of hirsutism if used excessively or indiscriminately. The use of plucking or waxing in androgenized skin areas should be discouraged since these techniques not only do not kill the hair follicles, but also can induce folliculitis and trauma to the hair shaft with subsequent development of ingrown hairs and further skin damage. Electrolysis (i.e., electroepilation) results in long-term hair destruction, but this therapy is time consuming. Side effects may include temporary skin irritation, and rarely burning and scarring of the skin. Hair reduction via lasers can also be useful for selected patients. The main objective of laser therapy for hair removal is to selectively cause thermal damage of the hair follicle without destroying adjacent tissues, a process termed *selective photothermolysis.* Selective photothermolysis relies on the selective absorption of a brief radiation pulse to generate and confine heat at specific pigmented targets. Lasers useful in hair removal may be grouped into three categories based on the type of laser or light source each employs:

1. red light systems (694 nm ruby)
2. infrared light systems (755 nm alexandrite, 800 nm semiconductor diode, or 1,064 nm neodymium: yttrium-aluminum-garnet [Nd:YAG])
3. intense pulsed light (IPL) sources (590–1200 nm).

In general, laser hair removal is most successful in patients with fairer skin, who have dark color hairs. However, repeated therapies are necessary, and complete alopecia is rarely achieved. In general, treatment with the ruby, alexandrite, or diode lasers, or the IPL results in similar success rates, although it appears to be somewhat lower for the Nd:YAG laser. After laser-assisted hair removal, most patients experience erythema and edema lasting no more than 48 hours. Blistering or crusting may occur in 10% to 15% of patients. Temporary hyperpigmentation occurs in 14% to 25% of patients and hypopigmentation occurs in 10% to 17% of patients. Dyspigmentation is less common with the use of longer wavelengths, as in the alexandrite or diode lasers, and longer pulse durations. Overall, laser hair removal is a promising technique for the treatment of the hirsute patient. Nonetheless, we should note that most studies have been uncontrolled and included fewer than 50

patients, none have been blinded, and all have used a variety of treatment protocols, equipment, skin types, and hair colors studied.

Treatment of Associated Metabolic Abnormalities

The treatment of any associated metabolic abnormalities includes lifestyle alterations and weight reduction, and the use of insulin sensitizers and possibly lipid-lowering agents. Multiple studies have shown that improving insulin sensitivity, through lifestyle modifications or by pharmacologic intervention, can result in lowered circulating androgens (primarily mediated through a reduction in bioavailable androgen), and an increase in the spontaneous ovulation and pregnancy rates. In addition, it is possible that a decrease in insulin resistance may decrease the risk that patients with PCOS will develop type 2 DM. In support of this, data from the Diabetes Prevention Program, which enrolled men and women at risk for diabetes, demonstrate that lifestyle interventions have a more profound effect on preventing the development of subsequent type 2 DM than does the sole use of metformin, although both interventions were superior to placebo. However, long-term studies documenting a decrease in such sequelae as endometrial cancer, type 2 DM, or CVD with improvements in insulin sensitivity are still lacking among women with PCOS.

The gold standard for improving insulin sensitivity in obese women with PCOS should be weight loss, diet, and exercise. Obesity has become epidemic in our society and contributes substantially to reproductive and metabolic abnormalities in PCOS. Unfortunately there are no effective treatments that result in permanent weight loss, and it is estimated that 90% to 95% of patients who experience a weight decrease will relapse. In addition to improving the endocrine aspects of PCOS, weight loss can decrease circulating insulin levels. Unfortunately there have been few studies on the effect of exercise alone on insulin action in women with PCOS, although it is reasonable to assume that exercise would have the same beneficial effects in women with PCOS as women with type 2 DM.

Treatment of Hyperandrogenic Oligoovulatory Infertility

A full discussion of the treatment of oligoovulatory infertility is beyond the scope of this chapter. In brief, ovulation induction for the treatment of androgen-excess–related infertility typically includes the use of clomiphene citrate and human gonadotropins. In women with PCOS there are a variety of methods available to improve ovulatory function that act through a different mechanism (Fig. 37.10). For example, in patients with PCOS, insulin-sensitizer therapy, either alone or in combination, may be useful for improving ovulatory function and pregnancy rate. One of the more commonly used drugs for this purpose is metformin.

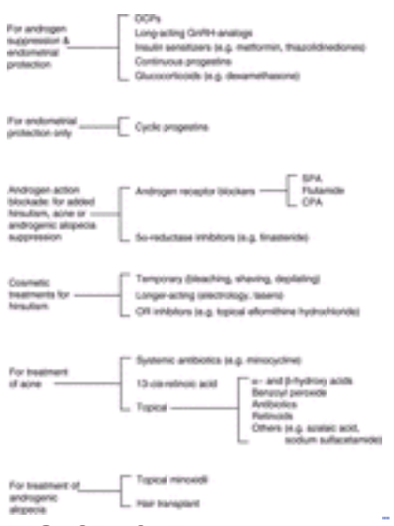

FIG. 37.10. Treatment strategies in the patient with androgen excess.

SUMMARY POINTS

- Androgen excess (i.e., hyperandrogenism) is one of the most frequent, albeit heterogeneous, endocrine disorders of women; the most common etiology of androgen excess, polycystic ovary syndrome (PCOS), affects 4% to 6% of unselected women of reproductive age.
- Androgen excess results in various clinical signs and symptoms including abnormalities of the pilosebaceous unit (hirsutism, acne, and androgenic alopecia), the hypothalamic–pituitary–ovarian axis (i.e., ovulatory and menstrual dysfunction), and the hypothalamic–pituitary–adrenal axis (adrenal androgen excess). If the androgen excess is very severe, virilization or masculinization can also be apparent.
- Common signs of androgen excess are hirsutism and acne, although in up to 15% of such patients, no obvious ovulatory or endocrine abnormality may be observed (i.e., idiopathic hirsutism). Alternatively, not all women with androgen excess will have hirsutism or acne.
- The vast majority of androgen excess is due to PCOS, with 21-OH–deficient nonclassic adrenal hyperplasia (NCAH), the hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome, androgen-secreting tumors, and drug-induced hyperandrogenism generally accounting for less than 10% of such patients.
- PCOS is a diagnosis by exclusion, basically defined as the presence of androgen excess (hyperandrogenemia or clinical evidence of androgen excess) combined with chronic oligoanovulation, after the exclusion of related disorders (e.g., 21-OH–deficient NCAH, thyroid dysfunction, hyperprolactinemia). Polycystic-appearing ovaries alone are insufficient for the diagnosis of PCOS, and their absence is not exclusionary.
- Approximately 50% to 60% of patients with PCOS suffer from insulin resistance and hyperinsulinism, and are at higher risk for the development of endometrial cancer, glucose intolerance, and type 2 diabetes mellitus. They also have an adverse cardiovascular risk profile.
- The history and physical examination are essential to making a diagnosis of the underlying cause of androgen excess. The laboratory evaluation should have the objective of excluding related and specific disorders and, if necessary, providing confirmation of androgen excess. As well, the presence of metabolic abnormalities, particularly in patients with PCOS or the HAIRAN syndrome, should be sought out.
- Treatment of androgen excess tends to be symptom-based, with reasons for treatment including: (a) regulation of uterine bleeding and reducing the risk of endometrial hyperplasia and cancer, dysfunctional uterine bleeding, and secondary anemia; (b) improvement of dermatologic abnormalities such as hirsutism, acne, or alopecia; (c) amelioration and prevention of associated metabolic abnormalities, particularly insulin resistance and hyperinsulinemia; and (d) treatment of anovulatory infertility.
- Overall, avenues of treatment of androgen excess include the suppression of androgen production, the blockade of peripheral androgen action, the improvement of any associated insulin resistance and dyslipidemia, and topical, mechanical, or cosmetic measures for improving the dermatologic manifestations of these disorders. The vast majority of patients with androgen excess will require and benefit the most from combination therapy.

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Chapter 38

Julia Johnson

Infertility

EVALUATION: INITIAL ASSESSMENT
EVALUATION: TESTING
EVALUATION: ADVANCED
- Male Factor
- Ovulation Dysfunction
- Uterine/Tubal Factor

TREATMENT
- Male Factor
- Ovulatory Dysfunction
- Uterine/Tubal Factor
- Unexplained Infertility
- Advanced Maternal Age

SUMMARY POINTS

SUGGESTED READINGS
- Evaluation: Testing
- Evaluation: Advanced
- Treatment

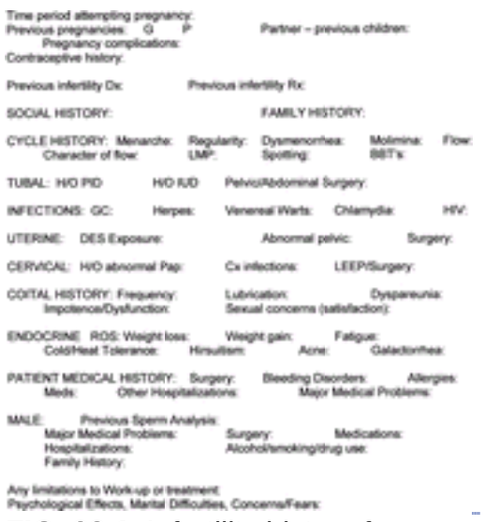
Infertility affects approximately 14% of couples and is a medical concern for 2.7 million women of reproductive age in the United States. Over the past decade, successful treatments for virtually all causes of infertility have been developed, offering hope for couples with this medical condition. Unfortunately, many states continue to offer limited insurance coverage for infertility minimizing effective diagnosis and treatment despite evidence that providing infertility care does not increase insurance costs. It is the goal of this chapter to identify the basic diagnostic testing for couples with infertility that can allow the couple to rapidly move on to proven therapeutic options. Prompt diagnosis and effective treatment will maximize the opportunity for conception while minimizing the cost of infertility care.

Infertility is defined as 1 year of unprotected intercourse without conception. Fecundability is the chance of conception in one menstrual cycle, and per cycle fecundity is commonly used to identify the success rate of an infertility treatment. It is expected that approximately 25% of healthy young couples will conceive in a single cycle, although clearly the chance of conception drops throughout the first year without contraception. The per cycle fecundity falls below 10% after 7 cycles and only 3% of couples conceive during the 12th cycle. Although it is reasonable to wait 1 year to begin the infertility evaluation for young couples with no history suggestive of reproductive disorders, it is reasonable to begin the workup sooner in couples with a positive history for a fertility-lowering disease or advancing age. Decreased fecundity begins for women in the mid-30s, making it reasonable to begin the diagnosis and treatment of infertility for this age group following 6 months of unsuccessful attempts at pregnancy. When one or both members of the couple have a history suggestive of a disorder potentially altering reproduction, the diagnostic testing of infertility should begin immediately. Thus, it is critical for the obstetrician-gynecologist to consider both the history and physical examination of both members of the couple as well as advanced maternal age when deciding when to begin the infertility evaluation.

The increased diagnostic techniques and available treatments for infertility have raised the concern that infertility is a new disorder, increased by the exposure of men and women to environmental factors or high-risk behavior. Although the advancing age of the first pregnancy in our society does increase the risk of infertility, the primary explanation for advancing infertility treatment is the increased awareness of this disorder by patients. It is now socially acceptable for men as well as women to seek treatment for infertility. As patients continue to increase their knowledge of this disorder and learn of successful therapies, providers will increasingly be asked to provide prompt diagnosis and effective treatment.

EVALUATION: INITIAL ASSESSMENT

As with all medical problems, the first step in the evaluation of infertility is a thorough medical history and physical examination. Figure 38.1 demonstrates the history form used by the Reproductive Endocrinology and Infertility Division at the University of Vermont. Ovulation dysfunction, tubal risk factors, uterine and cervical abnormalities, peritoneal factors, and male factors are often identified at the initial visit. It is important for both members of the couple to be interviewed at this first meeting with the health care provider.


Time period attempting pregnancy:
Previous pregnancies: G P Partner – previous children:
Pregnancy complications:
Contraceptive history:

Previous infertility Dx: Previous infertility Rx:

SOCIAL HISTORY: FAMILY HISTORY:

CYCLE HISTORY: Menarche: Regularity: Dysmenorrhea: Molimina: Flow:
Character of flow: LMP: Spotting: BBT's:

TUBAL: H/O PID H/O IUD Pelvic/Abdominal Surgery:

INFECTIONS: GC: Herpes: Venereal Warts: Chlamydia: HIV:

UTERINE: DES Exposure: Abnormal pelvic: Surgery:

CERVICAL: H/O abnormal Pap: Cx infections: LEEP/Surgery:

COITAL HISTORY: Frequency: Lubrication: Dyspareunia:
Impotence/Dysfunction: Sexual concerns (satisfaction):

ENDOCRINE ROS: Weight loss: Weight gain: Fatigue:
Cold/Heat Tolerance: Hirsutism: Acne: Galactorrhea:

PATIENT MEDICAL HISTORY: Surgery: Bleeding Disorders: Allergies:
Meds: Other Hospitalizations: Major Medical Problems:

MALE: Previous Sperm Analysis:
Major Medical Problems: Surgery: Medications:
Hospitalizations: Alcohol/smoking/drug use:
Family History:

Any limitations to Work-up or treatment:
Psychological Effects, Marital Difficulties, Concerns/Fears:

FIG. 38.1. Infertility history form.

The known causes of infertility and their incidences are listed in Table 38.1. The history should explore for ovulatory dysfunction by examining the age of menarche, cycle length, history of increased or decreased intervals between cycles, and physical symptoms of ovulation and hormone production such as mittelschmerz and premenstrual molimina. If ovulatory dysfunction is identified, an endocrine review of systems is valuable to determine the etiology of the irregular menses. Information regarding thyroid symptoms, androgen excess, marked weight changes, and galactorrhea should be obtained. Signs of decreased ovarian function, such as shortened menstrual cycle length, new onset of irregular cycles, or hot flashes can indicate a contributing factor to infertility. The menstrual history may also point to other causes of infertility. Worsening dysmenorrhea, intermenstrual bleeding, and menorrhagia may point to diseases in the pelvic peritoneum or uterus.

Main causes
Sperm defects or dysfunction, 30% (including spermatogenic failure [i.e., complete or virtually complete failure leading to azoospermia] in 1%–2%, seminal sperm antibodies in 5%, and varicocele in 1%–2%).
Ovulation failure (amenorrhea or oligomenorrhea), 25% (including primary ovarian failure in 1%–2%).
Tubal infective damage, 20%
Unexplained infertility, 25%
Other causes
Endometriosis (causing tubal or ovarian structural damage), 5%
Coital failure or infrequency, 5%
Cervical mucus defects or dysfunction, 3%
Uterine abnormalities (e.g., fibroids), rare as a true cause
Genital tuberculosis, rare in developed countries
General debilitating illnesses, rare

TABLE 38.1. *Causes of infertility and their approximate frequencies*

Risk factors for tubal factor infertility have been shown to be excellent predictors of tubal damage. A history of sexually transmitted diseases (STDs), pelvic inflammatory disease, pelvic surgery, ruptured appendix, septic abortion, endometriosis, and ectopic pregnancy can point to a heightened risk of tubal factor infertility. A history of uterine leiomyoma or uterine and cervical surgery may also affect fertility. The abdominal and pelvic exam can identify pelvic masses, cul-de-sac nodularity, irregular uterine contour, and fixed pelvic structures, suggestive of tubal damage or peritoneal disease.

The history from the male partner is crucial, as sperm abnormalities account for 30% to 40% of infertility. STDs and other genitourinary infections, chemotherapy or radiation therapy, mumps during adolescence, testicular surgery or injury, and decreased ejaculatory function suggest reasons for infertility. Chronic exposure to extreme heat may alter sperm motility and exposure to gametotoxic chemicals, such as the nematocide dibromocloropropane, may affect sperm production. Certain medications, such as cimetidine and sulfasalazine, are associated with decreased sperm production. Cystic fibrosis is associated with bilateral absence of the vas deferens. An examination of the male partner, either by the obstetrician-gynecologist or a medical colleague, is critical. Abnormal body habitus, lack of testicular descent, penile abnormalities, diminished size and consistency of the testes, and the presence of a varicocele may offer explanations for infertility.

Medical histories and family histories from the couple are important to identify factors that may complicate pregnancy. Preconceptual counseling is typically recommended for women with a history of diabetes, hypertension, heart disease, autoimmune diseases, severe pulmonary disease, breast or gynecologic cancer, and infectious diseases such as human immunodeficiency virus (HIV) and hepatitis. The use of medications, particularly those associated with fetal malformations such as isotretinoin for severe cystic acne, should be considered. Carrier screening can be offered for inherited disorders, such as cystic fibrosis, Tay-Sachs, thalassemia, and sickle cell anemia, based on the risk profile for each couple. A family history of genetic disorders such as fragile X and Down syndrome (trisomy 21) may lead to a need for genetic counseling. Women anticipated to be over the age of 35 at delivery should receive information about diagnostic testing during pregnancy by chorionic villus sampling and amniocentesis. The American College of Obstetricians and Gynecologists (ACOG) technical bulletin on preconceptional care is a valuable tool for all providers evaluating couples with infertility.

The social and lifestyle history is also very important for the infertile couple. Smoking, alcohol abuse, and drug abuse have an adverse effect of fertility in both men and women. Smoking is particularly harmful as it is associated with oocyte toxicity and an earlier age of menopause. Excessive exercise and anorexia may adversely affect both ovulation and sperm production. Exposure to potential teratogens, such as lead, should be excluded by the history. Although alterations in the usual dietary intake do not benefit the infertile couple, it is critical for women to begin taking at least 400 µg of folic acid and avoid alcohol intake once they conceive. Victims of sexual and physical abuse may be markedly affected by the intensive testing and treatment required for infertility. It is important to identify these potential emotional barriers prior to beginning the evaluation. Finally, infertility is remarkably stressful and can lead to dysfunction or even dissolution of the couple's relationship. One of the key members of any infertility team is the counselor or psychologist who is experienced in helping couples deal with the stresses involved in testing and treatment for infertility. Appropriate referrals to this individual will be discussed in the “ Treatment” section of this chapter, but often it is best to involve this member of team from the start of the evaluation.

EVALUATION: TESTING

The amount of testing for most medical conditions has increased markedly over the past decade. By contrast, as our understanding of infertility increases, the testing has simplified. Some tests have been eliminated as they are now known to be of limited value or do not alter the treatment decisions. The basic evaluation now includes only three tests—semen analysis, ovulation monitoring, and uterine/tubal evaluation—that can be completed in 1 to 2 months. Although additional testing may be indicated, for most couples the cause of infertility is identified and they may proceed rapidly to the appropriate treatment. This lessens the stress of the workup and minimizes the cost. Studies suggest that the majority of reproductive endocrinology and infertility subspecialists have minimized their infertility evaluation and authors have noted that a “targeted” evaluation is cost-effective and limits stresses for the couple. This section will examine the basic evaluation, the indications for expanded evaluation, and the justification for the elimination of previous testing methods.

The semen analysis remains the primary method for evaluation of the male partner. This test clearly identifies subfertile men. The World Health Organization criteria in Table 38.2 are well established and were republished in 1999. Alternatives in the basic criteria may occur at some centers; the use of Kruger's strict morphology has been associated as an improved predictor of sperm function during in vitro fertilization (IVF) cycles. Some centers use a computer-assisted semen analysis (CASA). It is important that your laboratory is experienced in the assessment of sperm, but the basic semen analysis is satisfactory for clinical care. If the initial semen analysis is abnormal, it is important to be certain that the specimen was fully collected, without undue stress, not exposed to excessive heat, not contaminated by lubricants or soaps, and that the patient did not have a recent severe illness within the past 3 months that might adversely impact sperm production. Repeat semen analysis is typically obtained to confirm male infertility. Although it is ideal to wait 90 to 108 days to allow new production of sperm, this delay in the workup is not generally recommended, and collection within a month is acceptable.

Parameter	Value
Ejaculate volume	≥ 2.0 mL
pH	7.2–7.8
Sperm density	≥ 20 million/mL
Total sperm count	≥ 40 million
Motility	≥ 50%
Forward progression	
Morphology	> 30% normal forms
No significant sperm agglutination	
No significant pyospermia	
No hyperviscosity	

TABLE 38.2. *Semen analysis: minimal standards of World Health Organization (WHO) criteria for normal semen values*

Although ovulation can be assumed in women with regular menses and premenstrual moliminal symptoms, ovulation should be confirmed. Only 1 month of documented ovulation is required; there is no value and significant frustration with many months of ovulation testing. There are three methods to evaluate ovulation. The classic method is a basal body temperature chart. This method is low cost, fairly reliable, and informs the patient of her timing of ovulation. It is important for the provider to evaluate this form with the patient, as it is notoriously difficult for patients to interpret. A simpler, but more costly method is the luteinizing hormone (LH) or ovulation predictor kit. Unlike the temperature chart, this method identifies the timing of ovulation 24 to 36 hours prior to release of the oocyte. This may be of value to patients whose lifestyles limit midcycle coitus. Finally, a serum progesterone greater than 3 ng/mL indicates ovulation is occurring. Although the timing of ovulation and the length of the follicular and luteal phase are not identified, this simple test unequivocally documents ovulation. Ultrasound, cervical mucus examination, and endometrial biopsy can also suggest or confirm ovulation, though these tests are less frequently used because of consideration of reliability and cost.

For women over the age of 30, testing for decreased ovarian function should be added to the assessment of ovulation. The effect of advancing maternal age on fertility will be fully discussed later in the chapter, but there is no doubt that fertility begins to decrease in the mid-30s. Although the method of testing may improve as our understanding of the menopausal transition increases, the classic test is a day 3 follicle-stimulating hormone (FSH) level. Normal values for day 3 FSH vary between laboratories with the current assays identifying decreased ovarian function with a level greater than 10 to 15 IU/L. Although pregnancy can occur in women with elevated day 3 FSH levels, the chance of pregnancy is markedly reduced with IVF. Alternatively, a low day 3 FSH should not falsely reassure women of the success of infertility treatment. This test primarily reassures the number of oocytes remaining (i.e., ovarian reserve), not oocyte quality. The chance of pregnancy in the late 30s and 40s is reduced, compared to younger women, even with a normal day 3 FSH level. This test cannot be used to offer hope for women with advanced maternal age. Other forms of ovarian reserve testing: the clomiphene citrate challenge test and a day 3 inhibin B level, have been used by some infertility specialists but are not of general applicability. The clomiphene challenge test measures a day 3 FSH and estradiol level, followed by 100 mg per day of clomiphene citrate on cycle days 5 to 9 and a day 10 FSH. Studies have suggested that the clomiphene challenge test may be a better predictor of decreased ovarian reserve for older women and those with unexplained infertility.

Following the semen analysis and ovulation monitoring, the basic investigation is completed by an evaluation of the uterus and fallopian tubes. As with ovulation monitoring, there are several options for testing, but the primary method is the hysterosalpingogram (HSG). This test, although mildly uncomfortable and having a 1% risk of postprocedure infection, offers the benefit of visualization of both the uterine cavity and the fallopian tubes. The test is performed in the early to mid-follicular phase to avoid interfering with tubal function following ovulation. Slow introduction of dye into the cervical canal below the internal os by someone skilled in the technique allows the best visualization of the uterine cavity and minimizes discomfort during the procedure. If any abnormality of tubal architecture is identified, antibiotics, usually doxycycline 100 mg b.i.d. for 5 days, are typically advised. Oil-based dye has been associated with increased pregnancy rates for a few months following the HSG, but its persistence in obstructed tubes is problematic. Water-based dye can be used initially to assure tubal patency, followed by oil-based dye as a therapeutic measure. If tubal patency does not need to be assessed, the woman can undergo uterine evaluation using ultrasound with saline injection sonohysterography, or office hysteroscopy. For women with known or strongly suspected tubal damage, moving promptly to operative laparoscopy and diagnostic hysteroscopy avoids the need for the HSG. A strong argument can be made for screening for tubal damage secondary to sexually transmitted diseases by testing for antichlamydial antibodies, and proceeding directly to surgery if the testing is positive. For women with no apparent risk factors for tubal factor infertility, however, the

HSG offers valuable information and results in increased fertility.

Following the basic workup, the couple will benefit from consultation with the provider. If additional testing is required to fully define the cause of male factor, ovulatory factor, or tubal/uterine factor infertility, this advanced evaluation and potential treatment options can be discussed and planned with the couple. If infertility remains unexplained, the provider may advise moving directly to treatment. In the past, all couples underwent advanced male factor testing, postcoital testing, timed endometrial biopsies, and laparoscopy/hysteroscopy before the infertility evaluation was considered complete. Although advanced testing may still be advised in selected cases, most couples benefit from rapid completion of testing and prompt initiation of effective therapy. The value of advanced testing for selected patients will be considered, but the basic workup is adequate to determine effective treatment options for most couples. Figure 38.2 demonstrates the basic infertility workup followed by more advanced evaluation.

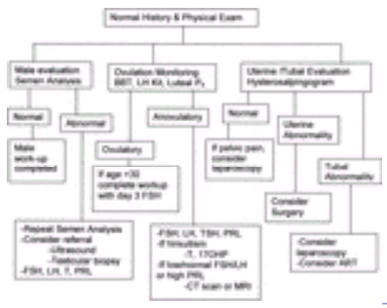


FIG. 38.2. Basic workup for couple with infertility.

EVALUATION: ADVANCED

Male Factor

If an abnormal semen analysis is identified, further workup may be indicated prior to moving on to treatment. If a history and physical exam have not yet been done, this may identify the cause of the abnormal test. Although controlled trials have not demonstrated efficacy, surgical ligation of a varicocele increases sperm motility, and finding a varicocele may lead to potential therapy. Hormonal testing—testosterone, FSH, LH, and prolactin—is of value for identifying a hypothalamic, pituitary, or testicular etiology for oligospermia or azoospermia, particularly when low male libido is noted. A fructose level and possible testicular biopsy can differentiate obstruction from testicular failure in men with azoospermia. If leukocytes are present in semen, bacterial cultures and antibiotic treatment are indicated. Unfortunately, most men with an abnormal semen analysis have idiopathic oligoasthenospermia. Although this is frustrating for the patient, very effective treatment options are available for unexplained male factor infertility.

The value of additional sperm testing in men with normal examination and hormonal testing, prior to proceeding with therapy, is debated. Abnormalities in seminal fluid have also been evaluated by antisperm antibody testing. Although studies suggest decreased fertility with the presence of antisperm antibodies, this finding does not affect the therapeutic choices of intrauterine insemination (IUI) or IVF. As a result, the value of this test remains unproven. The value of sperm function testing is also controversial. Many assays have been developed to evaluate sperm function—in vitro sperm penetration of hamster oocytes, hypoosmotic swelling, viability staining, sperm capacitation, acrosomal reaction bovine cervical mucus, sperm penetration, and human zona binding. Unfortunately, these tests have limited prognostic value and cannot consistently predict the effectiveness of selected treatments. Currently, these tests are limited to experimental use.

Inherited and medical problems can adversely affect fertility. Retrograde ejaculation can occur with diabetes, certain neurologic disorders, and pelvic surgery. The presence of sperm in the bladder can be determined by examining a post-ejaculation urine sample. Klinefelter syndrome can result in azoospermia and men with cystic fibrosis may have bilateral congenital absence of the vas deferens. Microdeletions of the Y chromosome have been associated with oligospermia. Testing for microdeletions of the Y chromosome is not yet standard practice, but it is important to inform men of the possibility of an inherited condition being passed to male children as a result of newer treatment techniques. Genetic screening can be offered to all men with nonobstructive severe oligospermia and azoospermia.

Ovulation Dysfunction

Women with oligomenorrhea and amenorrhea should be evaluated for the hypothalamic, pituitary, ovarian, or adrenal etiology of their condition. Often the history and physical examination will point to the cause of her irregular menses; there is limited value in obtaining a basal body temperature chart of LH predictor kit for women with markedly irregular menses. The most common causes of hypothalamic amenorrhea are due to weight loss (eating disorders) and excessive exercise. Rare causes include Kallmann syndrome and hypothalamic lesions. Pituitary disorders include hyperprolactinemia, thyroid disease, Cushing disease, and Sheehan syndrome. Women with significant hyperprolactinemia or unexplained hypothalamic hypogonadism should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) to determine if a hypothalamic lesion or pituitary adenoma is present. Ovarian dysfunction is most commonly due to anovulation (World Health Organization [WHO] type II or polycystic ovarian syndrome accounting for the majority of cases). A less common etiology is premature ovarian failure, although decreased ovarian function occurs many years before menopause. The classic laboratory testing for women with oligoamenorrhea is a fasting prolactin, thyroid-stimulating hormone (TSH), FSH, and LH. Women with hirsutism should also have testosterone and 17-hydroxyprogesterone levels drawn to rule out ovarian neoplasm or late-onset adrenal hyperplasia. Women with suspected polycystic ovary syndrome (PCOS) are known to be at increased risk for hyperlipidemia, insulin resistance, and adult-onset diabetes (type II); a lipid profile and fasting glucose are recommended. The classic progestin challenge test, 10 mg of medroxyprogesterone acetate for 10 days, may be of some value, as women with hypoestrogenism will typically not have withdrawal bleeding due to progestins. Chapter 34 and Chapter 37 further discuss the evaluation of women with ovulatory dysfunction.

The use of the timed, luteal phase endometrial biopsy to assess for a minor ovulatory disturbance is now in question. There is a false-positive rate of 30% to 40% with a single endometrial biopsy. The rate of luteal phase defect when two biopsies are performed is estimated to be 7%. Luteal phase defects appear to be a rare cause of infertility and extensive testing is required to identify this problem. Additionally, the medications used for the treatment of unexplained infertility are also used to correct luteal phase defects, making a precise diagnosis less important. Women with a markedly shortened luteal phase by basal body temperature chart and normal hormonal workup may be treated empirically with medication, such as progesterone, clomiphene citrate, and gonadotropins for correction of a presumed luteal phase defect or unexplained infertility.

Uterine/Tubal Factor

Women with a history of tubal disease or significant risk factors for pelvic adhesions, such as extensive pelvic surgery, a ruptured appendix, or pelvic inflammatory disease, may elect to avoid the hysterosalpingogram and proceed directly to laparoscopic surgery. The risk of postprocedure infection is increased in these women and some authors have recommended preprocedure antibiotic therapy (100 mg doxycycline p.o. b.i.d. × 5 to 7 days). For most women, however, the HSG remains a reasonable test for uterine and tubal disorders. To evaluate the uterus alone, or in women with iodine allergies, sonohysterography or hysteroscopy can identify leiomyoma, polyps, and müllerian anomalies, and can replace the HSG.

The use of routine diagnostic laparoscopy following a normal HSG is no longer the standard infertility workup. Extensive peritubal adhesions in women with a negative history and normal HSG is rare. The most common finding at laparoscopy for women with otherwise unexplained infertility is endometriosis. The effect of severe endometriosis on fertility is not questioned, but the link between mild to moderate endometriosis and infertility remains an enigma. Research does suggest decreased fertility in women with endometriosis undergoing donor insemination. One study demonstrated an increase in fertility following laparoscopic laser ablation of mild endometriosis, but the value of surgical therapy requires further evaluation. Women with debilitating pain related to possible endometriosis, such as dysmenorrhea and dyspareunia, may benefit from laparoscopic treatment. The delay in conception required by medical therapy for pain argues for surgical treatment when symptomatic endometriosis is suspected. However, routine diagnostic laparoscopy for the identification and treatment of possible endometriosis must be compared to the benefit of proceeding with other treatment options. As will be discussed, the successful treatment of unexplained and endometriosis-related infertility argues for the selected use of laparoscopy surgery for the infertile woman.

Evaluation of cervical mucus was previously a routine part of the evaluation for infertility. Although women with a history of cervical surgery such as conization or loop electroexcision may benefit from treatment that bypasses the cervix, the postcoital test was shown to have limited predictive value of future fertility. The primary limitation of this test is its inability to predict fertility based on the number of motile sperm. It is clear that the postcoital test cannot replace the semen analysis as a test for male factor infertility. An argument can be made for an evaluation of preovulatory cervical mucus without a postcoital evaluation of sperm in the mucus. The woman herself can assess her spinnbarkeit, or mucus stretchability to 8 to 10 cm, prior to ovulation. If she has a history of cervical surgery and poor mucus production, a

cervical factor can be presumed and treated appropriately.

The evaluation for infertility is now simplified in couples with negative histories and normal physical examinations. Although hormonal testing may be indicated for both men and women, and laparoscopy or hysteroscopy has a role in the evaluation of selected women, the basic workup should be limited to semen analysis, ovulation monitoring, and uterine/tubal evaluation. The value of advanced male testing, endometrial biopsy, and postcoital test is limited. Until research can confirm that these tests are consistent and have predictive value, they can be removed from the basic infertility evaluation.

TREATMENT

Once the cause of infertility is determined to the extent possible by current techniques, the health care provider can advise the couple regarding treatment choices. Advances in infertility treatment offer virtually all couples a reasonable opportunity for pregnancy. Before moving onto treatment, it is critical for the provider to recognize the stress of infertility therapy and actively involve a counselor or psychologist in the care of couples with infertility. There are limited data that suggest increased pregnancy rates with stress reduction, but the primary benefit is to maintain the well-being of couples seeking to achieve their family. RESOLVE, the national support organization for couples with infertility, is an excellent source of information and support for infertile men and women. It is also important for providers to encourage and support a couple's decision to pursue adoption or remain child-free. The program at the University of Vermont College of Medicine offers free exams for adoption physicals for the couple as a symbol of our support for these alternative decisions.

The remainder of this section highlights the treatment options for male factor, ovulatory disorders, uterine/tubal factor, unexplained infertility, and advanced maternal age.

Male Factor

The basic treatments for male factor infertility have improved over the past decade. Although donor sperm continues to be a viable option for many couples, IUI (intrauterine insemination) and IVF (in vitro fertilization) with intracytoplasmic sperm injection (ICSI) now offer an excellent opportunity for many couples. Surgery remains the primary treatment for obstructive azoospermia secondary to previous vasectomy or injury. Additionally, surgical ligation of a varicocele improves sperm motility, although controlled trials demonstrating an improvement in fertility are lacking. Medical therapy for male factor infertility, with the exception of treatment for hypothalamic hypogonadism, has not been shown to be effective.

When there is a relatively mild oligoasthenospermia, IUI with the male partner's sperm offers a reasonable chance for pregnancy. Successful treatment with less than 1 million motile sperm is low, but most studies have shown improved pregnancy rates with higher levels of motile sperm. Whole semen cannot be used for IUI due to the reactions to the prostaglandins and bacteria in the semen. The IUI sample uses sperm washed in culture medium, often using a swim up procedure to isolate motile sperm. The IUI is often combined with ovarian stimulation and timed ovulation, although it can be timed using an ovulation predictor kit.

With more severe oligoasthenospermia, or as a primary treatment for less severe male factor infertility, IVF offers the highest per cycle fecundity of any therapy. ICSI has increased the ability of sperm to fertilize oocyte in vitro, even with very low numbers of motile sperm. ICSI is typically recommended with severe oligospermia ($<2–10 \times 10^{6}$ sperm/mL), severe asthenospermia (<5%–10% motile sperm), or poor morphology (<4% normal forms by strict criteria). Fertilization rates match those seen with traditional IVF procedures. Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) obtain epididymal sperm for the treatment of obstructive azoospermia. Cases such as failed vasectomy reversal, postinflammatory obstruction, and congenital obstruction can be treated with MESA or PESA. Testicular sperm extraction (TESE) can be used to obtain sperm with nonobstructive or severe obstructive azoospermia. Even men with Sertoli-cell-only syndrome (up to 40%) have successful sperm retrieval with TESE.

Concerns about the risks associated with IVF and ICSI continue to be raised. Most studies to date have not shown an increase in congenital anomalies in children born by ICSI as compared to standard IVF. However, when a Y chromosome deletion is present, the defect will be passed to any male offspring. Data from the Society for Assisted Reproductive Technology and the Centers for Disease Control and Prevention have shown the risk of serious malformations to be 2%, which is the same rate as found with spontaneous pregnancies. Studies have suggested a possible increased risk of sex chromosome aneuploidy, particularly monosomy X and the presence of an extra X or Y chromosome. There is no increased risk of chromosomal structural defects with intracytoplasmic sperm injection.

Ovulatory Dysfunction

Excellent treatment options are available for all causes of amenorrhea and anovulation. The ACOG Practice Bulletin on the management of infertility caused by ovulation dysfunction offers a well-written overview of these therapies. Hypothalamic hypogonadism due to weight loss or excessive exercise may be treated by a change in lifestyle, although this does not always result in correction of menstrual cyclicity. Ovulation can be accomplished with either pulsatile gonadotropin-releasing hormone (GnRH) administration or injectable gonadotropins in women with ongoing amenorrhea or Kallmann syndrome. The GnRH pump delivers 50 to 75 ng per kg every 60 to 90 minutes; ovulation typically occurs in 10 to 20 days. Although side effects are minimal and the risk of multiple gestations is not increased over the general population, this method is labor-intensive for patients and health care providers, requiring continuous use of the pump for up to 3 weeks. Injectable human gonadotropins are now available as human menopausal gonadotropins, purified urinary FSH, and recombinant FSH, and can be given intramuscularly and subcutaneously. The use of any of these products requires close monitoring, including ultrasound and estradiol levels to lower the risk of multiple gestation and ovarian hyperstimulation. Human chorionic gonadotropin (hCG) is typically given when the follicle diameter reaches 15 to 18 mm. The risk of these medications will be further discussed in the section on “ Unexplained Infertility” later in the chapter.

Women with hyperprolactinemia can be treated with dopamine-agonist therapy. Bromocriptine mesylate and cabergoline are oral agents that successfully lower prolactin levels and routinely restore ovulation. Side effects, including headache, nausea, orthostatic hypotension, and dizziness, can be severe. Starting with a low dose and a slow, steady increase in the medication will minimize side effects. With bromocriptine we typically start with one-half tablet, 1.25 mg, at bedtime, increasing weekly to a maximum of 2.5 mg twice daily. Often one tablet at bedtime is sufficient to lower prolactin levels and restore ovulation. Cabergoline is taken only once or twice weekly at doses of 0.5 to 3 mg per week. Side effects are reported to be lower with this dopamine agonist, although it is still important to gradually increase the dose of the medication. Once women achieve pregnancy the medication is stopped, although there are no reports of harmful effects on the fetus. There is no restriction to breast-feeding in women with hyperprolactinemia, assuming there is no worsening of symptoms after pregnancy.

Our understanding of the etiology of PCOS has undergone a rapid expansion over the past decade. The methods of inducing ovulation have expanded, although the standard treatments remain effective for many women. For some women weight loss will allow them to ovulate and achieve pregnancy. Although long periods of time cannot be spent on unsuccessful attempts at weight loss, it is reasonable to start with this treatment option for obese women with PCOS. For slender women with PCOS or those who are not successful with weight loss, many other options are available. The classic medication is clomiphene citrate. The usual dose starts with 50 mg, or one tablet, daily on cycle days 5 to 9 following spontaneous or progestin-induced menses. Ovulation should be confirmed using temperature charts, ultrasound, or luteal progesterone levels. The maximal dose is typically 150 mg for 5 days, although higher doses (to 250 mg) for a longer period (to 8 days) are occasionally successful. In general, the higher the dose required for ovulation, the lower the pregnancy rate. Adding 0.5 mg of dexamethasone to clomiphene may increase the response in women with high adrenal androgen levels. Eight-five percent of women with PCOS will ovulate after taking clomiphene citrate. Side effects include hot flashes, headache, visual changes, breast tenderness, and bloating. Serious side effects are rare. A 10% chance of twins is the greatest risk, and the risk of higher order multiple gestations is less than 1%. It is important for women to realize that not all women conceive with clomiphene citrate; typically do not administer this medication beyond six ovulatory cycles.

Three additional options for women with PCOS include surgical treatment, injectable human gonadotropins, and insulin-sensitizing agents. The classic ovarian wedge resection for the treatment of PCOS fell into disrepute due to a high incidence of postoperative adhesions. Laparoscopic cautery, diathermy, and laser treatment have been used to allow spontaneous ovulation. The theory is that a reduction in the ovarian cortex by the surgical injury will allow ovulation to occur. Fifteen to twenty sites on each ovary are removed and 70% to 80% of women ovulate following surgery. Studies are currently limited and the advantages of surgical therapy versus medical therapy are limited as well. A significant advantage is a decrease in the risk of multiple gestations. Injectable gonadotropins affectively induce ovulation in women with PCOS. The need for close monitoring, to minimize the risk of multiple gestation and ovarian hyperstimulation, is greatest for women with PCOS. For women who do not ovulate with clomiphene, injectable gonadotropins are usually successful at inducing ovulation.

Studies suggest that a large percentage of women with PCOS are insulin-resistant and the use of insulin-sensitizing medications will restore ovulatory menstrual cycles. It is clear that women with PCOS are at increased risk for adult-onset diabetes and often have elevated fasting insulin levels despite a normal fasting glucose. The impact of insulin resistance and chronically elevated insulin levels on ovarian function has been studied and treatment with insulin-sensitizing agents—biguanide and thiazolidinediones—may induce ovulation in women with PCOS. Indeed, in comparison to low-dose clomiphene citrate alone, metformin increases ovulation rate in limited studies. Although the side effects with these medications are common, primarily nausea and diarrhea, they offer a potential treatment option for women with PCOS. This is not a Food and Drug Administration–approved use of these medications, and insulin-sensitizing agents may be less effective in slender women and those with normal fasting insulin levels. Future research on the use insulin-sensitizing agents to control obesity, hirsutism, and anovulation in women with PCOS will be

of great interest to patients and providers alike.

Limited treatment options are available for women with premature ovarian failure. Women with hypergonadotropic hypogonadism, secondary to a chromosomal abnormality, chemotherapy or radiation therapy, autoimmune disorder, or idiopathic loss of ovarian function, do not respond to gonadotropins, as there are simply no functional follicles remaining. Although pregnancies are reported with ovulation-induction agents after use of hormone replacement therapy, these are rare cases and do not justify the use of fertility medications with these women. Hormone replacement, to prevent osteoporosis and minimize hypoestrogenic symptoms, is the standard of care. Fortunately, donor oocytes can be offered as an option for these women. The generous contribution of oocytes by a donor undergoing gonadotropin stimulation and oocyte retrieval, offers women with premature ovarian failure an opportunity for pregnancy. As with women of decreased ovarian reserve and advanced maternal age, donor oocyte is a reasonable option for women with premature ovarian failure. The choice to pursue adoption or the decision to remain child-free should also be discussed with these couples in a nonjudgmental fashion.

Uterine/Tubal Factor

Limited studies are available to determine the value of surgical treatment of uterine abnormalities in women seeking fertility. Some studies demonstrate increased pregnancy rates in women undergoing hysteroscopic polypectomy or myomectomy, suggesting the value of this surgery. It is presumed that submucosal lesions, leiomyoma or endometrial polyps, should be removed prior to attempting pregnancy. Hysteroscopic surgery is recommended for women with intrauterine adhesions, or Asherman syndrome, and for removal of a uterine septum. The benefit of abdominal surgery—laparotomy or laparoscopy—for the removal of intramural and subserosal leiomyoma is less clear. An increase in pregnancy rate of 40% to 60% following abdominal leiomyoma was reported, but this surgery increases the risk of peritubal and periovarian adhesions. The risk of recurrence following surgery of leiomyoma is at least 30% and increases with time.

The treatment of known tubal factor infertility depends on the severity of the disease. Proximal tubal blockage can be treated hysteroscopically, radiographically, or by microsurgical reanastomosis. A meta-analysis documented an intrauterine pregnancy rate of 50% in women undergoing surgery for proximal tubal blockage, with the highest success rates achieved with selective salpingography and transcervical cannulation. Laparoscopic removal of thin, avascular adhesions involving the tube and ovaries offers a reasonable chance for pregnancy, with a success rate up to 70% but with an ectopic pregnancy rate of 20%.

Women with significant symptoms, such as pelvic pain, secondary to adhesions or endometriosis, also benefit from laparoscopic surgery. Removal of severe tubal adhesions and treatment of hydrosalpinges by neosalpingostomy offers a less predictable pregnancy rate. The per cycle fecundity following extensive tubal surgery is only 2% to 4%. Repair of bilateral tubal damage—proximal and distal tubal adhesions—has the lowest chance of an intrauterine pregnancy and is not recommended. The success of IVF, as will be discussed in Chapter 39, suggests this is a superior treatment for women with severe tubal factor infertility. IVF offers a reasonable chance for pregnancy, lowers the risk of ectopic pregnancy, and avoids the prolonged delay required to determine the success of treatment. Studies suggest an increased pregnancy rate if large hydrosalpinges are removed laparoscopically prior to IVF. Thus tubal surgery, with removal of the damaged fallopian tubes prior to IVF, increases the chance for successful infertility treatment.

Cervical factor infertility, although difficult to identify with standard testing, can be treated effectively with IUI. Limited studies have suggested a benefit of low-dose oral estrogen 1 week prior to ovulation for women with decreased cervical mucus; this treatment can be attempted for women with a history of cervical trauma, surgery, or diethylstilbestrol exposure. The standard therapy for these women is timed IUI, using washed sperm placed in the uterus the day following the LH surge or using ovarian hyperstimulation for timing ovulation.

Unexplained Infertility

Unexplained infertility is determined in 15% to 25% of infertile couples. This diagnosis often leads to significant distress, as the cause of infertility remains unknown. The good news is that treatment options for these couples allow a significant chance for pregnancy. One option, for a young couple, may be no therapy. Approximately one-half of couples who do not conceive in 1 year will do so within 2 years; up to 70% to 80% will conceive in 5 years. The primary benefit of treating unexplained infertility is to shorten the time to conception, a treatment of particular interest to couples in which the woman is over 30. The three primary treatment options are clomiphene with IUI, injectable gonadotropins with IUI, and IVF. IUI alone may also significantly increase per cycle fecundity from 1% to 3%, to 7%. Adding clomiphene citrate to the IUI, 50 to 100 mg daily on cycle days 5 to 9, increases the per cycle fecundity to 7% to 9% per cycle. A large group study demonstrated a two- to three-fold increase in pregnancy rate when controlled ovarian hyperstimulation occurred with gonadotropin and IUI compared to insemination alone. Studies have reported a per cycle fecundity rate of 10% to 18% with injectable gonadotropins and IUI; meta-analysis reports a 33% pregnancy rate with three cycles of gonadotropins and IUI. The pregnancy rate is increased with injectable gonadotropins alone, but the chance for pregnancy is increased with the addition of an IUI. The highest per cycle fecundity is accomplished with IVF. The 1998 data collected by the Society for Assisted Reproductive Technology reported a delivery rate per retrieval of 29.1% per IVF cycle. Gamete interfallopian transfer and zygote intrafallopian transfer also offer an excellent per cycle fecundity of 27.4% and 29.6%. The cost and invasive nature of these procedures however has limited their use. IVF, compared to clomiphene or citrate gonadotropin use, requires the greatest commitment of time, effort, and financial resources. But as is the case for couples with male factor or tubal factor infertility, IVF provides the highest per cycle fecundity for couples with unexplained infertility.

Women with endometriosis are often placed in the unexplained infertility category. Debate continues regarding the effect of mild endometriosis on fertility. If a woman is asymptomatic and has completed the evaluation, laparoscopy can be bypassed allowing the couple to move on to treatment for unexplained infertility. If laparoscopy is elected, and mild endometriosis is identified and removed, the treatment options are the same. As with unexplained infertility, the young couple with treated endometriosis may elect to have no infertility therapy.

Advanced Maternal Age

The American Society for Reproductive Medicine began a campaign in 2001 designed to alert women to the causes of infertility. Included in this campaign was information regarding the effect of advanced maternal age on fertility. Indeed, the age of first pregnancy has increased over the past several decades. In 1975 less than 20% of women attempted their first pregnancy between the ages of 35 to 39; in 1995, 44% of first pregnancies were attempted among this age group.

The Hutterites study published in the 1950s demonstrated the effect of age on fertility. In this population the overall rate of infertility was 2.4%; after age 34 it rose to 11%, after age 40 to 33%, and after age 45 to 87%. The average woman did not conceive after age 40. Donor insemination studies in France and the U.S. confirm this pattern. Cycle fecundity clearly increases with advancing age, likely beginning in the mid-30s. The risk of infertility increases at least 10 to 15 years prior to menopause, as does the risk of spontaneous abortion and chromosomal anomalies of ongoing pregnancies. Unfortunately, many women expect normal fertility until shortly before menopause and are surprised by the realization that natural infertility begins many years before their last menstrual period.

What can health care providers do to prevent this health issue from affecting their patients? Discussing the effect of aging on natural fertility with patients seeking contraceptive care provides them with useful information with which to make personal decisions. Although many women and couples do not pursue pregnancy until their lifestyle allows them to support and care for a child, awareness of age-related infertility is of great value. An active decision to remain child-free is better for women than an unexpected outcome due to simply delaying conception based on misinformation. Once a woman of advanced maternal age decides to pursue pregnancy, information about the timing of intercourse during the cycle is of value. If history or exam suggests a potential cause of infertility, for example irregular menses or history of STD, the workup can begin immediately. The new basic workup can be accomplished in 1 to 2 months, allowing rapid diagnosis of the cause of infertility once a couple does not conceive within a year or earlier, if the woman is over 35. Providing patients with information and rapid evaluation and treatment maximizes the chance that they will achieve their desired family.

It is now easier and faster for couples to determine the cause of infertility. The limited basic workup includes a semen analysis, ovulation monitoring, and uterine/tubal evaluation. For women over 30, a day 3 FSH or clomiphene challenge test is recommended to screen for decreased ovarian reserve. For selected couples, further male factor evaluation, hormonal testing, postcoital testing, endometrial biopsy, and laparoscopy can be considered. Treatment options for infertility now offer a variety of highly successful options for male factor infertility, ovulation dysfunction, uterine/tubal factor, and unexplained infertility.

SUMMARY POINTS

- Infertility is a common problem in the United States, occurring in approximately 14% of couples.
- The basic workup for infertility should begin 1 year after discontinuance of contraception. The workup includes a semen analysis, documentation of ovulation, and uterine/tubal evaluation with a hysterosalpingogram.
- A thorough history and physical examination of both the man and woman may identify the etiology of infertility and direct further testing to the most likely cause of infertility.
- Treatment for male factor infertility includes donor insemination, surgery, IUI, and IVF. Intracytoplasmic sperm injection and testicular sperm extraction, despite severe oligoasthenospermia or azoospermia, allow couples to conceive.
- Treatment of hypothalamic dysfunction includes the GnRH pump and injectable gonadotropins. Hyperprolactinemia is successfully treated with dopamine agonists. Polycystic ovarian syndrome can be treated with clomiphene citrate, surgery, injectable gonadotropins, and insulin-sensitizing medications. Premature ovarian failure can be treated with donor oocytes.
- Uterine and tubal factor infertility may be treated surgically. Severe tubal factor infertility is most successfully treated with IVF.
- Unexplained infertility can be treated with clomiphene citrate/intrauterine insemination, injectable gonadotropin/intrauterine insemination, or IVF.
- Women with advanced maternal age are best served by rapid workup and treatment.

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Chapter 39

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Assisted Reproductive Technology

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Success Rates

On July 25, 1978, the field of reproductive medicine and infertility changed forever with the birth of Louise Brown in England by in vitro fertilization (IVF). Her birth gave hope to many couples not able to conceive conventionally. The initial indication for IVF was tubal factor or pelvic adhesive disease as IVF bypasses the fallopian tubes by using controlled ovarian hyperstimulation (COH), egg retrieval, and insemination with ultimate embryo transfer. COH produces large numbers of mature eggs for insemination extracorporally. Intracytoplasmic sperm injection (ICSI) injects a single sperm into the cytoplasm of an egg. It has revolutionized the treatment of men with oligospermia or azoospermia in whom intratesticular sperm are present. The uccess rate of IVF with ICSI approaches the pregnancy rate with conventional IVF for nonmale factor etiologies. Women with premature ovarian failure, decreased ovarian reserve, or age factor infertility, can chose to undergo an IVF cycle with donor oocytes and enjoy excellent pregnancy rates.

INITIAL EVALUATION FOR IVF

The initial evaluation includes a review of the couples' medical, surgical, and infertility history and informed consent process is obtained. Topics of discussion should include:

- genetic screening, testing, and counseling
- COH and retrieval techniques and risk factors
- fresh and frozen embryo transfer procedures
- a discussion of nonselective reduction
- ICSI and its indications
- an estimate of the number of embryos to be transferred
- an estimate of the individual couple's pregnancy rate with IVF
- potential adverse events such as cancellation of cycles, gamete/fertilization problems, and pregnancy risks (multiple gestation, spontaneous abortion, and ectopic pregnancy).

The couple should have access to a referral for psychological testing, particularly in cases of donor egg.

Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) are alternatives to conventional IVF. GIFT places retrieved oocytes and sperm into the fallopian tube via laparoscopy or laparotomy where fertilization takes place, while ZIFT places zygotes created by IVF, at the stage prior to cleavage, into the fallopian tube. ZIFT and GIFT require at least one normal fallopian tube. ZIFT allows evaluation of the rate of fertilization while GIFT does not. Initially, pregnancy rates with GIFT and ZIFT were higher than conventional IVF, but this occurred at a time when IVF success rates were relatively low. For religious reasons, some couples prefer GIFT because fertilization occurs in the fallopian tube and not in the laboratory. Both GIFT and ZIFT require an additional procedure—a mini-laparotomy or laparoscopy, for placement of the gametes or zygotes. This additional procedure carries an inherent surgical risk and added cost, which makes IVF the choice of virtually all couples. Pregnancy rates with IVF have improved sufficiently so that that the added surgical risk of GIFT and ZIFT is simply not warranted. With the advent of ICSI, assisted hatching, and advanced laboratory techniques (i.e., culture media and embryo day 3 or 5 transfers), IVF success rates rival and exceed ZIFT/GIFT rates and very few of these procedures are performed.

PATIENT SELECTION FOR IVF

Although tubal factor infertility was the original indication for IVF, the indications for IVF have now been expanded to make this the final step in virtually all infertile couples. Tubal factor infertility can arise from various etiologies, including pelvic inflammatory disease, endometriosis, prior abdominopelvic surgery (including tubal ligations), ectopic pregnancy, or a ruptured appendix. This diagnosis is made by hysterosalpingogram (HSG) or laparoscopy. Although surgical therapy may be a very reasonable option in some patients, IVF may be the best option, especially for women with significant tubal damage, older women, or those with multiple factor

infertility. Because of the poor prognosis for repeat tuboplasty, IVF is the treatment of choice.

The treatment of male factor infertility has been drastically advanced by IVF and ICSI. Men who have a motile sperm count below 10×10^6 with poor morphology have a significant reduction in pregnancy rates. ICSI has been used to treat severe male factor infertility, with pregnancy and fertilization rates similar to couples with normal semen parameters who are undergoing conventional IVF. Oligospermic and selected azoospermic males, who have intratesticular sperm, have high fertilization and pregnancy rates with ICSI, regardless of motility, morphology, or sperm concentrations.

Reduced fertility with advancing maternal age seems to be more common as women delay childbearing. In noncontracepting populations, fertility starts to decrease at age 30 with a severe decrease in fertility after age 40. This decline is manifested as an age-related decrease in ovarian follicles and a decline in oocyte quality. Women over 35 have a significantly decreased chance of pregnancy, compared to younger patients. Data from women of all ages, who have received an oocyte from a young donor, reveal that pregnancy rates are excellent, and independent of the recipient's age, implying that the uterus does not age. At present there are provocative tests that evaluate a patient's fecundity.

Women with diminished ovarian reserve (DOR), regardless of their age, have significantly lower pregnancy rates with any modality. They also have an increased risk of aneuploid pregnancy and spontaneous miscarriage compared to patients with normal ovarian reserve. Day 3 or basal follicle-stimulating hormone (FSH) and the clomiphene challenge test (CCT), correlate best with conception using assisted reproductive technologies (ARTs), and are also applicable to an infertility population. Typically, an abnormal day 3 FSH is =12.6 IU/L. These values are dependent on the particular assay used and are patient population–dependent. Infertile patients who are older than 43 years or have an elevated FSH, have a less than 5% pregnancy rate per cycle, and are encouraged to pursue donor egg or adoption.

Endometriosis affects 30% to 40% of infertile women. Endometriosis involving the ovaries, fallopian tubes, and pelvis may cause anatomic distortion and adhesions of the tubes and ovaries hampering ovum pickup. Patients with moderate to severe endometriosis (stages III and IV) are encouraged to attempt IVF, especially those with severe adhesive disease. Many of these patients have had one or more conservative surgeries and have not achieved pregnancy despite optimal debulking of their disease. Surgery prior to IVF to improve pregnancy rates is not recommended. Surgical excision of endometriomas prior to stimulation improves the stimulation and oocyte retrieval.

Many couples who fail clomiphene citrate (CC) and gonadotropin therapy eventually require IVF. Patients under 36 years of age, World Health Organization (WHO) group I and II, frequently try three to four cycles of CC or gonadotropins with intrauterine insemination (IUI). Of patients who become pregnant with CC and IUI, over 85% become pregnant within the first four cycles of treatment.

Patients with unexplained infertility are by definition ovulatory, with normal fallopian tubes and uterine cavity or stage I or II treated endometriosis, and a normal semen analyses by WHO criteria. The majority of these patients have already attempted other therapeutic strategies such as timed intercourse, CC, or gonadotropins with IUI. Women with unexplained infertility have a combined per cycle IVF pregnancy rate of approximately 20% compared to 8% and 17% for CC with IUI and gonadotropin with IUI, respectively. In 2000, IVF pregnancy rates for unexplained infertility were appreciably higher indicating this technique should be more rapidly offered.

Premature ovarian failure (POF) is defined as hypergonadotropic hypogonadism prior to the age of 40. Causes of premature oocyte loss include gonadal dysgenesis (Turner syndrome), failure of germ cell migration in fetal life, and postnatal germ cell loss (castration, autoimmune disease, infections). Iatrogenic oocyte depletion occurs with chemotherapy, radiotherapy, and ovarian surgery for benign disease. Patients with POF have excellent success when receiving donor oocytes with a delivery rate/cycle of approximately 30% and a cumulative delivery rate after four cycles approaching 86%. There is no decrease in pregnancy or delivery rates with increasing age or diagnosis of the recipient (i.e., POF, surgical castration, previous IVF failure, menopause, DOR). Thus, endometrial receptivity does not appear to be altered by recipient age or diagnosis. Using young oocyte donors optimizes success rates by having a greater chance of transferring healthy embryos.

TESTING PRIOR TO ASSISTED REPRODUCTION

Previous IVF cycles should be reviewed in detail focusing on the number and quality of embryos, the method of insemination (conventional vs. ICSI), follicular and endometrial development, estradiol levels throughout the stimulation, length of the stimulation, and the pregnancy outcome. In addition we review the method and number of embryos transferred. Frozen embryo transfer cycles are also assessed, noting the endometrial stimulation and embryo quantity and quality after thawing.

Evaluation should also consider thyroid disease (thyroid-stimulating hormone), hyperprolactinemia (prolactin), an insulin and glucose test to screen for hyperinsulinemia (if indicated), and a blood type and Rh. An infectious disease panel will consist of hepatitis B and C, syphilis, human immunodeficiency virus (HIV), and rubella titer. Initial selected genetic tests for carrier status are offered and include Tay-Sachs disease (Ashkenazi Jews), sickle cell anemia (African descent), ß-thalassemia (Mediterranean/Chinese), a-thalassemia (Southeast Asians), and cystic fibrosis (Caucasians). A day 3 or basal FSH and estradiol may be useful in selected patients.

Ovarian Reserve Testing

Testing ovarian reserve can be useful for all IVF patients regardless of age. These tests are inexpensive, noninvasive, and highly predictive of ultimate outcome with ARTs. Most IVF programs routinely check all patients 35 years or older or those at risk, including patients with multiple surgeries, stage III or IV endometriosis, severe adhesive disease, and cigarette smokers. A day 3 basal FSH is obtained during a natural cycle. Based on our laboratory assay, a day 3 FSH greater than 12.6 mIU/mL predicts a less than 5% chance of achieving a pregnancy per IVF cycle, regardless of age. In order to counsel patients effectively, each institution and laboratory must establish their own critical cutoff point, above which, a pregnancy becomes highly unlikely. In a large study, both FSH and estradiol were shown to be excellent predictors of IVF performance. As a “single predictor,” basal FSH was better than age at predicting a successful pregnancy. Regardless of age or fertility history, women with diminished ovarian reserve as manifested by an elevated day 3 FSH, ultimately conceived with a high rate of first trimester pregnancy loss. The live-birth rate in patients with DOR was less than 1%.

Significant intercycle variability can be found among basal FSH values, especially in patients with widely fluctuating FSH levels. This variability reflects the physiologic inability of the follicle cohort to suppress FSH as a result of declining follicular health. FSH levels rise as granulosa cell production of inhibin-B decreases. Inhibin exerts negative control on the pituitary. Studies have shown that patients with intermittently elevated basal FSH levels stimulate poorly, need more medication for stimulation, have fewer aspirated follicles, and lower peak estradiol levels compared to patients with minimal intercycle variability. Once a patient has an isolated elevated day 3 FSH, even among normal cycles, her chance for IVF pregnancy is poor.

Due to the intercycle variability of day 3 FSH values, a normal value has limitations. The CCT uses the day 3 FSH value, and a provoked day 10 response to 100 mg of clomiphene citrate, administered cycle days 5 through 9. The CCT specifically evaluates the day 10 FSH. An abnormal day 10 FSH carries the same poor prognosis as an abnormal day 3 FSH. A poor CCT response predicts a decreased pregnancy rate for an infertile population as well as for IVF patients. Unexplained infertility comprises 52% of the patients with an abnormal CCT.

A CCT should be performed on all patients over the age of 37, or in women who have a borderline day 3 FSH. Patients may be tested earlier if they have had ovarian surgery, are diagnosed with stage III or IV endometriosis, or have severe adhesive disease. The results of these tests help direct patient counseling. An elevated day 3 basal FSH value, or an abnormal CCT, predicts a less than 5% chance of pregnancy with ART.

Evaluation of the Uterus and Fallopian Tubes

An HSG, sonohysterogram, or office hysteroscopy should be done before starting IVF. An HSG aids in the diagnosis of hydrosalpinges or an intrauterine filling defect, both of which decrease IVF pregnancy rates. Since patients can develop uterine or tubal pathology in intervening years, a repeat study should be considered if the previous uterine evaluation is more than 1 year old. A complete pelvic ultrasound, a trial embryo transfer, vaginal cultures, and a Pap smear are done on all patients. During the ultrasound, the adnexae are evaluated for ovarian cysts, endometriomas, and hydrosalpinges, while any leiomyomas or polyps are noted in the uterus. Sonohysterography is almost as accurate as hysteroscopy, and more sensitive and specific than transvaginal ultrasound or HSG in diagnosing intrauterine pathology. Additionally, sonohysterography is less invasive, relatively inexpensive, and does not require the use of contrast dyes.

Hydrosalpinges and IVF

Tubal disease is one of the main indications for IVF with hydrosalpinges accounting for 10% to 30% of tubal factor infertility. Compared to other types of tubal pathology, women with hydrosalpinges (including surrogate carriers) have reduced IVF success. Hydrosalpinges decrease IVF implantation, pregnancy, and delivery rates while increasing early pregnancy loss. This has been confirmed by large meta-analyses as well as numerous retrospective studies.

Only two randomized, prospective studies have evaluated whether prophylactic salpingectomy of hydrosalpinges prior to IVF improves pregnancy rates. Pregnancy rates after a single IVF cycle are approximately 37% in women after salpingectomies and 24% when the hydrosalpinges were not removed. Subgroup evaluation of

these patients revealed that women with bilateral hydrosalpinges, visible on ultrasound, had a significant increase in implantation and delivery rates after salpingectomy compared to the nonintervention group. Ultimate delivery rates more than double in patients with ultrasound visible hydrosalpinges after salpingectomy.

Many mechanisms have been proposed to explain the adverse effects hydrosalpinges have on IVF success rates. Fluid that accumulates in the hydrosalpinx can move retrograde into the uterine cavity. Endometrial receptivity marker molecules have been shown to be decreased in patients with hydrosalpinges, while inflammatory cytokines within the fluid may act as inhibitors. Salpingectomy is recommended when the fallopian tubes have visible fluid within the tube on sonogram. Polyps, müllerian anomalies, intrauterine synechiae, and leiomyoma are all associated with reproductive loss or failure. In women undergoing IVF, a midfollicular office sonohysterogram (intrauterine saline infusion) can further delineate the nature of the lesion. After the lesion is identified, a diagnostic or operative hysteroscopy should be performed to correct the abnormality.

Uterine leiomyomas may contribute to infertility and miscarriage but the data are limited by the uncontrolled retrospective nature of the reports. Most IVF studies distinguish between submucosal (leiomyomas that distort the uterine cavity), intramural (leiomyomas confined to the myometrium with no cavity distortion), and subserosal leiomyomas (leiomyomas protruding from the serosal surface). Subserosal leiomyomas, which are not adjacent to the endometrium, do not decrease pregnancy rates or increase miscarriages rates. Submucosal leiomyomas, which protrude into the uterine cavity, have been shown to decrease IVF pregnancy and implantation rates when compared to nonprotruding intramural and subserosal myomas. Prior to starting an IVF cycle, removal of submucosal distorting myomas is strongly recommended. Depending on location, leiomyomas are removed abdominally or hysteroscopically.

The literature is controversial regarding the removal of intramural leiomyomas prior to an IVF cycle, especially if they do not distort the endometrial cavity. In retrospective studies in patients under 40 years of age with intramural myomas, there is a significant decrease in implantation rate. There is only a trend toward decreased live-birth rates in women with intramural myomas, independent of the size of the leiomyoma volume.

Debate remains as to whether endometriomas should be removed prior to IVF. The few retrospective studies performed have not shown an increase in pregnancy rates with removal of endometriomas. However, some studies have shown a decrease in peak estradiol, fertilization, and implantation rates with advanced stages of endometriosis, including endometriomas. Most experienced clinicians remove endometriomas prior to IVF because there appears to be a significant improvement in the recruitment of follicles. However, debulking endometriosis is not warranted before IVF except in cases of endometriomas or pelvic pain. Women with stage III or IV endometriosis have a decreased pregnancy rate and their embryos are often poor in quality with thickened zona pellucida.

EVALUATION OF MALE FACTOR INFERTILITY

Male factor infertility will affect 50% of infertile couples in some fashion. In the vast majority of cases, this diagnosis is known prior to IVF. During the initial IVF consultation, the male partner is encouraged to be present so we can review his medical history and any prior semen analyses. Men suspected of male factor infertility are typically evaluated with regard to the following:

- infertility history
- sexual history
- childhood and developmental history
- medical history
- surgical history
- prior infections
- gonadotoxins
- family history
- a review of systems.

Multiple semen analyses should be evaluated in addition to any appropriate hormonal and genetic screening.

Semen Analysis and Sperm Preparation

Semen samples should be collected after an abstinence interval of 2 to 3 days. WHO criteria are a rough guideline for evaluating semen samples. These criteria include assessment of volume, sperm concentration, motility, morphology, pH, and total sperm count. Sperm morphology has become a useful indicator of successful fertilization with IVF. Kruger coined the term “strict criteria,” which includes only morphologically normal sperm. In studies using strict morphologic criteria, men with greater than 14% normal forms had normal fertilization rates in vitro. Patients with 4% to 14% normal forms had intermediate fertilization rates, while men with less than 4% normal forms had fertilization rates of 7% to 8%. ICSI should be recommended for any factor or combination of factors that are abnormal, including count, motility and score, as well as sperm morphology. In men with poor sperm parameters, ICSI produces fertilization and pregnancy rates similar to conventional IVF.

Semen samples need to be washed and processed prior to their use in IVF. Washing techniques isolate motile capacitated sperm for insemination. Sperm isolation may be performed on ejaculated semen, sperm retrieved from the epididymis or testes, or cryopreserved samples. Several isolation techniques are currently used. The “swim-up” method is used for samples with normal concentration and motility. For low motility and decreased sperm counts, the semen sample is layered over discontinuous Percoll gradients (45% and 90%) and centrifuged. The resulting pellet separates normal spermatozoa from lymphocytes, epithelial cells, abnormal sperm, cell debris, and bacteria.

Many tests have been proposed to evaluate sperm function, including the immunobead test, the interspecies sperm penetration assay, a hemizona assay, the hypoosmotic swelling test, and the mannose binding assay. These are not part of a semen analysis and purportedly predict the ability of sperm to fertilize an oocyte. These tests have poor inter- and intralaboratory reproducibility and the information gained from these studies rarely changes management, which is ultimately to proceed to IVF either with or without ICSI. Even without these studies, the nonfertilization rate is less than 1%. If the semen analysis is normal, a fresh sample for IVF insemination will be produced the day of oocyte retrieval.

Azoospermic or severely oligospermic men will be further evaluated. If necessary, a sperm retrieval procedure may be required. One or two of these sperm samples will be cryopreserved prior to starting an IVF/ICSI cycle. At the time of oocyte retrieval, a frozen sample will be thawed for ICSI.

Genetic and Hormonal Evaluation of the Infertile Male

Azoospermic and severely oligospermic males require genetic and hormonal evaluation. Men with nonobstructive azoospermia or severe oligospermia have a Y chromosome microdeletion assay performed. Thirteen percent of men with nonobstructive azoospermia will have a deletion in the gene cluster termed *DAZ* (deleted in azoospermia), which resides in the AZFc region, within the *DAZ* gene cluster. Men with this Y chromosome deletion produce male offspring that are severely infertile or sterile. Prior to ICSI, we test for *DAZ*, and provide genetic counseling if needed. Nonobstructive azoospermic men often have karyotype abnormalities that cause reproductive failure. Ten percent of these men have a sex chromosome abnormality, with the most common being Klinefelter syndrome (47 XXY). Men who have obstructive azoospermia, with congenital bilateral absence of the vas deferens (CBAVD), require testing for mutations in the cystic fibrosis gene. Ninety percent of patients with CBAVD will have gene aberrations. Since these genes are transmitted in an autosomal recessive fashion, genetic counseling is advised for these men and their families. Evaluation of oligospermic and azoospermic men requires serum measurements of luteinizing hormone (LH), FSH, prolactin, and testosterone. These often aid in the diagnoses of testicular resistance or failure, and hypogonadotropic hypogonadism.

PREPARATION FOR IVF

A trial or “mock” embryo transfer should be performed with the same catheter used during the actual embryo transfer. This enables the physician to measure the uterine length and note the curvature of the cervix and uterus. The goal of this precycle trial transfer is to facilitate a nontraumatic embryo transfer which has been shown to increase pregnancy and implantation rates. If there is cervical stenosis precluding easy access to the uterine cavity, it will be detected before undergoing an IVF cycle. Severe cases of cervical stenosis may require dilation of the cervix with hysteroscopic guidance prior to starting the IVF cycle.

IVF PROTOCOLS

Many protocols have been described for COH designed to increase the number of mature follicles for retrieval. All protocols aim to maximize the number of mature oocytes retrieved per stimulation cycle. The information needed to make a protocol decision is based on:

- medical and surgical history
- results from laboratory tests (i.e., ovarian reserve testing)

- extensive review of any previous assisted reproduction cycles (stimulation response, embryo quantity and quality, fertilization rate, embryo transfer).

In general, patients fit into one of three groups—normal, high, and poor responders.

COH Medications and Strategies

Gonadotropin releasing hormone-agonists (GnRH-a) have revolutionized the use of gonadotropin-based stimulation protocols. Pregnancy rates per IVF cycle have been shown in meta-analyses to significantly improve with gonadotropins because of the increased number of oocytes retrieved. GnRH-a, such as leuprolide acetate, substitute amino acids at position 6 and 10 on the GnRH molecule. This decreases the degradation rate and increases the binding affinity of the agonist to the GnRH receptor. GnRH-a initially produce a surge or flare that increases circulating LH and FSH levels. The flare lasts 7 to 10 days, followed by down-regulation and desensitization, resulting in a hypogonadal state and eventual withdrawal bleeding. This suppression of endogenous gonadotropins prevents the spontaneous LH surge prior to oocyte retrieval. The flare protocols begin GnRH-a the day before or the first day of gonadotropin stimulation. Before the advent of GnRH-a, detection of the LH surge was necessary as 15% of IVF cycles were cancelled due to premature LH surges. Protocols using GnRH-a either capitalize on the down-regulation (long protocol) feature of GnRH-a or the flare (short protocol), which adds endogenous gonadotropins to those administered therapeutically.

At the present time, the majority of IVF cycles use GnRH-a in either a “long” or “short” protocol. GnRH antagonists have been introduced for COH. Third-generation antagonists (ganirelix and cetrorelix) are more complex than agonists, having substitutions on the GnRH molecule at positions 1, 2, 3, 6, and 10. They bind competitively to the GnRH receptor, decreasing gonadotropin secretion within 4 to 8 hours in a dose-dependent manner. GnRH antagonists prevent the risk of a premature LH surge by using either a “single-dose” or “multiple-dose” protocol. Both regimens initiate stimulation with gonadotropins on day 2 of a spontaneous menstrual cycle. The “single-dose” protocol uses 3 mg of cetrorelix based on follicle size and LH level, while the “multiple-dose” protocol uses 0.25 mg of antagonist, starting on stimulation day 6 and then daily up to and including the day of human chorionic gonadotropin (hCG) administration.

Large, prospective, randomized clinical trials comparing agonist to antagonist protocols have demonstrated no significant differences in fertilization, implantation, and pregnancy rates between the two analogues. With GnRH-a there can be difficulty timing cycles since the antagonist protocol depends on the initiation of a natural cycle. GnRH-a protocol requires 2 to 4 weeks for complete pituitary desensitization before starting stimulation, requires longer treatment, and increases total number of gonadotropin ampules needed to achieve follicular maturation. When compared to antagonists, long-acting agonists appear to have an increased risk of ovarian hyperstimulation syndrome (OHSS) and produce estrogen withdrawal effects. While the ideal stimulation protocol has yet to be developed, GnRH agonist and antagonist protocols will undoubtedly continue to be universally used.

There are two major classes of gonadotropins, urinary–derived human menopausal gonadotropins (hMG) which contain both LH and FSH, and recombinant gonadotropins which contain pure FSH. The goal of any gonadotropin therapy is to maximize follicular recruitment for oocyte retrieval. The urinary hMG typically has 75 IU of FSH and 75 IU of LH per ampule. Since FSH is the most important gonadotropin for folliculogenesis, newer preparations of hMG have decreased substantially or removed LH by purification techniques. This can result in a highly purified gonadotropin product with only negligible amounts of LH present (<0.1 IU LH/ampule). The newer recombinant gonadotropins are genetically engineered by inserting the human gene for FSH in cultured immortal mammalian cells. Mammalian cells are needed as bacteria are unable to glycosylate FSH and glycosylation is required for FSH to be biologically active. Recombinant gonadotropin products (r-FSH) are devoid of LH and are highly pure, have specific activity, maintain excellent batch-to-batch consistency, and are tolerated well upon injection. It remains uncertain whether the recombinant FSH products (r-FSH) or hMG (u-FSH and u-LH) preparations have any advantages in clinical pregnancy rates with IVF but if a difference exists, it is modest.

Metformin, an insulin-sensitizing agent, has been successfully used to induce ovulation in a small number of women with polycystic ovary syndrome (PCOS) and is now being investigated in women with PCOS undergoing IVF. Early reports suggest increased fertilization and pregnancy rates when using metformin in patients with PCOS who are resistant to clomiphene citrate. Metformin should be started at least 1 month prior to the IVF cycle with a slow increase to a therapeutic metformin dose to minimize the gastrointestinal side effects. Hopefully, this approach will result in fewer cases of OHSS due to a decreased number of small follicles and an increased number of larger follicles (>16 mm).

Those with a high response rate to gonadotropin stimulation are typically young and thin, and often have the diagnosis of PCOS. They are at risk for producing elevated estradiol levels (>5,000 pg/mL) with few mature preovulatory follicles. This results in cycle cancellation (withholding hCG), to avoid the development of OHSS. Poor responders recruit fewer oocytes than normal responders, and have decreased pregnancy rates. Patient characteristics that predict a poor response include women over 40 years of age, a prior cancelled standard long protocol IVF cycle, severe endometriosis (stage III or IV), diminished ovarian reserve, and cigarette smoking. Normal responders are often patients with unexplained infertility, mild endometriosis, tubal disease, or male factor infertility.

Normal and high responders use leuprolide (1.0 mg subcutaneous daily), given in the midluteal phase (7 days after a positive LH surge) of the menstrual cycle preceding their stimulation (Fig. 39.1). Patients who are on a contraceptive pill, for cycle control and gonadotropin suppression, simply overlap the last 7 days of their pill with leuprolide. The leuprolide dose is decreased to 0.5 mg per day on the day gonadotropin stimulation is continued until the day of hCG administration. An estradiol level and baseline transvaginal ultrasound are obtained. Gonadotropin stimulation is initiated when:

FIG. 39.1. Example of a long gonadotropin-releasing hormone (*GnRH*) protocol. The dosage of follicle-stimulating hormone (*FSH*) and human menopausal gonadotropin (*hMG*) will vary depending on the patient characteristics. *hCG*, human chorionic gonadotropin.

- the uterine lining is less than 6 mm
- no functional ovarian cysts are larger than 1 cm
- women are adequately suppressed with an estradiol level less than 20 pg/mL and an FSH less than 12.6 pg/mL.

Women with functional ovarian cysts larger than 1 cm should continue to be suppressed until the cysts are resolved before initiating gonadotropin stimulation. Those with an endometrial thickness greater than 6 mm should continue leuprolide for another week, and have a repeat scan. In the majority of cases the lining will then be sufficiently thin, allowing the start of gonadotropin stimulation.

To maximize follicular recruitment in normal and high responders, gonadotropin stimulation is started (day 2–3) at a dose between 3 to 6 ampules per day. The starting dosage of gonadotropin is based on age, prior stimulation cycles, and the patient's diagnosis. Women who are poor responders, with a history of pelvic adhesive disease or endometriosis stage III or IV will start at a higher dose (up to 8 ampules/d), while patients with PCOS start at a much smaller dose. The daily dose of gonadotropins is fixed until day 5 of stimulation.

After the first 5 days of stimulation, the daily dose of gonadotropin is adjusted based on the patient's ultrasound and estradiol level. When at least two lead follicles reach 18 mm, or one follicle becomes 19 mm, ovulation is triggered with 10,000 IU of hCG and the leuprolide is discontinued. In addition to follicular size, the decision to trigger ovulation depends upon the rate of follicular growth and estradiol rise. Oocytes are retrieved 35 hours later.

On occasion, high responders will hyperstimulate, producing multiple follicles with estradiol levels greater than 3,000 pg/mL. These patients are at risk for OHSS. Cancellation of the cycle prior to hCG stimulation almost always thwarts the development of OHSS. Another approach to avoid OHSS is to retrieve all of the patient's follicles after hCG, and cryopreserve the embryos for future frozen embryo transfers.

“Coasting” refers to withholding gonadotropin administration for 1 to 3 days while continuing leuprolide until the estradiol falls below 3,000 pgmL so as to be able to proceed with retrieval. Follicles at the time of coasting are typically 16 mm, and are able to continue developing without gonadotropin stimulation. If the estradiol level declines and the number of small follicles declines, hCG may be given and the cycle proceeds to retrieval. Very acceptable pregnancy rates with very few cancelled cycles for fear of OHSS can be achieved when employing “coasting” or cryopreserving all embryos for later transfer.

While antagonist protocols are becoming more commonplace in IVF centers, the efficacy of antagonist stimulation protocols only will be realized when supported by prospective randomized studies. Presently there are two antagonist protocols, a “single-dose” and a “multiple- dose” regimen, both of which are evolving as clinicians become more experienced. When using the “multiple-dose” protocol, antagonist is given when follicles reach 12 to 14 mm. From that day onward, the gonadotropin dose is adjusted depending upon ovarian response. At this point, one ampule of r-FSH is substituted for one ampule of hMG. The antagonist is given (0.25 mg of

ganirelix/d) until the triggering hCG injection. The natural cycle length of the patient is taken into consideration when deciding when to trigger ovulation.

Several protocols have been proposed for the poor responder. Simply increasing the dose of gonadotropins may increase numbers of follicles and oocytes, but pregnancy rates remain low. An alternative protocol and strategy is the flare-up or co-flare. The “co-flare” regimen, which is a short protocol, uses the initial increase of gonadotropins from leuprolide to begin follicular stimulation. Leuprolide is initiated on cycle day 2 after an estradiol and FSH are drawn. On day 3, eight ampules of gonadotropins are administered. Target follicle size is 16 to 17 mm, with a progesterone level below 1.0.

Ovulation is usually triggered on day 8 or later as a shorter interval is associated with immature oocytes. Poor responders often have estradiol levels that plateau associated with postmature oocytes. Most patients receive 10,000 IU hCG at 16 mm. Poor responders are most often placed on a “co-flare” protocol rather than a long, down-regulation protocol.

OOCYTE RETRIEVAL

Oocyte retrieval is performed 35 hours after hCG injection. Retrieval is performed in an operating room or procedure room using conscious sedation. The perineum and vagina are prepped with warm sterile saline prior to retrieval. Oocytes are retrieved by vacuum aspiration of follicles under transvaginal ultrasound guidance. A sharp 17-gauge needle is used, allowing precise penetration of the ovary. The ovary is stabilized with the vaginal probe prior to needle penetration. To reduce patient discomfort, follicles are usually aspirated through a single entry into each ovary (Fig. 39.2). Aspirates are collected into 15-mL heated collection tubes. The patient is discharged once she is tolerating liquids and has recovered sufficiently from the conscious sedation.

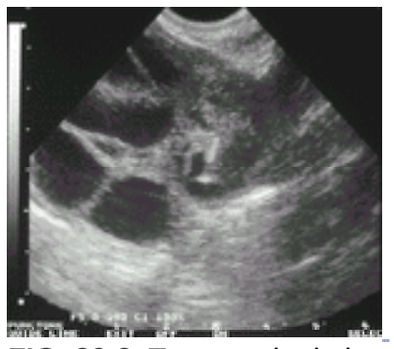

FIG. 39.2. Transvaginal ultrasound probe with needle-guided aspiration. Oocytes are removed through the needle and tubing using negative vacuum pressure.

In the laboratory, follicular aspirates are examined under a dissecting microscope and blood and cumulusgranulosa cells are removed. Oocytes are placed in culture media, and graded for maturity and quality. The optimum stage of oocyte maturity is metaphase II, with one polar body extruded. At this stage, conventional insemination or ICSI can be performed (Fig. 39.3). Oocytes are placed into culture media in microdroplets under oil. With conventional insemination, oocytes are inseminated 40 hours after hCG injection with 50,000 normal motile sperm per mL, with greater than 4% normal forms by strict Kruger criteria. One hour later, oocytes are removed from the insemination droplets and placed into clean, sperm-free microdroplets under oil. Fertilization is checked 18 hours later. Normal fertilized embryos are moved to individual microculture droplets and remain there until embryo transfer. Embryo transfer occurs 72 hours after insemination.

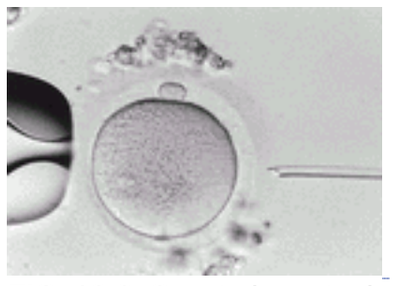

FIG. 39.3. Oocyte in metaphase II about to undergo intracytoplasmic sperm injection (ICSI). Ooplasm is clear with the first polar body at 12 o'clock. During ICSI, the introducing pipette (*right*) places a single sperm (at the tip of the pipette) into the cytoplasm of the egg. The holding pipette (*left*) holds the egg in place with gentle suction.

LUTEAL PROGESTERONE SUPPORT AFTER OOCYTE RETRIEVAL

The use of exogenous progesterone, during the luteal phase of an IVF cycle, to increase pregnancy rates is supported by large meta-analyses. Progesterone prepares the endometrial lining for implantation and pregnancy maintenance. The timing of progesterone supplementation seems to be critical and is started the evening of the day of retrieval. There has been much debate in the literature with regard to the route of administration of progesterone for IVF luteal support.

Proponents of intramuscular administration argue that levels are measured more accurately in the serum, helping clinicians modify progesterone administration throughout the luteal phase and early pregnancy. Physicians who prefer intravaginal progesterone point to its local effects on the uterus and endometrial lining.

Most programs prefer progesterone in oil (given intramuscularly), starting the night of oocyte retrieval and continuing until the patient has her first pregnancy test. If the peak progesterone level is greater than 40 µg/L, the supplementation is continued until the patient is 8 weeks pregnant and then a change to vaginal suppositories, 100 mg twice daily, is made until 12 weeks. If the progesterone level is less than 20 µg/L, 100 mg vaginal progesterone suppository twice a day is added. Levels will be rechecked in 1 week and are titrated accordingly.

ICSI AND SPERM RETRIEVAL TECHNIQUES FOR SEVERE MALE FACTOR

ICSI has given men with severe male factor infertility the ability to produce offspring. Prior to microinsemination techniques, severe male factor infertility was essentially untreatable. ICSI delivers a single sperm into the cytoplasm of an egg through the zona pellucida and egg membrane (see Fig. 39.3). Fertilization rates with ICSI using viable motile spermatozoa are very similar to rates achieved with conventional IVF with standard insemination.

Sperm retrieval techniques have given hope to men with obstructive and nonobstructive azoospermia. The etiology of obstructive azoospermia includes men with a previous vasectomy, ejaculatory duct obstruction, and congenital bilateral absence of the vas deferens. Sperm production is normal in these men, though sperm parameters may decrease with chronic obstruction. Sperm are extracted using both percutaneous sperm retrieval and open microsurgical techniques. In percutaneous epididymal sperm aspiration (PESA), sperm are aspirated through a butterfly needle that is placed into the caudal portion of the epididymis. Adequate numbers of sperm are often retrieved allowing for cryopreservation and future ICSI cycles. With the advent of microsurgical epididymal sperm aspiration (MESA), sperm are retrieved in higher numbers than with PESA, allowing for cryopreservation of large numbers of sperm. In our practice, PESA is attempted first since it is a less invasive procedure that often produces enough sperm for ICSI. If sperm collection fails, MESA is the second option. Men with nonobstructive azoospermia have an impairment of normal spermatogenesis. Their pregnancy and fertilization rates with ICSI are lower than for men with obstructive azoospermia. These men normally do not have sperm present in their epididymis for retrieval. Thus, testicular sperm retrieval is performed with either testicular fine- needle aspiration of the testes (TESA) or open testicular biopsy. Recovered sperm can either be used for ICSI or cryopreserved and thawed on the day of retrieval. Nonobstructive azoospermic patients need to be counseled that sperm retrieval techniques may fail to recover sperm. In the event that sperm is not retrieved, couples may opt for donor sperm.

ICSI uses a single washed sperm placed into a viscous solution of 10% polyvinyl pyrrolidine which impedes sperm movement. The spermatozoa flagellum is crushed, which causes immobilization and increases permeability of the sperm membrane, enhancing nuclear decondensation and pregnancy rates. A morphologically normal sperm is aspirated tail-first into an injecting pipette. The sperm is injected through the zona pellucida and into the ooplasm with the polar body at 12 o'clock (see Fig. 39.3). Injected sperm are placed into culture microdroplets under oil. Eighteen hours later, oocytes are examined for fertilization comparable to standard insemination in vitro. Normal fertilized eggs are moved to individual culture microdroplets under oil and transferred 72 hours from insemination.

ASSISTED HATCHING PRIOR TO EMBRYO TRANSFER

The majority of morphologically “normal” embryos do not implant. Other embryos may have decreased cell numbers, cleave slowly, or have impaired blastocyst hatching. The embryo “hatches” from the zona pellucida before implantation. Assisted hatching (AH) has been suggested to enhance the ability of viable embryos to implant after transfer in IVF cycles. AH is the process by which the zona pellucida is artificially breached or opened (e.g., drilling) (Fig. 39.4). This disruption of the zona pellucida theoretically facilitates the hatching of embryos by opening a hole and allowing blastomeres to more easily be extruded. Studies suggest that thick and hardened zona may prevent or reduce the efficiency of hatching of otherwise normally developing embryos and, hence, improve the rate of implantation. A thickened or hardened zona has been postulated to result from gonadotropin stimulation, the laboratory environment, culture techniques, age (>38), or in women with an elevated day 3 FSH. Most commonly, zona drilling is performed with acid Tyrode solution approximately 72 hours after oocyte retrieval, on the day of embryo transfer. This “drilling” creates a defect in the zona pellucida approximately 30 µm in diameter (see Fig. 39.4). Indications for AH include:

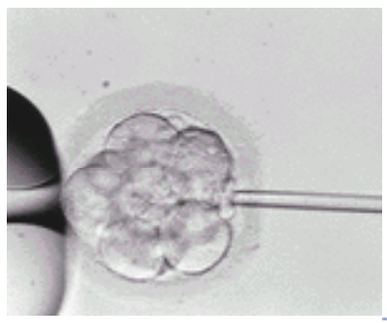

FIG. 39.4. Assisted hatching. The zona pellucida is opened with acid Tyrode solution. To the left is the holding pipette. The pipette on the right delivers acid Tyrode next to the zona pellucida.

- age greater than 38
- elevated day 3 FSH
- a prior failed IVF cycle with suspected implantation failure
- increased zona thickness on microscopy
- excess oocyte fragmentation.

AH for the selected indications may increase implantation and pregnancy rates but randomized trials are needed in order to determine the best candidates for AH.

EMBRYO TRANSFER

Embryo transfer melds the efforts of the clinician and laboratory. The success of implantation hinges in part on the success of the embryo transfer. The controversy remains as to the optimal timing of embryo transfer. Embryos can be transferred up to 6 days after fertilization. However, most embryos are transferred at 3 days, at the 8 to 10 cell stage (Fig. 39.5). Proponents of later embryo transfer argue that implantation and pregnancy rates are higher at the blastocyst stage as the embryo is further developed and the embryos that progress in vitro to this stage are healthier and more likely to implant. This has the theoretic advantage of decreasing the need to transfer more than one or two embryos, and thereby reduce the multiple pregnancy rate.

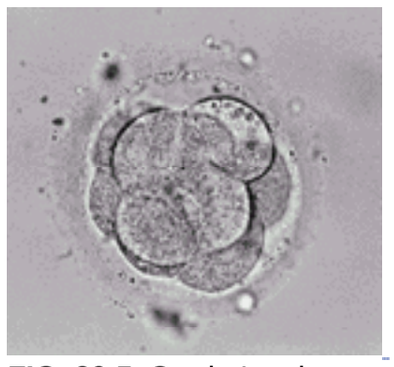

FIG. 39.5. Grade I embryo ready for transfer. This excellent embryo has 10 to 12 even cells and less than 15% fragmentation.

Embryos can be transferred with a variety of soft catheters. A soft-tipped catheter conforms to the contour of the cervix and endometrial cavity and reduces tissue trauma. The catheter is attached to a 1-mL syringe containing approximately 30 µL of transfer medium in a continuous column with the embryos placed toward the tip. Patients should have a full bladder prior to transfer which helps straighten out the angle between the uterus and cervix in women with an anteverted uterus. The cervix and vagina are prepped and draped and care is taken not to introduce blood, mucus, or bacteria with the catheter tip as these contaminants produce a poor environment for implantation. Using abdominal ultrasound guidance, embryos are deposited between 1 and 1.5 cm from the fundus without actually contacting it. Touching the fundus during transfer may cause uterine contractions thereby increasing the intrauterine pressure and expelling the embryos through the cervix, which reduces the pregnancy rate. Ultrasound guidance facilitates embryo transfer and confirms that the embryos are placed correctly high in the uterine fundus. There appears to be a significant increase in implantation and pregnancy rates using ultrasound-guided embryo transfer when compared to touching the fundus prior to transfer to determine the catheter tip location in the uterine fundus. After transfer, the catheter is checked for any retained embryos that were not expelled.

The best quality day 3 embryos are selected for fresh embryo transfer. The morning of transfer, embryos are graded and selected for transfer in order of their grade. They are graded as I, II, or III depending on the number and evenness of the dividing blastomeres, the percentage of extracellular fragmentation, and their cleavage rates. Ideally, grade I embryos (see Fig. 39.5) are selected first for transfer. These are “excellent” embryos with 8 even cells and less than 15% fragmentation, while grade II embryos have 6 to 8 even or slightly uneven cells with up to 25% fragmentation. Grade III embryos have less than 6 uneven cells and excessive fragmentation and are typically not transferred fresh or are cryopreserved because their obvious degeneration renders them virtually unable to develop further. If the patient has a significant number of excellent embryos or a uterine anomaly she may be offered day 5 embryo transfer with one or two embryos.

Patients 35 years and under are routinely transferred with two embryos; three embryos are transferred in women over age 35.

OOCYTE DONATION

Oocyte donation consists of oocyte retrieval with subsequent embryo transfer to a third party (the infertile patient or surrogate carrier). Oocyte donors can be either known or anonymous. Oocyte donation is used for women with:

- POF
- a history of surgical castration
- diminished ovarian reserve
- a risk of transmitting a heritable disease to an offspring
- older menopausal patients.

Donor-recipient IVF cycles typically have the highest pregnancy rates among all ARTs and the number of donor-recipient cycles is increasing. In 1999, the ASRMSART (American Society for Reproductive Medicine/Society for Assisted Reproductive Technology) registry reported that 10% (9,066) of all ART cycles used donor oocytes.

The success of donor recipient cycles is based on the tenet that the capacity to conceive is not based on uterine aging but on the quality of the oocyte. Younger donors have higher implantation and pregnancy rates when compared to older donors, with a decreased incidence of preclinical and clinical pregnancy loss. There does not

appear to be a decrease in the per cycle or cumulative pregnancy rates as endometrial receptivity is maintained and not altered by advancing maternal age. In addition, there was no association between cumulative pregnancy rates and the etiology of the infertility of the recipient.

Patients with Turner syndrome are a special class of patient using donor oocytes. They are infertile due to gonadal dysgenesis, with natural pregnancies occurring in approximately 2% of these women, usually in patients with mosaicism (XX,XO). Small studies comparing oocyte donation in patients with Turner syndrome to controls report conflicting pregnancy and implantation rates. There may be an inherent endometrial receptivity problem in Turner syndrome with lower implantation and pregnancy rates. Women with Turner syndrome should be carefully screened as cardiovascular abnormalities and arterial hypertension are common, with coarctation of the aorta seen in 10% of patients, and bicuspid aortic valve noted in about one-third of patients without coarctations. Even fatal aortic dissection has been reported in pregnancies established by oocyte donation in women with Turner syndrome.

Donor Oocyte Recipient Endometrial Preparation

Embryos are transferred into the recipient's uterus after exogenous endometrial preparation using sequential estrogen and progesterone and gonadotropin down-regulation if they are still cycling. This hormonal manipulation primes the endometrium for embryo transfer by mimicking the natural menstrual cycle. Leuprolide acetate (0.1 µg) is started on cycle day 21 for gonadotropin down-regulation. Bleeding will typically begin after adequate gonadotropin suppression and the decline in the luteal support. After a normal baseline ultrasound and low endogenous estradiol level is created, estrogen therapy is initiated, based on the date of anticipated embryo transfer. Transdermal estradiol patches (0.1 mg) are used in increasing doses that mimic the progressively increasing estradiol level in the follicular phase. By day 11, most women are using four patches.

Most IVF programs initiate aspirin (81 mg) at the start of stimulation in the hope of improving uterine and ovarian blood flow, implantation, and pregnancy rates. In an optimum fresh embryo transfer cycle, Lupron is maintained while transdermal estradiol is adjusted according to endometrial thickness and plasma estradiol levels. The recipient will receive between 2 and 3 weeks of estrogen for endometrial preparation. Once the endometrial lining is =8 mm (14 days) the recipient is ready for the pharmacologic conversion to luteal phase in coordination with the status of the oocyte donor. Both intramuscular (50 mg of progesterone in oil) and vaginal progesterone (100 mg b.i.d.) is started along with Medrol and tetracycline. The majority of fresh embryos are transferred on day 3 which translates into a day 18 transfer for cryopreserved embryos. After embryo transfer, the estradiol, the aspirin, and progesterone in oil are continued until the first pregnancy test, at which time the dose of progesterone is adjusted upward.

Oocyte donors must be screened prior to donation as outlined in the ASRM guidelines for gamete and embryo donation. Donors should be between the ages of 21 to 34 years. Screening for a personal genetic history as well as a sexual history is complemented by testing for infectious and genetic diseases. Psychological assessment by a qualified mental health professional for the donor and her partner is required. Minimal genetic laboratory screening is typically required.

Once prospective donors complete this initial evaluation, they are matched with potential recipients based on both physical and personal characteristics. Prior to starting a donor–recipient cycle, recipients have a precycle evaluation that includes an evaluation of the uterine cavity by sonohysterography or office hysteroscopy. If an intracavitary lesion or a hydrosalpinx is noted, surgical removal is conducted prior to embryo transfer.

Oocyte donation is not without risks to the donor. Donors are often concerned about the risks of ovulation-inducing drugs and ovarian cancer, although the aggregate of studies does not support any association. With COH, the risk of OHSS is always present, although it is decreased in donor oocyte cycles since conception does not ensue. Oocyte retrieval places the donor at risk for anesthetic complications, pelvic infection, and intraperitoneal hemorrhage. These complications are real, though exceedingly rare. There are also potential psychological risks that donors undertake. With appropriate pretreatment screening, we can hopefully minimize donors who may have feelings of ambivalence or regret after donation.

Recipients over 45 years of age are at an increased risk for obstetric complications including gestational diabetes mellitus, hypertensive disorders, cesarean delivery, intrauterine growth restriction, abruptio placentae, and preterm labor. These patients are referred to maternal–fetal medicine specialists for consultation prior to and after conception with IVF. Since there is an increasing risk of adverse pregnancy outcome with advanced maternal age, many centers do not perform donation for women over 50 years of age.

CRYOPRESERVATION

After COH and fresh embryo transfer, 60% of stimulated IVF cycles will produce excess viable embryos which are available for cryopreservation. Cryopreserved or frozen embryos can be thawed and transferred back into the uterus, during a subsequent frozen embryo transfer cycle. This allows for higher overall pregnancy rates per attempted IVF cycle. The indications for embryo cryopreservation include:

- storing excess embryos for future use after a fresh embryo transfer
- decreasing the risk of OHSS in a fresh embryo transfer cycle at very high risk of OHSS
- uterine conditions that are unfavorable for fresh embryo transfer after retrieval (e.g., uterine bleeding, polyps, leiomyomas, severe cervical stenosis, or a thin endometrial lining).

Uterine polyps, leiomyomas, and cervical stenosis are usually identified by sonohysterography, ultrasound, or at trial transfer prior to oocyte retrieval and corrected prior to IVF.

Cryopreservation techniques attempt to minimize cell damage to embryos during the freezing and thawing process with the aid of cryoprotectants. Embryos are frozen at a slow rate with the cryoprotectant. A gradient is induced that allows intracellular water to leave the cell. The embryo is dehydrated to avoid the formation of cytotoxic intracellular ice crystals. Once they are frozen, the embryos are loaded into cryostraws and stored in liquid nitrogen at -196°C. When embryos are needed for transfer, they are thawed rapidly to avoid formation of intracellular ice crystals. Typically, cryopreservation results in an 80% survival rate after thawing frozen embryos.

Patients should be extensively counseled prior to oocyte retrieval with regard to cryopreserving excess embryos. Informed consent is obtained as outlined in the ASRM committee opinion on elements to be considered in obtaining informed consent for ART.

Semen is cryopreserved in men who are not able to produce a sample on the day of oocyte retrieval (due to performance anxiety), who are oligospermic, or azoospermic (post-MESA, PESA, or TESA). Even with the use of cryoprotectants, freezing and thawing sperm samples can decrease motility by 50%. This is usually not a problem as original ejaculate samples contain large numbers of sperm. In men with azoospermia, epididymal or testicular samples are usually cryopreserved until the day of oocyte retrieval. On the day of oocyte retrieval, the semen sample(s) are thawed, the cryoprotectant is removed, and ICSI is performed.

FROZEN EMBRYO TRANSFER

The morning of “frozen embryo transfer,” embryos are thawed and surviving embryos are again graded. Pregnancy rates for fresh embryo transfer and frozen embryo transfer are very similar when similar grade embryos are transferred. This is due to selection criteria for embryo freezing. As discussed previously, day 3 embryos are graded as excellent (grade I), average (grade II), and poor (grade III). After the highest graded embryos are transferred fresh, the remaining grade I and II embryos are cryopreserved, while grade III embryos are not usually transferred or cryopreserved. The number of frozen embryos that are transferred is based on the same criteria as for fresh embryo transfer. Prior to frozen embryo transfer, the recipient will receive between 2 and 3 weeks of estrogen for endometrial preparation. Once the endometrial lining is =8 mm (14 days), intramuscular and vaginal progesterone is started for endometrial support.

RISKS OF IVF

Couples who present for ARTs are usually healthy with no significant medical history aside from their infertility. In the treatment of their infertility, they are asked to take significant risks. The two major complications of ARTs are OHSS and multiple gestation. There has been a proposed association between ovulation-induction drugs and gynecologic cancers, although this is not supported by well-controlled retrospective trials. Prior to initiating an IVF cycle, the risks and benefits of ARTs should be discussed, and formal written consent is obtained. In addition, patients should be counseled on fetal reduction of higher-order multiple pregnancies to decrease perinatal morbidity of infants and mother.

OHSS

OHSS is a potentially life-threatening complication of gonadotropin-induced COH. Although the signs and symptoms of impending OHSS usually become evident during stimulation, this syndrome does not become fully manifested until after hCG administration and oocyte retrieval. Patients typically resolve the OHSS within 10 to 14 days after onset of their initial symptoms. The syndrome is prolonged if a triggering dose of hCG is followed by a supplemental dose of hCG or if the patient

becomes pregnant and produces her own hCG.

Patients who develop OHSS complain of abdominal bloating and pain due to ovarian enlargement. The pathophysiology of OHSS includes increased capillary permeability with “third spacing” of protein-rich fluid. This can result in hemoconcentration and ascites with dramatic fluid accumulations in the abdomen, pleura, or pericardial spaces. Patients can develop nausea, vomiting, diarrhea, and a decrease in appetite if OHSS progresses. As significant amounts of “third spacing” ensue, we often see shortness of breath and decreased urine output. The precise pathophysiology of OHSS is still not completely understood, though vascular endothelial growth factor (VEGF) also known as “vascular permeability factor” has been implicated. It has been shown that follicular fluid from patients with OHSS produce VEGF in increased quantities which, in a dose-dependant manner, increase vascular permeability.

OHSS can be staged based on clinical signs and symptoms, ultrasound features, and laboratory findings and is used to help predict which women require hospitalization. Patients with mild OHSS present with abdominal discomfort, distention and pain, with ovaries enlarged up to 12 cm. Patients may have nausea, vomiting, or diarrhea. Moderate OHSS includes all the features of mild OHSS, but ultrasonographic evidence of ascites as well. Severe OHSS complicates less than 2% of stimulations. It includes features of mild and moderate OHSS as well as clinical evidence of ascites or hydrothorax and difficulty breathing. In addition, severe OHSS patients are at risk for hemoconcentration, coagulation and electrolyte abnormalities, diminished renal perfusion and function, and even adult respiratory distress syndrome.

Risk factors for developing OHSS include young age, low body mass index, and elevated estradiol levels with an increased number of stimulated follicles during COH. In addition, women with a previous pregnancy complicated by a history of OHSS are at great risk of recurrence. If early manifestations of OHSS appear (i.e., abdominal pain, rapidly increasing estradiol levels [>3,000 pg/mL], and extensive follicular recruitment), preventive treatment strategies are employed. On rare occasions, when follicular development and estradiol levels are excessively high early in the stimulation protocol, all stimulation medications are stopped and the cycle cancelled. More often, gonadotropin dosages are adjusted so that estradiol levels increase more slowly, or “freeze all” the embryos rather than transfer them as fresh embryos. Alternatively, using a “coast” by withdrawing gonadotropins and withholding hCG until the estradiol level decreases often allows retrieval and transfer of fresh embryos.

Once OHSS develops, a complete physical exam and ultrasound are performed including blood tests for sodium, potassium, creatinine, and hematocrit. On physical exam, patients often have abdominal distension and tenderness. Decreased breath sounds may be heard at the bases with pleural effusions. Ultrasound is performed to note the presence of ascites and ovarian size. Patients with OHSS can develop hyponatremia, hemoconcentration, hyperkalemia and even decreased renal perfusion. These patients are monitored as outpatients daily until the condition improves significantly. Patients with severe OHSS are admitted to the hospital for inpatient management using intravenous albumin. Patients are instructed to weigh and measure their abdominal girth daily, drink eight glasses of a high sodium drink, and maintain a high protein diet. In addition, they monitor their urine output, and are instructed to report any changes. An increase in abdominal pain or girth, nausea, vomiting, or decreased appetite necessitates a prompt phone call to the health care provider and an office visit.

Fertility Drugs and Cancer

The potential association between ovulation induction drugs and ovarian cancer remains controversial. The data suggesting an association have been based on meta-analyses, but more recent, well-done case-control studies reassuringly have not found any association when evaluating treatment of infertile women with fertility medications compared with infertile women not treated with ovulation-induction drugs. Patients should be informed about the available studies on this issue. It is appropriate to minimize the number of ovulation-induction cycles, both with clomiphene citrate and gonadotropins, as long as there is any concern surrounding ovulation-induction agents and ovarian cancer.

Multiple Pregnancy

Multiple pregnancies occur with a higher frequency in pregnancies resulting from ARTs than spontaneous conception. Since there is a low implantation rate per embryo (10%–25%) with IVF, more than one embryo is often placed into the uterus. The goal is to minimize the number of multiple pregnancies while maintaining good pregnancy rates. Multifetal gestations confer significant morbidity and mortality to both the mother and fetuses because of a high rate of prematurity and in utero mortality. Maternal risks include preterm labor, placental abruption and previa, cesarean section, postpartum hemorrhage, gestational diabetes, and preeclampsia. According to the U.S. Department of Health/Centers for Disease Control and Prevention's 1999 National Summary and Fertility Clinic Reports, 37% of all ART births using fresh nondonor eggs were multiple births (84% twins and 16% triplets and higher), while less than 3% of births in the general population are multiples.

Patients under 34 years of age with a history of a full-term pregnancy and no history of female infertility have the highest implantation rates with IVF. This includes women with previous tubal ligations, normal ovarian reserve testing, donor oocyte recipients, and couples with male factor infertility. In contrast, women older than 34 years of age, with no pregnancies, and extended histories of infertility, have lower implantation rates. Quite often these patients have a history of endometriosis, poor ovarian reserve, and previous failed IVF cyclesembryo transfers.

During the initial IVF consultation, the IVF success rates and the patient's infertility history are reviewed. Based on this information, the number of embryos we recommend transferring and the number of embryos a couple is willing to accept is defined. The goal is that each patient will have two excellent quality embryos replaced, adjusting (up or down) the number of embryos according to embryo quality and each patient's infertility history. Multifetal pregnancy reduction should be discussed as an option for couples with high-order multiple pregnancy. The aim is to reduce preterm deliveries by decreasing the number of fetuses a woman carries. Besides being an invasive procedure, pregnancy reduction, either transabdominal or transvaginal, risks the loss of the entire pregnancy. In experienced centers, pregnancy loss after transabdominal fetal reduction occurs in 6% to 8% of these pregnancies. In addition, the data suggest that pregnancies reduced to twins proceed as if the fetuses were naturally conceived as twins. There is a psychological toll on couples who are making decisions regarding multifetal reduction, especially in women who have experienced difficulty becoming pregnant. If fetal reduction is not acceptable to a patient under 40, a maximum of three embryos is transferred.

High-order multiple pregnancies (triplets and higher) can no longer be viewed as an acceptable risk of IVF and transferring two embryos will decrease the risk. Proponents of two-embryo transfers argue that pregnancy rates in large series are equivalent when compared to three-embryo transfers. Multiple pregnancy rates in patients 30 to 35 years of age are significantly increased from approximately 29% when two embryos were transferred to 40% with the transfer of three embryos. Interestingly, the twin birth rate with transfers of two and three embryos is 26% and 29%, respectively. Thus, a decrease in embryos transferred from three to two decreases the incidence of high-order pregnancies, but does not reduce the twinning rate.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis (PGD) enables couples who are carriers of genetic diseases to test embryos in vitro for genetic abnormalities prior to embryo transfer and select the embryos free of the genetic error for transfer. Traditionally, carrier couples have used chorionic villus sampling and amniocentesis, during the first and second trimesters respectively, to determine if they have a genetically abnormal fetus. The major disadvantage of this type of prenatal diagnosis is the need for second trimester pregnancy termination when genetically abnormal fetuses are detected. PGD provides couples the option to select genetically normal embryos for embryo transfer prior to transfer. PGD involves performing a blastomere biopsy and then genetic testing to determine the genetic complement of the embryo. Blastomeres can be removed from oocytes and embryos at three different stages, polar body analysis, 6- to 10-cell cleavage stage biopsy, and blastocyst stage biopsy. Cleavage stage biopsy is the most widely used technique. In order to biopsy a blastomere or polar body a hole is made in the zona pellucida using micromanipulation instruments with either acid Tyrode or laser. Since these embryos are transferred back into the uterus on day 4 or 5, a genetic diagnosis is determined within 48 hours. First and second polar body biopsies evaluate only maternal chromosomes. Crossover recombination events between homologous chromosomes can create improper diagnoses of heterozygous genetic defects. Presently, polar body biopsy is not performed by most centers offering PGD.

Cleavage stage biopsies are performed on one or two blastomeres of 6- to 10-cell stage embryos 3 days after insemination. These cells are used for diagnosis with polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH). PCR amplifies fragments of DNA for specific single gene defects. DNA amplification requires careful monitoring to avoid the problems of accidental contamination and allele dropout (ADO) leading to an erroneous genetic diagnosis. ADO or preferential amplification occurs when one of two alleles amplifies preferentially over the other. In a heterozygous cell, the normal allele may be amplified over the abnormal allele and the embryo would be diagnosed as “normal,” and then transferred. PGD has been applied to many monogenic diseases including autosomal recessive, dominant, and X-linked diseases. Examples include cystic fibrosis, Tay–Sachs, spinal muscular dystrophy, Huntington disease, Marfan syndrome, and fragile X syndrome.

Defining the number and structure of metaphase chromosomes is carried out by FISH, not PCR. FISH is used to examine chromosomes in embryos for aneuploidy in patients with male factor infertility and women of advanced maternal age, as well as to detect chromosomal translocations. Common aneuploidies occurring and creened for with FISH include defects in chromosomes 13, 16, 18, 21, 22,X, and Y. FISH uses fluorochrome-labeled probes that hybridize to complementary DNA sequences. The fluorescence produced by the probes allows a color and number notation of these probes which aids in diagnosis. PGD is successful in about 80% to 90% of biopsied embryos, with 50% of these embryos being unaffected and suitable for transfer. Amniocentesis and chorionic villus sampling continues to be recommended because of possible errors in cell sampling or technical difficulties with PCR or FISH. Despite this concern, the risk of carrying a genetically abnormal fetus is limited to the risk of a testing error which is far less than the spontaneous risk of the genetic disease.

SUCCESS RATES

The Fertility Clinic Success and Certification Act of 1992 required all clinics performing ARTs in the United States to annually report their success rates to the Centers for Disease Control and Prevention (CDC). Through SART, the CDC obtains clinic data. The CDC compiles these data and publishes a yearly report which is also available on the CDC website. The first year this clinical data became available for review was 1995. There is a 3-year lag between the time clinics report to the CDC and the time that these reports are available to the public which reflects the time for the last delivery in a calendar year and the subsequent time needed to compile and publish the data.

Each clinic reports on their “pregnancy success rates” based on the type of cycle performed (fresh embryos from nondonor eggs, frozen embryos from nondonor eggs, and donor eggs) as well as the age of the women (<35, 35–37, 38–40, and >40.). The number of ART cycles in the United States has steadily increased as well as the success rates. In 1995, 45,906 fresh nondonor IVF cycles were performed as compared to 65,751 in 1999 (Table 39.1). For patients using their own oocytes, pregnancy rates decrease with increasing age. It is difficult to directly compare the success rates between individual ART programs as they each treat different populations of infertile couples, they may focus on specific infertility factors rather than others (e.g., male factor, preimplantation genetic diagnosis, etc.), and different judgments are often made as to the number of embryos to transfer, IVF protocols, and success rates.

Live Birth Rate percentages per IVF Cycle with Respect to Age Using Fresh Nondonor Embryos				
1999	<35 years	35–37 years	38–40 years	41–42 years
	32.2%	26.2%	18.5%	9.7%
1995	<35 years	35–39 years	>39 years	
	25.3%	18.2%	8.0%	

CDC/SART, Centers for Disease Control and Prevention/Society for Assisted Reproductive Technology; IVF, in vitro fertilization.

TABLE 39.1. *1999 CDC/SART assisted reproductive technology success rates*

SUMMARY POINTS

- IVF was initially developed to treat tubal factor infertility but now represents the final therapy for virtually all infertile couples, regardless of the etiology.
- There is a significant maternal age-related decline in IVF pregnancy and delivery rate which should be taken into account when discussing infertility therapies.
- Day 3 FSH ± estradiol and clomiphene challenge test is a more accurate predictor of IVF success than simply maternal age.
- IVF with ICSI has allowed procreation in men with severe oligospermia and in azoospermic men after retrieval of sperm from the epididymis and testes.
- High-order multiple gestation significantly increases maternal and fetal morbidity and mortality. Careful consideration should be given to transferring the fewest number of embryos possible.
- Donor oocyte IVF is very successful for women with ovarian failure, limited oocyte reserve, advanced maternal age, and genetic disorders.
- Preimplantation genetic diagnosis is being increasingly performed using blastomere biopsy and genetic screening to avoid transferring embryos with aneuploidy and autosomal recessive or autosomal dominant gene mutations.

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Chapter 40

Robert S. Schenken

Endometriosis

INTRODUCTION

Pathogenesis
Epidemiology
Pathology
Symptoms
Diagnosis
Classification
Treatment

SUGGESTED READINGS

Pathogenesis
Epidemiology
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Treatment

INTRODUCTION

Endometriosis is defined by the presence of endometrial glands and stroma outside the endometrial cavity and uterine musculature. The pelvis is the most common site of endometriosis, but endometriotic implants may occur nearly anywhere in the body. Although there are numerous theories to explain why women develop endometriosis, no one theory has been proven conclusively. Endometriosis is a common gynecologic problem in reproductive-age women who have pelvic pain, dyspareunia, or infertility. The management of endometriosis is controversial, but randomized clinical studies have substantiated some therapeutic approaches.

Pathogenesis

Several theories have been proposed to explain the histogenesis of endometriosis. The *implantation* theory proposes that endometrial tissue desquamated during menstruation passes through the fallopian tubes, where it gains access to and implants on pelvic structures. The incidence of retrograde menstruation is similar in women with and without endometriosis. Thus, the development of endometriosis could depend on the quantity of endometrial tissue reaching the peritoneal cavity, specific factors enhancing attachment of endometrial cells to the peritoneum and ovary, or the capacity of a woman's immune system to remove the refluxed menstrual debris.

The *direct transplantation* theory is the probable explanation for endometriosis that develops in episiotomy, cesarean section, and other scars following surgery. Endometriosis in locations outside the pelvis likely develops from dissemination of endometrial cells or tissue through lymphatic channels or blood vessels. The *coelomic metaplasia* theory proposes that the coelomic (peritoneal) cavity contains undifferentiated cells or cells capable of dedifferentiating into endometrial tissue. This theory is based on embryologic studies demonstrating that all pelvic organs, including the endometrium, are derived from the cells lining the coelomic cavity. The *induction* theory, an extension of the coelomic metaplasia theory, postulates that the refluxed endometrial debris releases a product that activates undifferentiated peritoneal cells to undergo metaplasia. There is no conclusive proof that peritoneum can undergo spontaneous or induced metaplasia.

Anatomic alternations of the pelvis that increase tubal reflux of menstrual endometrium increase a woman's chance of developing endometriosis. The incidence of endometriosis is increased in young women with genital tract obstructions that prevent expulsion of menses into the vagina and increase the likelihood of tubal reflux. Other studies have suggested that deficient cellular immunity results in an inability to recognize the presence of endometrial tissue in abnormal locations. Decreased natural killer cell activity resulting in decreased cytotoxicity to autologous endometrium has been reported in women with endometriosis. The presence of increased concentrations of leukocytes and their cytokine products in peritoneal fluid of women with endometriosis may play a role in the initiation and growth of the ectopic implants. The immune system clearly has an important, albeit unclear, role in the pathogenesis of endometriosis.

The possibility of a familial tendency for endometriosis has been recognized for several decades. If a patient has endometriosis, a first-degree female relative has a 7% likelihood of being affected similarly.

Epidemiology

The true prevalence of endometriosis in the general population is unknown. Estimates of its prevalence are based on visualization of the pelvic organs. Pelvic endometriosis is present in approximately 1% of women undergoing major surgery for all gynecologic indications, 6% to 43% of women undergoing sterilization, 12% to 32% when laparoscopy is performed to determine the cause of pelvic pain in reproductive-age women, and 21% to 48% of women undergoing laparoscopy for infertility. Endometriosis is found in 50% of teenagers undergoing laparoscopy for evaluation of chronic pelvic pain or dysmenorrhea.

The influence of age, socioeconomic status, and race on the prevalence of endometriosis remains controversial. The age at time of diagnosis is commonly 25 to 35 years, and endometriosis rarely is diagnosed in postmenopausal women. Many believe that endometriosis is more common in women of upper economic classes because they delay pregnancy, which is postulated to increase the risk of developing endometriosis. It is unknown whether this reflects a true increased incidence or results from greater access to medical care. Evidence indicates that blacks have a prevalence of endometriosis similar to that in whites when controlled for socioeconomic status.

Pathology

The most common sites of endometriosis, in decreasing order of frequency, are the ovaries, anterior and posterior cul-de-sac, posterior broad ligaments, uterosacral ligaments, uterus, fallopian tubes, sigmoid colon, appendix, and round ligaments. Other sites less commonly involved include the vagina, cervix, and rectovaginal septum. These latter lesions usually result from extension and invasion of posterior cul-de-sac implants. Uncommon locations include the inguinal canal, abdominal or perineal scars, ureters, urinary bladder, umbilicus, kidney, lung, liver, diaphragm, vertebrae, and extremities.

Macroscopic Appearance Endometriotic implants have a variety of appearances. Superficial lesions on the ovarian or peritoneal surface are commonly reddish maculae or nodules similar in consistency to normal endometrium. These implants vary from 1 millimeter to several centimeters in size. Collection of hemosiderin results in yellow-brown or black discoloration (“powder-brown” lesions). Nonpigmented disease appears as whitish opacified peritoneum, translucent blebs, or pinkish polyploid implants. Scarring with retraction of adjacent peritoneum and peritoneal pockets may occur. Endometriosis also may appear as a deeply infiltrative disease. Tumorlike masses form from invasion, and diffuse fibrosis usually develops in the posterior cul-de-sac, pelvic sidewall, or posterior broad ligament and ovary and may extend deep into the retroperitoneal space, occasionally constricting the ureter. Lesions in the cul-de-sac may invade the rectovaginal septum. The rectosigmoid and small bowel may become adherent to these areas. Endometriotic foci on the ovarian surface may develop a fibrous enclosure and manifest cyst formation as a result of accumulation of fluid and blood. These endometriotic cysts (endometriomas) vary from several millimeters to over 10 centimeters in size. Bleeding with menses gives the cyst a dark red or bluish hemorrhagic color. The degradation of blood pigment over time results in thick, tarry contents, hence the term *chocolate cysts.* Occasionally, the content changes to a yellow straw color or clear fluid. Filmy or dense fibroid adhesions from these cysts to the pelvic sidewall and fallopian tubes are common and may obscure visualization of the cyst.
Microscopic Appearance Endometriosis is histomorphologically similar to eutopic endometrium. The four major components of endometriotic implants are endometrial glands, endometrial stroma, fibrosis, and hemorrhage. The relative amount of each component is highly variable and dependent, in part, on the age and location of the lesions. Identifying the endometrial elements in individual implants requires an adequate tissue specimen, proper orientation, and often serial sections of the specimen. The endometrial glands in ectopic implants lack uniform size and shape. The glands may show normal cyclic change with mitotic figures and pseudostratification in response to estrogen, or vacuoles and intraluminal secretion in response to progesterone. The response to endogenous and exogenous hormones is inconsistent. This may imply differences in steroid hormone receptor content and function or a loss of the normal gland-stromal interaction. When glands are responsive, the epithelium becomes attenuated, and hemorrhage ensues at the time of menstruation. The stromal cell morphologies of ectopic and eutopic

endometrium are similar. Small arterioles, similar to the spiral arterioles of normal endometrium, usually are present in implants. Interstitial hemorrhage with accumulation of blood products and hemosiderin-laden macrophages is a frequent finding. Fibrosis may occur in older endometriotic implants. This is very common in the lining of endometriomas, where the only histologic finding may be fibroblast proliferation and hemosiderin pigment deposition.

Symptoms

The common signs and symptoms of endometriosis are pelvic pain, dysmenorrhea, dyspareunia, abnormal uterine bleeding, and infertility. The type and severity of symptoms are dependent on the extent of disease, the location, and the organs involved. Even limited amounts of disease may cause significant symptomatology.

Endometriosis is present in approximately one third of patients with chronic pelvic pain. The pain may be described as crampy, dull, or sharp and usually increases around menses. The discomfort may be unilateral or bilateral, and many patients complain of rectal pressure or low backache. Acute abdominal pain may result from hemorrhage secondary to a ruptured endometrioma.

Dysmenorrhea is a more frequent complaint than dyspareunia. There is some correlation between the extent of disease and the severity of pain. The morphologic appearance of an endometriotic implant appears to be unrelated to pain symptomatology. Dyspareunia is more common in women with invasive endometriotic nodules in the cul-de-sac, uterosacral ligaments, rectovaginal septum, and vagina.

Abnormal uterine bleeding occurs in up to one third of women with endometriosis with symptoms of oligomenorrhea, polymenorrhea, and midcycle or premenstrual spotting. The abnormal bleeding likely results from conditions associated with endometriosis: oligoanovulatory, luteinized unruptured follicles, luteal phase defects, and other pathology such as uterine fibroids.

Endometriosis involving the gastrointestinal or urinary tracts and extrapelvic sites causes symptoms characteristic of the location of disease. Bladder involvement is associated with frequency and urgency. Invasion of the mucosa results in hematuria. Ureteral and rare cases of renal endometriosis occasionally cause flank pain or gross hematuria. Symptoms suggestive of gastrointestinal involvement include, in decreasing order of frequency, diarrhea, rectal bleeding, constipation, and dyschezia. All symptoms usually are exacerbated catamenially.

There are numerous case reports of extrapelvic endometriosis. Pulmonary endometriosis causes catamenial hemoptysis and dyspnea. Cutaneous lesions are associated with catamenial bleeding, tenderness, and swelling.

It is estimated that 25% to 50% of infertile women have endometriosis, and 30% to 50% of women with endometriosis are infertile. Although the association of endometriosis and infertility is well recognized, the pathophysiologic mechanisms are poorly understood. Endometriomas and endometriosis with adhesions distort pelvic anatomy and impair tubal ovum pickup, which is an acceptable explanation for infertility. In less severe cases, there are several theories to explain the observed subfecundity (Table 40.1).

Anatomic distortion and tubal obstruction
Anovulation, luteal phase defects, and hormonal abnormalities
Galactorrhea or hyperprolactinemia
Autoimmunity
Peritoneal leukocytes and the peritoneal inflammatory response
Peritoneal fluid prostaglandins
Peritoneal fluid cytokines
Embryo implantations defect and spontaneous abortions

Source: Adamson GD, Pasta DJ. *Am J Obstet Gynecol* 1994;171:1488–1505, with permission.

TABLE 40.1. *Proposed mediators and mechanisms of infertility*

Research to explain the subfertility has focused on peritoneal fluid leukocytes and their cytokine products. Studies have suggested that constituents in the peritoneal fluid inhibit sperm function, fertilization, embryonic development, and implantation. The clinical significance of these findings has not been established.

Diagnosis

Endometriosis usually is diagnosed during the third and fourth decades of life. It has not been found in prepubertal girls and rarely is diagnosed in postmenopausal women unless they are taking replacement hormones. Endometriosis should be suspected in any woman having the classic symptoms of pelvic pain, dysmenorrhea, dyspareunia, abnormal menstrual bleeding, and infertility. These symptoms are present in other gynecologic disorders. No one constellation of signs or symptoms is pathognomonic of endometriosis. Many women with endometriosis are completely asymptomatic, and endometriosis should be considered in all reproductive-age women with infertility or an adnexal mass.

Physical findings in women with endometriosis are variable and dependent on the location and severity of disease (Table 40.2). Frequently there are no obvious findings on pelvic examination. When findings are present, the most common is tenderness when palpating the posterior fornix. Nodules of endometriosis on the uterosacral ligaments, enlarged ovaries as a result of endometriotic cysts, and a uterus fixed in the cul-de-sac by adhesions may be detected during a pelvic examination. Uterosacral implants are best palpated during a rectovaginal examination. On the other hand, some patients with these clinical findings turn out not to have endometriosis.

Localized tenderness in the cul-de-sac or uterosacral ligament
Palpable tender nodules in the cul-de-sac, uterosacral ligament, or rectovaginal septum
Pain with uterine movement
Tender, enlarged adnexal masses
Fixation of adnexa or uterus in retroverted position

TABLE 40.2. *Clinical signs*

The optimal way to diagnose endometriosis is by direct visualization of the site of suspected involvement. Because endometriosis is located primarily in the pelvis, laparoscopy is the preferred technique to make an accurate diagnosis. A double-puncture technique is necessary to view adequately all structures that may contain implants. Peritoneal fluid should be aspirated to see the entire cul-de-sac. Adhesions should be lysed to view the entire surface of the ovaries and the fossa ovarica. These sites are commonly involved with endometriosis when the ovary is adherent to the pelvic sidewall. Suspected endometriomas should be aspirated and resected to confirm the diagnosis. Biopsy and histologic study of any suspicious areas are helpful when the diagnosis is questionable, but often the visual diagnosis by the surgeon is more accurate than histologic sections of small peritoneal biopsies.

Transvaginal ultrasonography can be used to identify ovarian endometriomas, but it is of little utility to diagnose peritoneal implants. The use of other radiologic studies and blood tests to diagnose endometriosis rarely is required. Radioimmunoassay for the tumor marker CA-125 has been used, but the test is not sufficiently sensitive or specific, and patients having conditions other than endometriosis may have positive results.

Classification

A number of classifications have been developed for staging endometriosis. The most widely used system was introduced by the American Society for Reproductive Medicine (ASRM) in 1979 and revised in 1985 and in 1997. This system assigns a point score for the size and location of endometriotic implants and associated adhesions. The new ASRM endometriosis classification for infertility includes the morphologic appearance of the implant. There is a form published by the ASRM to assist in the management of endometriosis in the presence of pelvic pain.

Endometriosis is classified as minimal, mild, moderate, and severe. Mild disease is characterized by superficial implants less than 5 square centimeters in aggregate scattered on the peritoneum and ovaries. Minimal or no adhesions are present. Moderate forms are characterized by multiple implants, both superficial and invasive. Peritubal and periovarian adhesions may be evident. Severe forms are characterized by multiple superficial and deep implants, including large ovarian endometriomas.

Filmy and dense adhesions are usually present. However, no staging system has been validated to correlate with the symptoms of pain or infertility.

Treatment

The treatment of endometriosis is dependent on (a) the severity of symptoms, (b) the extent of disease, (c) the location of disease, (d) the patient's desire for pregnancy, and (e) the age of the patient. Treatment options are presented in Table 40.3.

Expectant Management
Medical Therapy
Progestins
Danazol
GnRH analogs
Surgical Therapy (laparoscopy or laparotomy)
Conservative: retains uterus and ovarian tissue
Definitive: removal of uterus and possibly ovaries
Combination Therapy
Preoperative medical therapy
Postoperative medical therapy

GnRH, gonadotropin-releasing hormone.

TABLE 40.3. *Treatment options*

Expectant Management Avoiding specific therapy is considered when patients have minimal or no symptoms and have suspected minimal or mild endometriosis. Patients in this category may benefit from cyclic oral contraceptives to retard progression of the disease and protect against unwanted pregnancy. Minor pain may be controlled by nonsteroidal antiinflammatory drugs and/or analgesics. Infertile women having suspected limited disease may be observed without treatment. One study suggests that surgical treatment of mild endometriosis results in higher pregnancy rates than expectant management. Another study with fewer subjects failed to confirm the benefit of laparoscopic surgery for infertile women with endometriosis. If pregnancy occurs, regression or complete resolution of the disease is common. Perimenopausal women may be managed expectantly even when the disease is advanced, because endometriotic implants usually regress in the absence of ovarian hormone production after menopause.

Medical Therapy Endometriotic implant growth is highly dependent on ovarian steroids. Medical therapy attempts to “induce” pseudopregnancy or menopause, the two physiologic states believed to inhibit or delay progression of endometriosis by interrupting cyclic ovarian hormone production. Progestins alone or in combination with estrogen hormonally mimic pregnancy. Danazol and gonadotropin-releasing hormone (GnRH) analogs induce a state of pseudomenopause. Medical therapy has the following advantages over surgery: (a) avoidance of the surgical risks of damaging pelvic organs and causing postoperative adhesions, and (b) treatment of implants that are not visible at surgery. Disadvantages of medical therapy are the associated side effects, high recurrence rates following discontinuation of treatment, lack of an effect on endometrioma and adhesions, and inability to conceive because of medically induced anovulation. Medical therapy never has been shown to enhance fertility (Fig. 40.1). Thus, it is not appropriate for women with advanced stages of endometriosis and adhesions causing symptoms or women desiring pregnancy. The medications used most commonly to treat endometriosis are continuous oral contraceptives, progestins, including oral contraceptives, danazol, and GnRH analogs. They should be considered after a definitive diagnosis of endometriosis has been made by direct visualization of the implants.

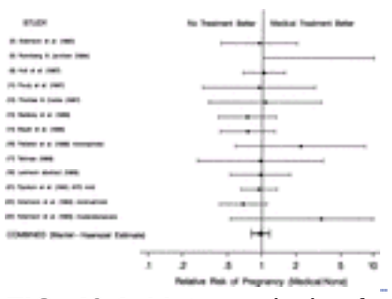

FIG. 40.1. Meta-analysis of studies comparing medical treatment with no treatment.

Progestins inhibit endometriotic tissue growth by a direct effect on the implants, causing initial decidualization and eventual pseudodecidual necrosis or atrophy (progestins). Progestins also inhibit pituitary gonadotropin secretion and ovarian hormone production. Treatment may consist of medroxyprogesterone acetate (10 mg 3 times a day) or norethindrone acetate (5 mg daily for 2 weeks), then increase by 2.5 milligrams per day every 2 weeks until a daily dose of 15 milligrams is reached. Depot-medroxyprogesterone may also be given as an injection (100 to 150 mg monthly). Treatment usually is continued for at least 6 months. Side effects include irregular menstrual bleeding, nausea, breast tenderness, fluid retention, and depression. The effectiveness of continuous oral contraceptives or progestins in eliminating implants and the risk of recurrent endometriosis following treatment are not precisely known. Over 80% of women have partial or complete pain relief. Low-dose cyclic oral contraceptives are effective in relieving dysmenorrhea in women with endometriosis, but they are less likely to relieve dyspareunia. Pregnancy rates in patients with less severe stages of disease are equivalent to those following expectant management. Danazol is the isoxazole derivative of 17a-ethinyltestosterone. Danazol has the following three mechanisms of action: (a) inhibition of pituitary gonadotropin secretion, (b) direct inhibition of endometriotic implant growth, and (c) direct inhibition of steroidogenic enzymes. Danazol is given orally in divided doses, from 400 to 800 milligrams daily, generally for 6 months. Most women taking danazol have side effects, but only a small percentage of patients discontinue the drug because of unwanted effects. Side effects, in decreasing order of frequency, include weight gain, muscle cramps, decreased breast size, acne, hirsutism, oily skin, decreased high-density lipoprotein levels, increased liver enzyme levels, hot flashes, mood changes, and depression. Danazol decreases the size of implants, especially in treating mild or moderate stages of disease. Endometriomas and adhesions do not respond well to danazol treatment. More than 80% of patients experience relief or improvement of pain symptoms within 2 months of treatment. Pregnancy rates following treatment approximate 40% and are independent of the disease severity. However, danazol is no more effective than expectant management for treating infertility. The GnRH analogs profoundly suppress ovarian estrogen production by inhibiting pituitary gonadotropin secretion. These medications are administered by nasal spray or depot injections. The usual dosage is 400 to 800 milligrams daily for nasal nafarelin, 3.6 milligrams for monthly subcutaneous goserelin, and 3.75 milligrams for monthly intramuscular leuprolide. Side effects of the hypoestrogenemia are common and include hot flashes, vaginal dryness, decreased libido, insomnia, breast tenderness, depression, headaches, and transient menstruation. In addition, GnRH analog treatment for the recommended 6-month period decreases bone density and total body calcium, but most of the bone loss is reversible. Hypoestrogenic side effects and bone loss may be prevented by “add-back” therapy with high-dose norethindrone (10 mg daily) or the daily combination of low-dose norethindrone (2.5 mg), sodium etidronate (400 mg), and calcium carbonate (500 mg) (Table 40.4). The GnRH analogs effectively reduce the size of endometriotic implants, even with add-back therapy. Recurrence rates over 5 years range from 37% for patients with mild disease to 74% for severe disease. The GnRH analogs are as affective as other medical therapy in relieving pain symptoms, but they do not enhance fertility.

Norethindrone acetate	5–10 mg/d
Norethindrone acetate	2.5 mg/d
Sodium etidronate	400 mg/d
Calcium carbonate	500 mg/d
Conjugated estrogen	0.3–0.625 mg/d
Medroxyprogesterone acetate	5 mg/d
Micronized estradiol	2 mg/d
Medroxyprogesterone acetate	5 mg/d
19β-Estradiol	25 μg twice weekly
Medroxyprogesterone acetate	5 mg/d

TABLE 40.4. *Endometriosis “add-back” therapy*

Surgical Management Surgery for endometriosis is considered conservative when the uterus and as much ovarian tissue as possible are preserved. Definitive surgery involves hysterectomy with or without removal of the fallopian tubes and ovaries. Surgery is indicated when the symptoms are severe, incapacitating, or acute and when the disease is advanced. Surgery is preferred over medical therapy for advanced stages of disease with anatomic distortion of the pelvic organs, endometriotic cysts, or obstruction of the bowel or urinary tract. Women who are older than 35 years, infertile, or symptomatic following expectant or medical management should be treated surgically. Laparoscopy is the preferred approach to perform conservative surgery. Treatment of endometriosis is possible during the initial laparoscopy, used to diagnose the condition. This offers the advantage of ablating the implants and adhesions, while avoiding possible progression of disease or symptoms and the expense and side effects of medical therapy. Disadvantages include possible damage to bowel and bladder, infection, and mechanical trauma that may result in adhesion formation. Conservative surgery involves excision, fulguration, or laser ablation of endometriotic implants and removal of associated adhesions. The goal is to restore normal pelvic anatomy. Laparoscopic treatment offers advantages over laparotomy, including shorter hospitalization, anesthesia, and recuperation times. Laparotomy is advisable to deal with extensive adhesions or invasive endometriosis located near structures such as the uterine arteries, ureter, bladder, and bowel. Ancillary procedures include presacral neurectomy or uterosacral transection for interruption of sensory nerves innervating the pelvis to relieve midline pelvic pain. The Cochrane Review of three trials involving destruction of pelvic nerve pathways concluded that there is insufficient evidence to recommend these procedures. Uterine suspension may be performed to avoid adhesion formation from the cul-de-sac to the posterior surface of the uterus, tubes, and ovaries. Surgery effectively removes pathology and restores normal anatomy in most cases. The disease recurrence risk is estimated to be as much as 40% with 10 years of follow-up. Pain relief is achieved in 80% to 90% of patients. Presacral neurectomy provides additional pain relief, but its benefit is not lasting, and bladder dysfunction occasionally occurs after the procedure. The chance for pregnancy following surgery is related to the stage of disease and presence of other infertility factors. Approximate pregnancy rates after surgery in patients with mild, moderate, and severe endometriosis are, respectively, 60%, 50%, and 40%. Surgery is preferred over expectant or medical management for infertile women with endometriosis (Fig. 40.2).

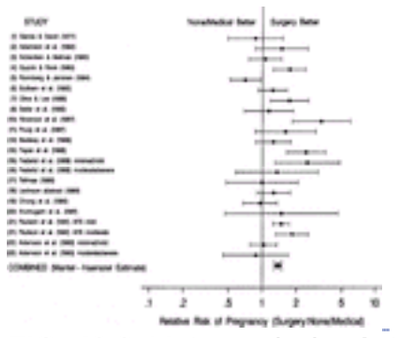

FIG. 40.2. Meta-analysis of studies comparing surgical treatment (operative laparoscopy or laparotomy) with nonsurgical treatment (medical treatment or no treatment).

Definitive surgery for treatment of endometriosis is indicated when significant disease is present and pregnancy is not desired, when incapacitating symptoms persist following medical therapy or conservative surgery, and when coexisting pelvic pathology requires hysterectomy. The decision to perform hysterectomy is dependent primarily on the patient's interest in maintaining childbearing potential and the severity of her symptoms. The ovaries may be conserved in younger women to avoid the need for estrogen replacement therapy. Removal of both ovaries is appropriate when the ovaries are damaged extensively by endometriosis or when menopause is approaching. Endometriosis may recur even with castration, presumably from microscopic foci of disease not visible at surgery. Menopausal hormonal replacement is indicated when the ovaries are removed, even when surgery has not removed all endometriotic implants. The chance for symptomatic recurrence in these cases is small except when endometriosis involves the bowel.

Combination Medical and Surgical Therapy Medical therapy is used before surgery to decrease the size of endometriotic implants and thus reduce the extent of surgery. When complete removal of implants is not possible or advisable, postoperative medical therapy is used to treat residual disease. Progestin, danazol, or GnRH analogs may be used in conjunction with conservative or definitive surgery. Preoperative medical therapy may decrease the amount of surgical dissection required to remove implants, but it does not prolong pain relief, increase pregnancy rates, or decrease recurrence rates. Postoperative treatment with GnRH analogs will delay somewhat the recurrence of pelvic pain, but there is no evidence to support its use in infertile patients.

SUMMARY POINTS

- The histogenesis of endometriosis is poorly understood, but emerging evidence supports the causative role of retrograde menstruation and implantation of endometrial tissue.
- Endometriosis is common in women with pelvic pain or infertility.
- Laparoscopy is the optimal technique to diagnose pelvic endometriosis.
- In most cases, surgical therapy at the time of initial diagnosis effectively relieves pain and may enhance fertility.
- Alternatively, medical therapy with progestins, danazol, or GnRH analogs will ameliorate pelvic pain, but they do not enhance fertility.
- Endometriosis is a recurrent disease, and definitive treatment with removal of pelvic organs may be necessary.

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Chapter 41

Marcelle I. Cedars and Michele Evans

Menopause

REPRODUCTIVE STAGES
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The ovary is unique in that the age associated with decline in function (to frank failure) appears to have remained constant despite the increase in longevity experienced by women over the last century. Because the loss of ovarian function has profound impact on the hormonal milieu in women and on the subsequent risk for the development of disease via the loss of estrogen production, improving our understanding of reproductive aging is critical to care for all women.

Human follicles begin their development during the fourth gestational month. Approximately 1,000 to 2,000 germ cells migrate to the gonadal ridge and multiply, reaching a total of 5 to 7 million around the fifth month of intrauterine life. At this point, replication stops and follicle loss begins, declining to approximately 1 million by birth. In the human male, the dividing germ cells will become quiescent and maintain their stem cell identity. In women, between the weeks of 12 and 18, the germ cells will enter meiosis and differentiate. Thus, in the female, all germ stem cells have differentiated prior to birth. In the adult woman, the germ cells may remain quiescent, be recruited for further development and ovulation, or undergo apoptosis. Over time, the population of oocytes will be depleted, without regeneration, through recruitment and apoptosis until fewer than a thousand oocytes exist and menopause ensues. Approximately 90% of women experience menopause during the early 50s. The other 10% of women experience menopause prior to 46 years (often termed *early menopause*), with 1% of women experiencing menopause at an age less than 40 years *(premature menopause* or *premature ovarian failure)*.

Menopause occurs at a median age of 51.4 years, with the age range in normal women being 42 to 58 years. The age of menopause appears to be determined largely by genetics and is due to exhaustion of the oocyte pool. Menopause and the years preceding are characterized by hormonal changes, decline in reproductive potential, and increased risk for physical and psychological changes.

The average age of menopause has remained constant throughout recorded history. It does not appear to be related significantly to race, parity, height, weight, socioeconomic status, or age at menarche. Evidence suggests that genetic and environmental factors influence age of menopause, although the specific nature of these relationships is poorly characterized. Given the strong association between age at menopause between mothers and daughters, this is likely a largely genetically determined trait. Environmental factors may not have a significant effect in themselves, but the interplay among environmental factors such as smoking (known to accelerate the age of menopause by 1.5–2 years), body mass index (BMI), alcohol use, and socioeconomic status and genetic risk, may be important.

According to the 2000 census data, 35% of the population is age 45 or older and 21% are over 55 years of age. Of the population, 7.3% are women 65 years or older (approximately 20 million women in the United States). Over 50 million women in the United States are in the menopausal transition or menopause.

REPRODUCTIVE STAGES

Reproductive aging is a continuum beginning in utero and ending with menopause. The stages along this continuum have been difficult to define. Numerous terms have been used clinically, including *perimenopause, menopausal transition, climacteric, menopause*, and *postmenopause*, to describe the end of this continuum. The Stages of Reproductive Aging Workshop (STRAW) was convened in July 2001 to address the lack of a pertinent reproductive staging system and to establish a nomenclature and guidelines, a consistent reproductive aging system for health practitioners, the medical research community, and the public.

The staging system developed takes into account menstrual cyclicity, endocrinology and symptomatology beginning with menarche and ending with a woman's demise. The foundation of the staging system is the final menstrual period (FMP). Five stages precede the FMP and two follow it, for a total of seven stages. Stages -5 to -3 are called the *reproductive interval*, stages -2 to -1 are termed the *menopausal transition*, and stages +1 and +2 are known as the *postmenopause* (Fig. 41.1).

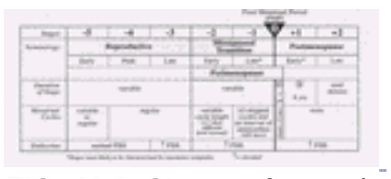

FIG. 41.1. Stages of reproductive aging. (From Soules MR, Sherman S, Parrott E, et al. Stages of Reproductive Aging Workshop (STRAW). J Womens Health Gend Based Med 2001;10:843–848, with permission.)

The menopausal transition begins with variation in the menstrual cycle length (>7 days different from normal) in a woman with an elevated follicle stimulating hormone (FSH) level. This stage ends with the FMP, which cannot be determined conclusively until after 12 months of amenorrhea. Early postmenopause is defined as the first 5 years following the FMP. Late postmenopause is variable in length, beginning 5 years after the FMP and ending with the woman's death.

Although this staging system is said to include endocrinologic aspects of ovarian aging, it still depends largely on menstrual cyclicity as a key indicator of ovarian aging. It does include measurement of FSH; however, by the time FSH is elevated, even with cyclic menstrual cycles, oocyte depletion already has proceeded to such an extent that fertility (as a marker of reproductive aging) is diminished significantly. As noted above, evidence suggests that genetic and environmental factors influence both age of menopause and the decline in fertility, although the specific nature of these relationships is characterized poorly. Premature menopause can be due to a failure to attain adequate follicle numbers in utero or to an accelerated depletion thereafter. Potentially, either of these factors could be affected by genetic and

environmental risk. The timing of menopause has a consistent impact on overall health with respect to osteoporosis, cardiovascular disease (CVD), and cancer risk. Over the next decade, it's estimated that more than 40 million women will enter menopause.

Oocyte Depletion

As discussed above, the leading theory regarding the onset of menopause relates to a critical threshold in oocyte number. Approximately 1,000 to 2,000 germ cells migrate to the gonadal ridge and multiply, reaching a total of 5 to 7 million around the fifth month of intrauterine life. At this point, replication stops and follicle loss begins, with a reduction to approximately 1 million by birth and 500,000 to 600,000 by menarche. As the number of oocytes in the reserve pool continues to decline, menstrual irregularity, followed by cessation, will occur. The theory that menopause is triggered primarily by ovarian aging is supported by the coincident occurrence of follicular depletion, elevated gonadotropin levels, and subsequent menstrual irregularity with ultimate cessation of bleeding.

A mathematical model that predicts the rate of follicular decline has been developed (Fig. 41.2). It utilized existing data, which ultimately showed a bi-exponential decline, with an acceleration in oocyte loss when the remaining oocyte number equaled approximately 25,000. In this model, the decline occurred at 37.5 years of age. At this point, the rate of follicular atresia accelerates. In the absence of this acceleration, the model suggests menopause would be delayed until age 71. The cause of this accelerated depletion is not well defined. It is also clear that if the factor influencing the rate of decline is follicle number and not age, other factors which might account for a diminished follicle number (genetic risk and possible toxic exposure) would lead to an earlier rate of accelerated decline and an earlier age of menopause.

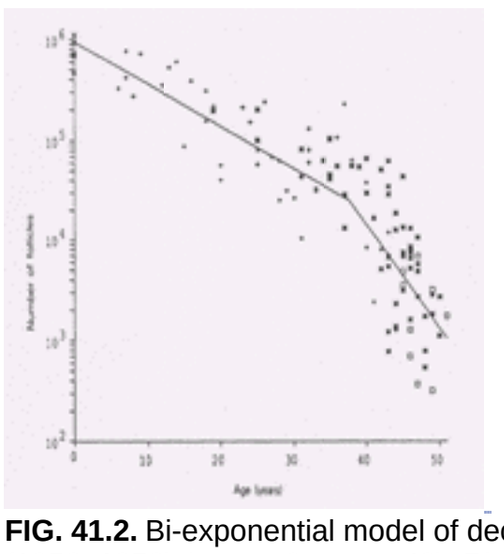

FIG. 41.2. Bi-exponential model of declining follicle numbers in pairs of human ovaries from neonatal age to 51 years old. Data were obtained from the studies of Block (1952, 1953) (*x*, n = 6; +, n = 43), Richardson and others (1987) (squares, n = 9), and Gougeon (unpublished) (*, n = 52). (From Faddy MJ, Gosden RG, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992;7:1342–1346, with permission.)

Coincident with the decline in the number of follicles in the ovary, there appears to be an increase in random genetic damage within these structures. Evidence for this comes from an observed increase in aneuploidy in the offspring of older mothers and the observation that, in women over 40 years old, oocytes harvested for in vitro fertilization are karyotypically abnormal approximately 40% of the time. Further examples in nature, such as Turner syndrome, shed some light on the process of oocyte aging. Individuals with this syndrome are, by and large, born with dysgenetic gonads which are devoid of follicles. Ninety-five percent of these individuals are aborted spontaneously prior to birth. If one examines the ovaries of a 20-week abortus, a full compliment of oocytes is present. Two factors have been isolated from the ovary: oocyte maturation inhibiting factor (OMI) and luteinizing inhibitor, which may control the rate of maturation of follicles. It has been suggested that individuals with dysgenetic gonads may fail to produce adequate OMI, thus allowing all follicles to progress prematurely toward maturity. The control mechanisms are conceptual rather than factual at this juncture, and new information will have to accumulate before the factors governing human oocyte atresia are elucidated more clearly.

Endocrinology

The entire endocrine system changes with advancing age. The somatotrophic axis begins to decline during the fourth decade prior to the loss of ovarian function. This decline in growth hormone is accelerated during ovarian failure and may, itself, accelerate the ovarian failure. However, pituitary concentrations of growth hormone, as well as adrenocorticotropic hormone and thyroid stimulating hormone, remain constant into the ninth decade. Although the thyroid gland undergoes progressive fibrosis with age and concentrations of T3 decline by 25% to 40%, elderly patients remain clinically euthyroid. Beta-cell function also undergoes degeneration with aging such that, by age 65 years, 50% of subjects have an abnormal glucose tolerance test result. Frank diabetes is rare, however, occurring in only 7%. The female reproductive system, on the other hand, undergoes virtually complete failure at a relatively early age.

As noted above, during the late fourth decade, FSH levels begin to rise even when cyclic menses continue. The most likely cause is a decrease in functional granulosa cells from the oocyte pool, with a decrease in inhibin B negative feedback allowing a monotropic rise in FSH. Early on, there is also a decline in luteal phase progesterone levels. As ovarian aging progresses, estradiol levels may be quite variable, with chaotic patterns and, occasionally, very high and very low levels. This dramatic variability may lead to an increase in symptomatology during the perimenopause (stages -2 to -1). As peripheral gonadotropin levels rise, luteinizing hormone (LH) pulsatile patterns become abnormal. There is an increase in pulse frequency with a decrease in opioid inhibition.

Estrogens The main circulating estrogen during the premenopausal years is 17ß-estradiol. These levels are controlled by the developing follicle and resultant corpus luteum. Oophorectomy will reduce peripheral estradiol levels from 120 to 18 pg/mL, which suggests more than 95% of circulating estradiol is derived from the ovary. Other sources include the peripheral conversion of testosterone and estrone. Very small amounts are secreted by the adrenal gland. Because the two-cell theory requires aromatization of androgens produced by the theca in the granulosa cell, follicular exhaustion is associated with gradual declines in estradiol concentrations. The predominant estrogen in the postmenopausal woman is estrone, which has a biologic potency of approximately one third that of estradiol. Estrone is derived largely from peripheral conversion of androstenedione. Extraglandular aromatase is found in liver, fat, and some hypothalamic nuclei. This activity increases with aging and with a higher fat content (also an age-related change). Estrone and estradiol production rates during the postmenopause are 40 and 6 µg/day, respectively. This compares with 80 to 500 µg/day for estradiol during the reproductive years. Essentially, all the estradiol in the postmenopausal women is derived from conversion of estrone.
Androgens Dehydroepiandrosterone (DHEA) and its sulfated conjugate, DHEAS, have been shown to decrease, along with adrenal corticotropin responsiveness, with aging. DHEAS levels decrease in both men and women. The decline is greater in women and may be due to the relative estrogen deprivation. Ovarian failure, at any age, accelerates this decline. Evidence suggests physiologic levels of DHEA may protect against neoplasia, enhance insulin action, protect against osteoporosis, increase immune competency, and offer some cardioprotection. Changes in DHEA levels also have been associated with alterations in body composition which, in themselves, appear to impact cardiac and breast cancer risk. DHEAS levels may also have an impact on “sense of mental well-being.” Androstenedione is the predominant androgen during the reproductive years and production declines from 1,500 to 800 pg/mL in postmenopausal women. The postmenopausal ovary contributes only 20% to the circulating androstenedione. Testosterone levels also decline after menopause, but not to the same extent as estradiol levels. Postmenopausal testosterone is derived from the ovary (25%), the adrenal gland (25%), and extraglandular conversion from androstenedione (50%). The postmenopausal ovary produces a larger percentage of testosterone (50%) than does the premenopausal ovary.

Systemic Effects of Declining Ovarian Function

The decline in ovarian function brings about profound changes in secondary sexual organs. The endometrium becomes atrophic and the uterus decreases in size. Evidence is accumulating in animal models that the uterus may be partially responsible for the initial decline in reproductive capacity. On the other hand, data from human oocyte donor programs have shown that transfer of ova from younger donors to menopausal recipients produced normal gestations and offspring. It should be noted that these women are stimulated with an artificial sequential overlapping regimen of estrogen and progesterone. This produces an endometrium that is indistinguishable from that of the premenopausal state. Our own data have shown high implantation rates in older women with a hormonally induced endometrium. Only those women who receive pelvic irradiation have responded poorly, suggesting an alteration of the microvascular system.

The postmenopausal vagina, devoid of estrogen treatment, becomes smaller in both length and caliber. There is decreased elasticity of the vaginal wall, and the karyopyknotic index changes to show fewer superficial cells. The fallopian tubes contain both ciliated and secretory components. After age 60, cilia begin to disappear in the isthmic region, although they remain until a very old age in the ampulla infundibulum. The mammary gland develops secretory potential at the time of puberty and maintains this function until menopause. Like other secondary sex organs, it is dependent on female sex steroids for its maintenance. With cessation of the production of estrogen and progesterone, glandular, ductal, and stromal involution occurs. The basement membrane thickens and the luminal space becomes obliterated.

Connective tissue of the lobule becomes indistinguishable from other types of connective tissue. There is an accumulation of adipose tissue in the breast, which occurs simultaneously with this involutional process.

Despite the involutional changes of the breast, 6% of patients with breast carcinoma are over the age of 50, with a median of 55. There is evidence for a bimodal distribution of breast carcinoma, with the first peak occurring at 45 years of age and the second at 65 years of age. The portion of estrogen receptor–positive breast cancers increases until ages 60 to 74 years. Therefore, a dichotomy appears to exist that ducts and glands, rapidly undergoing involution, the result of failing steroid production, become susceptible to malignant transformation while retaining a receptor molecule (E_2), which normally is self-induced.

PREMATURE OVARIAN FAILURE

Premature ovarian failure (POF) is a unique entity in which a woman undergoes changes consistent with menopause, such as amenorrhea, elevated FSH levels, and depletion of ovarian follicles, prior to the age of 40. POF occurs in 0.1% of women under 30 years of age and 1% of women by age 40.

Genetic factors are thought to have a strong relationship with POF. There is a higher incidence of family history of early menopause and a suggestive increase in the family history of infertility, as well as an increased incidence of familial cases of early menopause amongst patients with idiopathic POF. Twin studies have likewise noted a strong genetic component to the age of menopause. Although inheritance appears to be either X linked or autosomal dominant sex limited, paternal transmission cannot be excluded. Women who have idiopathic early menopause (between the ages of 40 and 45) have a genetic pattern similar to whose with POF. These observations support the hypothesis of common underlying genetic factors, which may lead to an early decrease in fertility, early menopause, and POF.

POF may not be the same as age-appropriate menopause, which results from the depletion of the primordial follicle pool, because POF may be reversible, with follicles in the ovary, estradiol production, and even pregnancies long after the diagnosis. When using ultrasonography to evaluate the follicles in women with POF compared with age-appropriate menopausal and young women on oral contraceptives (OCPs), the mean ovarian volumes were smaller in patients with POF compared with women on OCPs, but not different from the women with age-appropriate menopause. Approximately 40% of patients with POF had follicles in the ovary, albeit fewer than in the normal premenopausal women.

Menstrual Cycle

Prior to the menopausal transition, the average length of a menstrual cycle ranges from 21 to 35 days. The menopausal transition is defined partially by menstrual irregularity that occurs in response to changes within the ovary, specifically, a dramatic decline in follicle number (and granulosa cell content). As a result, inhibin B levels fall, decreasing negative feedback on FSH, causing a monotrophic rise in FSH. This early cycle rise in FSH may shorten the follicular phase due to accelerated folliculogenesis. Estradiol levels remain relatively constant with age until the menopausal transition, when they initially rise in response to increased FSH levels. As the ovary fails, progesterone levels decline, leading to a shortened (or inadequate) luteal phase. Thus, an early sign of waning ovarian function may be a decreased intermenstrual interval. Precycle spotting may also signal deficiencies in progesterone production. These clinical signs of reproductive aging indicate a poor prognosis for those women still interested in reproduction. As the FMP approaches and the oocyte complement declines to a critical level, estradiol levels fall, leading to hot flashes, vaginal atrophy, and accelerated bone mineral density (BMD) loss. Also, as the FMP approaches, there is a steady trend toward an increased mean cycle length. In a woman's final 10 to 20 cycles, average cycle lengths are characteristically 40 to 42 days.

As menstrual irregularity increases during the menopausal transition, many women seek medical care. Treatment can be approached in several ways. After a complete history and physical examination, bleeding irregularities can be treated with different hormonal regimens including OCPs, cyclic hormone replacement therapy (HRT), or progestin-only therapy. Many of these patients continue to ovulate, albeit irregularly, so the addition of cyclic progestin (without estrogen) may further increase cycle irregularity and does not offer contraceptive protection. Thus, treatment with OCPs or a combined, cyclic estrogen-progestin regimen is advisable.

There is always the risk of endometrial hyperplasia in this age group. Patients considered high risk (history of chronic anovulation or obesity, or suspicious bleeding patterns such a watery, bloody discharge) should undergo endometrial sampling. Pelvic ultrasonography for measurement of endometrial stripe thickness is not a reliable predictor of risk in cycling women. For those who have a relatively new onset of bleeding irregularity (consistent with the menopausal transition in a previously ovulatory woman), consideration can be given for initial hormonal treatment, with endometrial biopsy reserved only for those whose cycles fail to normalize after 3 months of therapy.

Postmenopausal bleeding always should be considered abnormal and must be evaluated accordingly. Bleeding can occur from the rectum, vagina, cervix, urethra, or uterus. A thorough history and physical examination is crucial. If the source of bleeding is uterine, a transvaginal ultrasonographic examination can be very helpful. If the endometrial stripe is thinner than 5 mm, the bleeding is typically the result of an atrophic endometrium. If the endometrium is 5 mm or thicker, it is imperative to perform a diagnostic test, either an endometrial biopsy or dilation and curettage, to sample the endometrium.

Menopausal Syndrome

Given the above endocrinologic changes with aging, many symptoms associated with aging in women are due to estrogen deficiency, but the decline in adrenal androgens and growth hormone may contribute. Symptoms definitely due to estrogen deprivation include vasomotor symptoms and urogenital atrophy. Osteoporosis is likely, largely due to estrogen deficiency, but this may be exacerbated by the relative growth hormone decline. The same may be said for the hormone-related changes of increasing atherosclerotic CVD and psychosocial symptoms including insomnia, fatigue, short-term memory loss, and depression. Both DHEAS and growth hormone may well have an impact on these age-related symptoms.

Vasomotor Symptoms Vasomotor instability in the form of a hot flash (flush) is one of the most consistent and bothersome symptoms that women face as they enter the menopausal transition and subsequent menopause. Hot flashes result from estrogen deficiency and a resetting of the hypothalamic thermoregulatory set point. They occur in 65% to 76% of women who undergo spontaneous menopause or surgical oophorectomy. Symptoms may begin during the menopausal transition, when estrogen levels may fluctuate dramatically from cycle to cycle and even day to day. A hot flash usually is characterized by intense warmth, described as “heat or burning” that usually begins in the head, neck, and thorax and can spread in waves over the entire body. It may be preceded by pressure in the head and may be accompanied by heart palpitations. The hot flash usually is followed by an outbreak of sweating, followed by chills as the body's thermostat resets. The length of the episode varies from seconds to approximately 5 minutes, although episodes as long as 30 minutes have been described. The event frequency varies from a few per year to 30 per day. For most women, the hot flashes commence prior to the FMP, although initially this may be perceived only as a sleep disturbance. In general, the episodes are noted more frequently at night, and the dysfunctional sleep pattern that follows may result in fatigue, irritability, loss of concentration, and depression, symptoms that often are elicited from patients in the menopausal transition. More than 80% of women who experience hot flashes will experience them for longer than 1 year. Twenty-five percent of women complain of severe hot flashes. Without treatment, the symptoms usually subside slowly over 3 to 5 years. Investigators in 25-year longitudinal study from Gothenburg, Sweden, with 1,462 participants, found the prevalence of hot flashes a maximum of 60% at 52 to 54 years of age. Interestingly, 9% of subjects still reported hot flashes at age 72. The etiology of hot flashes seems to be the withdrawal of estrogen rather than the state of hypoestrogenism. For example, women with Turner syndrome who have not been treated with exogenous estrogen do not experience hot flashes. Those who are treated with estrogen, which is later withdrawn, will experience symptoms of vasomotor instability. Obese women seem to be less symptomatic than matched controls with lower BMI. The explanation may be that obese women are less hypoestrogenic secondary to peripheral conversion of adrenal androgens into estrone or that obesity lowers sex hormone-binding globulin levels, allowing a greater proportion of their estrogen to remain unbound and able to act on target tissues. Studies of hot flashes with external monitoring of skin temperature and resistance have shown a frequency of approximately 54 plus or minus 10 minutes. This frequency has been shown to interrupt random eye movement sleep and potentially contributes to some of the psychosocial complaints. Hot flashes are correlated temporally with pulses of LH; however, exogenous LH does not induce a flash, suggesting there is some central mediator leading simultaneously to hot flashes and LH pulses. Several biochemical alterations are associated with the hot flash. During the actual episode, there is evidence of a rise in plasma LH, epinephrine, corticotropin, cortisol, androstenedione, DHEA, ß-lipotropin, ß-endorphin, and growth hormone. Levels of estradiol, estrone, prolactin, thyroid stimulating hormone, FSH, and norepinephrine are unchanged.

Treatment Vasomotor symptoms are the most common indication for use of estrogen treatment in menopause and are also a U.S. Food and Drug Administration (FDA)-approved indication. Estrogen therapy, in either oral or transdermal form, has a greater than 95% efficacy for the treatment of hot flashes. Hot flash frequency is first notably reduced after 2 weeks of treatment, and the full effect of a certain dosage can be determined reliably after 4 weeks. Due to concerns over the risk-benefit analysis of HRT use, it is recommended that women be treated for vasomotor symptoms for short periods (1-4 years) and then gradually tapered, because symptoms often recur when treatment is discontinued abruptly. For patients with contraindications to estrogen use, vasomotor symptoms can be treated, albeit less efficiently, with progestins, a2-adrenergic agonists (clonidine, methyldopa, lofexidine) and, possibly, antidepressants (selective serotonin reuptake inhibitors [SSRIs], venlafaxine hydrochloride [Effexor]). The role of serotonin (5-hydroxytryptamine [5-HT]) in symptoms of menopause is being investigated increasingly. Serotonin levels fall with menopause, either naturally or surgically induced, and replacement estrogen is known to increase serotonergic tone. The 5-HT_{2A} receptor subtype is thought to underlie changes in thermogenesis. Stimulation of this receptor may lead to changes in the set-point temperature, leading to autonomic changes which cool the body. An increased skin temperature and sweating may result. Thus, an involvement for the 5-HT_{2A} receptor in the etiology of hot flashes has been suggested. A theoretical model, illustrating a role for 5-HT in the mechanism of the hot flash, is shown in Figure 41.3.

FIG. 41.3. Possible mechanism by which a hot flush is induced. (From Berendsen HH. The role of serotonin in hot flushes. Maturitas 2000;36:155–164, with permission.)

Most studies using SSRIs for the treatment of vasomotor symptoms have been in patients with breast cancer. The differential between the antidepressant effects of these agents versus a direct effect on vasomotor symptoms may be more difficult to detect in this population.

Genitourinary Atrophy

Vagina A decrease in circulating estrogen levels has deleterious effects on urogenital epithelium. Up to 50% of postmenopausal women experience symptoms of vaginal atrophy. The most common symptoms include dryness, irritation, itching, burning, and dyspareunia. Atrophic vaginitis is associated with a rise in vaginal pH, which can lead to more frequent infections and worsening, irritative symptoms. A concurrent decrease in vaginal lubrication can lead to bleeding and decreased sexual comfort and pleasure. Estrogen replacement therapy (ERT) is an effective treatment for vaginal atrophy. The systemic dosage necessary for vaginal protection is somewhat higher than needed for bone protection (see below) and, thus, topical therapy by means of creams or vaginal rings may be advisable to limit systemic absorption. Unless systemic HRT is required for vasomotor instability, local estrogen therapy can be used effectively to treat urogenital atrophy. Vaginal estrogen cream or tablets can be used daily for approximately 2 to 3 weeks, and then twice weekly after initial symptoms have improved and vaginal vascularization (hence, hormone uptake) have increased. Treatment is usually long term, because symptoms tend to recur when estrogen is discontinued. The twice-weekly estrogen regimen can be used without supplemental progestin without an increase in endometrial thickness. The dosage should be kept low, however, because the well-vascularized vagina is extremely efficient in the absorption of steroids. The new low-dose vaginal ring may also be used without progestin protection of the endometrium. Vaginal estrogen frequently will improve symptoms of urinary frequency, dysuria, urgency, and post-void dribbling. A direct effect to improve urinary incontinence is less clear. Alternatives to estrogen include vaginal moisturizers and lubricants. There is no evidence to support the use of agrimony, black cohosh, chaste tree, dong quai, witch hazel, or phytoestrogens for the treatment of atrophic vaginitis.

Urinary Tract Infections Urinary tract infection (UTI) is common among women of all ages. Worldwide, an estimated 150 million UTIs occur annually. In the United States, UTIs account for more than $6 billion in health care costs. The incidence is highest in 18- to 24-year-old women at 17.5% and is 9% for women older than 50 years. In younger women, the major risk factors for recurrent UTI are sexual intercourse and spermicide exposure. In older, institutionalized women, the most important risk factors include urinary catheterization and functional status. Healthy, postmenopausal women have different risk factors for recurrent UTI than those mentioned above. Recurrent UTIs in healthy postmenopausal women are associated with urinary incontinence, cystocele, and increased post-void residual volumes. Other significant risk factors include at least one episode of UTI prior to menopause, urogenital surgery, and reduced urinary flow. From the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with coronary heart disease (CHD), additional risk factors included diabetes, vaginal itching, and vaginal dryness. Changes in the vaginal environment after menopause may also predispose to UTI. These alterations include the absence of lactobacilli, elevated vaginal pH, and increased rate of vaginal colonization with *Enterobacteriaceae.* The intravaginal administration of estrogen has been shown to reduce the rate of recurrent UTI by normalizing the vaginal environment. Low-dose oral hormone therapy, with conjugated estrogen plus medroxyprogesterone acetate (MPA), does not reduce the frequency of UTIs in older women.

Urinary Incontinence The prevalence of urinary incontinence in menopausal women is estimated to be in the range of 17% to 56%. Urinary incontinence is the eighth most prevalent chronic medical condition among U.S. women. Anatomic and physiologic alterations associated with aging and incontinence include thinning of the urethral mucosa, reversal of the proteoglycan-to-collagen ratio in the paraurethral connective tissue, decrease in urethral closure pressure, and changes in the normal urethrovesical angle. Many risk factors have been associated with incontinence. Menopause often is considered to be one of these risk factors, especially because a prevalence peak in midlife has been reported by many authors. Epidemiologic studies generally have not found an increase in the prevalence of urinary incontinence in the menopausal transition. A risk factor for incontinence is an increased BMI. This is an especially important factor, because it is modifiable. Vaginal delivery is associated with transient postpartum incontinence, as well as an increased risk of incontinence later in life. Interestingly, a study of nulliparous nuns, with mean age of 68, found that 50% of the nuns had urinary incontinence. Meta-analyses have found an association between hysterectomy and urinary incontinence, with an increase in incontinence of 60%. Considering that more than 600,000 hysterectomies are performed yearly in the United States and that approximately 40% of women have undergone hysterectomy by age 60, these results are quite relevant. Women should be counseled about this relationship prior to undergoing hysterectomy. Other significant risk factors include history of UTI and depression.

Treatment Oral ERT has been shown to restore the genitourinary connective tissues to that of premenopausal women, but it seems to have little short-term clinical benefit in regard to urinary incontinence. Interestingly, oral estrogen replacement is associated consistently with an increased risk of incontinence in women aged 60 years and older in epidemiologic studies. This increase may reflect that women with more severe symptoms seek medical care and HRT more often than asymptomatic women. It is also possible that the local levels of estrogen in these studies was too low to benefit fully the urogenital system, given the data suggesting higher systemic dosages may be needed for a vaginal effect.

Osteoporosis Osteoporosis is a condition in which bone loss has been sufficient to allow mechanical fracture with limited stress. The likelihood of developing osteoporosis is dependent on the combination of peak bone density (stressing the importance of bone building in the young) and the rate of loss (accelerated with estrogen deficiency). Primary, or “senile,” osteoporosis usually affects women between the ages of 55 and 70 years. The most common sites include the vertebrae and the long bones of the arms and legs. Secondary osteoporosis is caused by a specific disease (such as hyperparathyroidism) or medication usage (glucocorticoids, thyroid hormone excess, anticonvulsants). Menopausal bone loss begins before the FMP during stage -1. Postmenopausal osteoporosis causes over 1.3 million fractures annually. Most of the 250,000-plus hip fractures are due to primary osteoporosis. Excess mortality may exceed 20% within a year of a hip fracture and, because 75% of patients lose their independence, the social costs, not to mention the financial costs, are great. Bone loss following natural menopause is approximately 1% to 2% per year, compared with 3.9% per year following oophorectomy. A woman's genetic background, lifestyle, dietary habits, and coexisting disease will impact the development of osteoporosis. Cigarette smoking, caffeine use, and alcohol consumption are associated with increased bone loss, while weight-bearing activity appears to slow it. Approximately 30% of postmenopausal women have osteoporosis. The World Health Organization has defined osteoporosis as a hip BMD value, as measured by dual x-ray absorptiometry (DEXA), that is greater than 2.5 standard deviations below the adult peak (mean level for young, white women: *t*-score). Women with existing fractures, regardless of BMD, are also classified as osteoporotic. Both groups are at increased risk for fractures. Those patients with a low *z*-score (age-matched comparison) should be investigated for secondary causes of osteoporosis. Peak bone mass in women is achieved by the end of the third decade and is an important contributor to bone strength in later life. Adolescence is a critical period of rapid skeletal growth during which almost one half of the adult bone mass is accrued. Many factors contribute to a woman's peak skeletal mass including heredity, diet, physical activity, and endocrine milieu. Hormones which may be a factor in peak bone mass attainment include insulinlike growth factor (IGF)-1, which regulates skeletal growth, and gonadotropins which stimulate sex steroid production and epiphyseal maturation. Estrogen deficiency and amenorrhea can decrease peak bone mass, whereas weight-bearing exercise leads to an increase. Early influences, including birth weight and poor childhood growth, are linked directly to risk of hip fracture. Independent predictors of low peak bone mass include low body weight, menarche at over 15 years of age, and physical inactivity as an adolescent. Early intervention during childhood and adolescence may reduce a woman's risk for osteoporosis in later life—this includes adequate calcium intake and education regarding diet, ideal weight, and physical activity.

Treatment *Hormone Replacement Therapy.* HRT has been used widely for the prevention of osteoporosis and is FDA approved for this indication. It is clear that HRT helps prevent bone loss, as indicated by increased BMD. Whether these benefits translate into decreased fracture risk has been an important topic of research for the past decade. Observational studies have shown lower vertebral and nonvertebral fracture rates in women receiving estrogen compared with those not receiving this therapy. The addition of a progestin does not alter these results. However, observational studies may be biased, because women using HRT have better access to medical care and maintain healthier lifestyles in general. Estrogen therapy acts via an inhibition of bone resorption. Although both BMD and fracture rate are improved with estrogen therapy, there is a rapid and progressive loss of bone mineral content after cessation of estrogen therapy. By 4 years after therapy, bone density is no different from that of patients who were never treated with estrogen. Although estrogen is approved for *prevention* of osteoporosis, there is some evidence to support its usage in *treatment.* Dosages of 0.625 mg of conjugated estrogen and, more recently, as low as 0.3 mg have been shown to slow bone loss and provide adequate protection against the development of osteoporosis. Higher dosages may be required to *treat* existing disease. Meta-analysis of randomized trials shows an overall 27% reduction in nonvertebral fractures in a pooled analysis, with the effect being greater in women under 60 years of age. The HERS trial showed no evidence of reduction in incidence of fractures or rate of height loss in older women with CHD not selected for osteoporosis. The Women's Health Initiative (WHI), the first randomized primary prevention trial studying the effects of postmenopausal HRT, showed a significant reduction in hip fracture (hazard ratio [HR] = 0.66; CI = 0.45–0.98). It seems clear that HRT must be taken indefinitely to preserve bone mass. *Calcitonin.* Calcitonin is a hormone normally secreted by the thyroid gland and responsible for calcium homeostasis. Calcitonin is now available as a nasal spray, specifically developed to decrease local side effects caused by the earlier subcutaneous injection. Intranasal calcitonin has been shown to improve spinal bone density and decrease the vertebral fracture rate in women with established osteoporosis. The increase in bone density appears to peak in as little as 12 to 18 months. This may be due to down-regulation of the calcitonin receptors and the development of neutralizing antibodies. Although few studies have been performed and no data are available regarding calcitonin-related reductions in hip fracture, calcitonin does seem to be especially beneficial for women with a recent and still painful vertebral fracture. Unfortunately, it appears some patients do not respond to this therapy and those nonresponders cannot be identified prospectively. *Bisphosphonates.* These nonhormonal compounds are analogs of pyrophosphates which have an affinity for hydroxyapatite in bone. The basic molecular structure of bisphosphonates allows a large number of manipulations, producing different types of bisphosphonates which vary considerably in their potency. The first one used clinically was etidronate, the least potent. In succeeding order of development were pamidronate, alendronate, and risedronate, which is the most potent of these compounds. Etidronate, if given continuously for more than 6 months, impairs

mineralization of bone and may cause osteomalacia. There have been occasional reports of pamidronate also causing impairment of mineralization of bone. However, continuous administration of either alendronate or risedronate has not caused osteomalacia. Alendronate has been evaluated more extensively than calcitonin and has a proven track record, reducing the risk of all major fracture types (vertebral and nonvertebral) in women with osteoporosis. In one study, risk of hip fracture was reduced by 53%, clinical vertebral fracture by 45%, and wrist fracture by 30%. For all fracture types, some reduction in fracture risk was evident within the first year of treatment. Bisphosphonates have only a modest effect on BMD early in the treatment course. Because alendronate is effective so quickly in reducing fracture risk, mechanisms other than increased BMD, such as changes in bone remodeling rates, may play a role in fracture reduction. Alendronate has been shown to inhibit markers of bone remodeling and to increase BMD at the lumbar spine, hip, and in all other bones. Bone density increases with alendronate are greater than with calcitonin and are equal to that with HRT. The escape phenomenon seen with calcitonin is not seen with alendronate, which has the advantage of oral administration. The recommended daily dosage of 10 mg, however, must be taken according to a very strict dosing schedule (in the morning on an empty stomach, with the patient required to remain upright for 30 minutes thereafter). The medication has very poor bioavailability (approximately 1%) and, thus, these restrictions must be followed precisely. Alendronate also has a propensity for irritation of the esophagus and stomach, especially in women with preexisting esophageal reflux or gastric or duodenal disease. A newer formulation allows for once-weekly administration, and development of a once-yearly intravenous formulation may further decrease side effects and administration difficulties. Risedronate has been shown to reduce substantially the risk of both vertebral and nonvertebral fractures, also. Bone density is increased in both early postmenopausal women and those with established osteoporosis. The final remaining question concerning bisphosphonates has to do with the near-permanent changes in bone with the incorporation of this agent into the bone matrix. Although short-term fracture data appear favorable, the long-term effects of these agents and the ability of bone treated with bisphosphonates to heal (e.g., following hip fracture) are not known. *Raloxifene.* Raloxifene is the first of a new generation of compounds known as selective estrogen receptor modulators (SERMs) to have a treatment indication for osteoporosis. It is likely that there will be an explosion in the development of SERMs in the years to come. They may represent a new alternative for our patients with breast cancer or for long-term use in *all* patients. These new agents act as selective estrogen receptor *agonists* on the bone and possibly the heart and *antagonists* of estrogen action on the breast and uterus. Effects on the brain are not well characterized and likely will vary among compounds (see below). Data on raloxifene suggests good preservation of bone density, albeit less than seen with alendronate or HRT, and fracture data further supports a protective effect. It is believed that the differential effect of estrogen agonists (estrogens) and estrogen antagonists (“anti”-estrogens) is related to the transcriptional activation of specific estrogen-response elements. There appear to be two different domains of the estrogen receptor (AF-1 and AF-2) responsible for this transcriptional activation. Estrogen agonists and estrogen antagonists appear to act via different domains, resulting in their differential effects. Both appear to act to maintain bone density, at least partially, via regulation of the gene for transforming growth factor-ß. It has further been suggested that there may be a *raloxifene-response element*, which is distinctly different from the estrogen-response element. In women with osteoporosis, the 60-mg or 120-mg daily dose of raloxifene increases bone mass density in the spine and femoral neck and reduces the risk of vertebral fracture by 30% to 50% over no treatment. However, as with estrogen use, women receiving raloxifene have an increased risk of deep vein thrombosis compared with women receiving placebo. *Calcium and Vitamin D.* Calcium and vitamin D are important components of all three antiresorptive agents (calcitonin, bisphosphonates, SERMs). Decreased ability to absorb calcium among older women is due, in part, to impaired vitamin D activation and effect. In addition, older women may have limited exposure to sunlight, and their dietary vitamin D intake may be lower than that of their younger counterparts. Daily calcium intake of 1,500 mg and 400 to 800 IU of vitamin D per day is, in and of itself, probably sufficient to reduce the risk of fragility fractures by about 10%.

Summary-Osteoporosis Most current strategies regarding osteoporosis treatment have focused on identifying postmenopausal women who have low BMD and are already at increased risk for fracture. An evidence-based approach is to recommend appropriate calcium and vitamin D intake, smoking cessation, weight-bearing exercise, moderation in alcohol consumption, and fall prevention. If pharmacologic therapy is indicated, one of the above FDA-approved regimens should be instituted (Table 41.1 and Table 41.2). An alternative (complementary) approach to prevention is to focus on intervention beginning in childhood and adolescence, with attention to achieving maximal peak bone mass and minimizing premenopausal and postmenopausal bone loss.

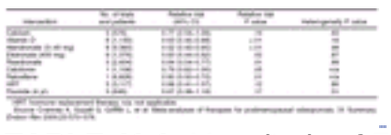

TABLE 41.1. *Magnitude of Effect on Vertebral Fractures*

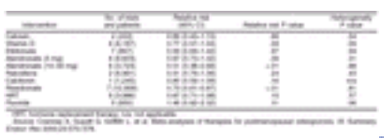

TABLE 41.2. *Magnitude of Effect on Nonvertebral Fractures*

Cardiovascular Disease CVD is the number one killer of both men and women in Western societies and is attributed primarily to age and lifestyle. Lifestyle modifications are well known to decrease the incidence of CVD. For women, CVD is largely a disease of the after menopause. Women will now spend more than a third of their lives beyond menopause and, thus, preventive measures are paramount. A large body of observational evidence supports a protective effect of ERT on CVD. Observational data, however, are limited by the confounding variables of patient self-selection. Animal and in vitro studies, as well as assessment of surrogate markers in women, have shown a positive effect of estrogen and (less so) HRT against CVD development. Approximately 2.5 million women in the United States are hospitalized each year for cardiovascular illness. CVD claims the lives of 500,000 women annually. One half of these deaths are due to CHD, making this the most frequent cause of death among U.S. women. CVD can be separated into two categories, (a) CHD and (b) noncoronary CVD, such as stroke, valvular heart disease, peripheral vascular disease, congestive heart failure, and sudden death from cardiac causes. A woman's risk of heart disease is far lower than a man's risk until after menopause. This change in incidence of heart disease may be related to advancing age, changes in hormonal milieu, or other unknown factors. CHD entails a worse prognosis for women than for men following either medical or surgical therapies. These sex discrepancies may reflect the older age, smaller body size, more frequent and severe coexisting illnesses of women and, perhaps, a higher incidence of delayed or suboptimal care. Chest pain or tachycardia may be overlooked as benign problems in women, potentially caused by depression, anxiety, or panic disorders. These misperceptions may lead to bias in evaluating women with chest pain. Chest pain in women may also have atypical clinical pictures compared with the more “classic” symptomatologty in men. Chest pain, regardless of symptoms compatible with angina pectoris, warrants evaluation for CHD, regardless of sex. If a woman seeks treatment for typical, or atypical, signs and symptoms of myocardial ischemia, a careful clinical history, including assessment of cardiac risk factors, should be taken. Electrocardiographic exercise testing is recommended for women who give a history typical of angina pectoris if the resting electrocardiogram findings are normal. When the resting electrocardiogram results are abnormal, the patient should be referred for either perfusion imaging studies or coronary arteriography. No screening test is of value for asymptomatic patients, even when risk factors are present. Fewer symptomatic women than men undergo diagnostic coronary arteriography and therapeutic angioplasty or bypass surgery. Women who do undergo bypass surgery more often require emergency surgery and typically are sicker than men at the time of intervention. They have increased operative mortality rates and postoperative complications. It seems that women are referred for revascularization procedures at a later, more symptomatic, stage of illness. Both coronary angioplasty and coronary bypass surgery have a comparable long-term survival for men and women who survive the initial hospital stay. Beta-blockers and aspirin are equally efficacious in both sexes in preventing reinfarction after myocardial infarction. Women should be encouraged to seek medical attention if they have any symptoms suggestive of myocardial ischemia. Physicians should emphasize the importance of modifiable risk factors for CHD, most notably weight management, fat restriction, increased physical activity, treatment of hypertension, and smoking cessation. Randomized, controlled studies have failed to support a protective role for HRT. This is in conflict with earlier observational studies, studies utilizing surrogate markers, and animal studies. The differences may be due to the unbiased sample of subjects taking HRT in these newer studies and, hence, may be a more realistic reflection of the impact of HRT on CVD. However, other potential confounders may be present, even in these studies, such as the menopausal stage when treatment was begun, the particular HRT regimen selected, and the individual risk factors of each subject (although the results may be more reasonably generalized, this may not accurately reflect clinician practice). The first reported trial evaluated HRT for secondary prevention. The HERS trial evaluated daily HRT (0.625 mg conjugated estrogen + 2.5 mg MPA) in 2,763 postmenopausal women with a mean age of 66.7 years and documented preexisting vascular disease. The study failed to demonstrate any overall difference in subsequent vascular events. This occurred despite improvements in lipid parameters in those patients receiving HRT. Although some have questioned the negative impact of the progestin, in this trial, the Estrogen Replacement and Atherosclerosis (ERA) trial published in 2000, compared 3.2 years of treatment with estrogen, combined estrogen and progestin, and placebo. Study participants were postmenopausal women aged 42 to 80 years. This, again, was a secondary prevention trial and also failed to demonstrate a significant difference in the rate of progression of coronary atherosclerosis among the three groups. The importance of this study was the inclusion of an estrogen-only arm. The WHI is the first large, randomized study to look at primary prevention. The same combined HRT regimen used in the HERS trial was evaluated. This study was stopped when interim analyses demonstrated an unacceptable risk profile for a drug in a prevention trial. There was an increase in the incidence in breast cancer (an increase of 8 cases per 10,000 women), with no cardiovascular protection (and potentially increased cardiovascular risk). There was an increase in the absolute number of blood clots, strokes, and CHD. The risk of stroke and clot continued for the 5 years of study, while most of the CHD was limited to the first year of treatment. Whether these finding were related to the intrinsic properties of HRT, the oral administration route, or the unique regimen tested is not clear. There were, however, documented decreases in the risk of fracture and colon cancer. Management for cardiovascular risk for women should parallel that for men. In other words, lifestyle modifications should be made and antihypertensive therapy given as needed. If hyperlipidemia persists, statin therapy should be instituted. And, as above, ß-blockers and aspirin should be given to prevent recurrent myocardial infarction. There is no evidence from well-designed prospective trials supporting a role for either ERT or HRT for the primary indication of cardiovascular protection.

HORMONE REPLACEMENT

Introduction

Approximately 38% of U.S. women aged 50 to 74 use HRT of some description. Of those surveyed, 59% of users had undergone a hysterectomy and 19.6% had a uterus. In 2000, Premarin (conjugated equine estrogen [CEE]) was the second most widely prescribed drug in the United States, accounting for 46 million prescriptions and over $1 billion in sales. Historically, patients desiring hormone treatment for menopausal symptoms were supplemented initially with unopposed estrogen, regardless of the presence of a uterus. This therapy was proven clearly to increase a woman's risk of endometrial cancer, which was eliminated with the addition of either cyclic or continuous low-dose progestin. Women who have undergone hysterectomy can, and should, be treated with estrogen alone.

According to the FDA, approved indications for ERT-HRT include treatment of menopausal symptoms (e.g., hot flashes and genital tract atrophy) and the prevention of osteoporosis. During the past 30 years, it has become popular to prescribe ERT-HRT to prevent a range of chronic diseases, most notably heart disease. As above, evidence has been accumulating which suggests that estrogen-progestin therapy for prevention of chronic diseases is not evidence based.

Benefits

With the publication of the WHI data, HRT risks and benefits have been examined critically (Fig. 41.4). HRT benefits include reduction in hot flash frequency and severity, improvement of atrophic vaginitis and UTIs, and prevention of osteoporosis and fractures. Neither vasomotor symptoms nor vaginal atrophy were evaluated in the WHI, although likely occurrence was low, because the participants were asymptomatic and not taking HRT when enrolled. The WHI results did support an additional benefit of decreased risk of colorectal cancer.

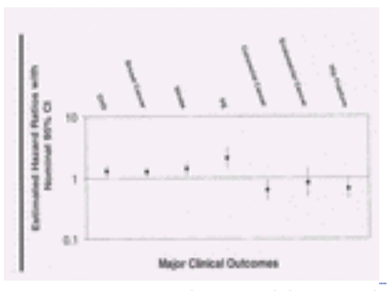

FIG. 41.4. Estimated hazard ratios for major clinical outcomes in the Women's Health Initiative trial of hormone replacement therapy. CHD, coronary heart disease; PE, pulmonary embolism. (Source: Writing Group for the Women's Health Initiative investigators. From Grimes DA, Lobo RA. Perspectives on the Women's Health Initiative trial of hormone replacement therapy. *Obstet Gynecol* 2002;100:1344–1353, with permission.)

A variety of areas have been studied in postmenopausal women, including estrogen effects on depression and Alzheimer disease (AD). The cognitive benefits of HRT remain more controversial than benefits in other areas. A meta-analysis from 1998 incorporating all studies published between 1966 and 1997 suggests several mechanisms by which estrogen may affect cognition, including maintenance of neural circuits, favorable lipoprotein changes, prevention of cerebral ischemia, and promotion of serotonergic and cholinergic activity in the brain. It is also possible that cognition improves in estrogen users during the menopausal transition because vasomotor symptoms improve, because there does not appear to be a clear benefit in asymptomatic women receiving HRT. The HERS data also support a cognitive benefit, concluding that the effects of HRT on emotional measures, of quality of life, depend on the presence of menopausal symptoms. The Seattle Midlife Women's Health Study showed that perceived memory functioning is more closely related to depressed mood, perceived stress, and perceived poor health than to age or reproductive stage.

AD is an enormous public health concern that intensifies as the population ages. In 1997, AD cases in the United States numbered 2.32 million, with 68% of individuals being female. In 1998, the annual number of new cases was 360,000. Interventions that could prevent this disease, or delay its onset, would have a major public health impact.

Women with high serum concentration of unbound (bioavailable) estradiol are less likely to develop cognitive impairment than women with low concentrations. Randomized trials studying estrogen use and AD are limited but suggest that estrogen users have a reduced risk of *developing* AD. However, there is no therapeutic benefit of estrogen usage in women with preexisting AD. Larger randomized trials are needed to evaluate the true significance of estrogen use and dementia. The WHI includes a memory study, and these results should be available in 2005.

Risks

As more randomized trials of HRT are conducted, the risk profile has broadened. CHD was once a main off-label indication for HRT, and former guidelines from the American College of Physicians even suggested that HRT be considered for all women. The HERS trial and, more importantly, the WHI have shown that nonfatal cardiac events are increased in HRT users in the regimen tested. These studies have also reemphasized known risks of HRT including pulmonary embolus, stroke, deep vein thrombosis, and gallbladder disease.

CONTROVERSIES

Cardiovascular Disease

During the 1990s, HRT was prescribed increasingly to postmenopausal women for CHD prevention. Much of this enthusiasm was based on a meta-analysis published in 1992 that concluded that “there is extensive and consistent observational evidence that estrogen use reduces risks for CHD about 35%.” This same year, the American College of Physicians published guidelines recommending that all postmenopausal women should consider HRT. They emphasized that those who are at increased risk of CHD are especially likely to benefit. Further observational studies have supported this recommendation. For example, the Nurse's Health Study of 1996 confirmed a 40% to 60% reduction in cardiovascular events in women taking HRT.

The HERS was a randomized, blinded, secondary prevention, clinical trial with results published in 1998. The study population was 2,763 postmenopausal women with documented CHD. The average age was 67 and all women had a uterus. Subjects were randomly assigned to receive either 0.625 mg CEE with 2.5 mg MPA daily or placebo. The average follow-up was 4.1 years. The investigators found that the women assigned to receive CEE plus MPA had a 50% increased risk of coronary events during the first year of the trial compared with the placebo group. The risk was greatest during the first 4 months. The risk returned to baseline over the next 2 years and seemed to be lower in the hormone-treated group beginning in the third year of the study. The changes could have occurred by chance or may be due to detrimental effects of the hormone replacement, the specific regimen studied, or the procoagulant effect associated with oral administration. An initial prothrombogenic effect was thought to be the cause of early morbidity, and there was some expectation that longer treatment would document an improved outcome. However, HERS II, which continued to follow this group (6.8 years of follow-up), failed to see a developing protective effect of HRT.

The WHI is the first randomized, primary prevention trial studying the effects of a specific postmenopausal HRT regimen (the daily regimen of 0.625 mg CEE plus 2.5 mg MPA). In contrast to the HERS trial, these 50- to 79-year-old women were considered healthy, with only a small proportion (7.7%) of subjects having clinical signs or symptoms of CHD. The subjects were randomized to receive the HRT regimen or placebo if they had a uterus. Women without a uterus received either the estrogen alone or placebo. The planned duration of the trial was 8.5 years, but the estrogen-plus-progestin arm (16,608 women) was stopped after 5.2 years because of concerns regarding cardiovascular events and breast cancer. “The test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits.” Estimated HRs for diseases other than breast cancer, including CHD, were also significant. The HR results were as follows: CHD, 1.29 (95% CI = 1.02–1.63); breast cancer, 1.26 (1.00–1.59); stroke, 1.41 (1.07–1.85); pulmonary embolus (PE), 2.13 (1.39–3.25); endometrial cancer, 0.83 (0.47–1.47); colorectal cancer, 0.63 (0.43–0.92); hip fractures, 0.66 (0.45–0.98).

This important study suggests that breast cancer, nonfatal CHD events, stroke, and PE are all significantly increased in the overall cohort, of women 50 to 79 years old using combined estrogen and progestin therapy. It showed that colorectal cancer and hip fracture risk are reduced significantly in the same group. Ultimately, the data suggest that the use of this combined HRT regimen for primary prevention of CHD is not justified.

In 2001, the American Heart Association published guidelines regarding HRT and CVD. They have taken a cautious stance. These recommendations were made prior

to the publication of the WHI results.

American Heart Association Recommendations
Secondary Prevention

- HRT should not be initiated for the secondary prevention of CVD.
- The decision to continue or stop HRT in women with CVD who have been undergoing long-term HRT should be based on established noncoronary benefits and risks and patient preference.
- If a woman develops an acute CVD event or is immobilized while undergoing HRT, it is prudent to consider thromboembolic prophylaxis while she is hospitalized to minimize risk of a venous thromoembolism associated with immobilization. Reinstitution of HRT should be based on established noncoronary benefits and risks, as well as patient preference.

Primary Prevention

- Firm clinical recommendations for primary prevention await the results of ongoing randomized clinical trials.
- There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD.
- Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference.

There is still some question about whether WHI was really assessing “primary” prevention based on concern about the preexistence of atherosclerotic disease. Enrollees were asymptomatic and older (mean age, 63 years) than the typical HRT-ERT user. Some vascular biologists have suggested the early institution of HRT may inhibit the *development* of atherosclerotic plaque and that a delay in treatment for several years after menopause, after plaque formation is well established, would not only not offer benefit but might increase risk by destabilizing existing plaque, leading to plaque rupture and thrombosis. Although this thesis is consistent with animal studies, little human data are available to support or repute it. It is yet another consideration for patients and physicians in making this difficult decision.

Breast Cancer

A woman's lifetime risk of breast cancer is 1 in 8. There are 192,000 new cases of breast cancer per year, accounting for 41,000 deaths per year. It is the second leading cause of cancer death after lung cancer and the leading cause of death among women ages 40 to 55.

The most compelling reason to believe that long-term use of postmenopausal estrogen increases the risk of breast cancer is the inherent biologic plausibility. Many of the risk factors associated with breast cancer are thought to be linked to increased duration of exposure to estrogen over a woman's lifetime. These risk factors include early menarche, late menopause, nulliparity, and older age at the birth of her first child. Oophorectomy can induce breast tumor regression and early oophorectomy is protective against breast cancer, which seem to support further the notion that estrogen is involved, but this remains controversial. All of these risk factors take ovarian function into account, but not necessarily estrogen exposure, because the ovary is responsible for the formation of many other compounds which may influence the risk, such as androgens.

The association of estrogen therapy and breast cancer remains controversial, despite the publication of over 50 epidemiologic studies during the past 25 years. This subject is of great public health concern because of women's understandable fear of breast cancer and the complexity of the decision-making process regarding hormone therapy.

A reanalysis of the world's data on HRT-ERT and breast cancer was performed in 1997. A team of epidemiologists invited all investigators who had previously studied the association of postmenopausal hormone use and the risk of breast cancer (51 studies) to submit their original data for a collaborative combined reanalysis, an undertaking more rigorous than a standard meta-analysis (Collaborative Group of Hormonal Factors in Breast Cancer).

This analysis reached the following conclusions:

- Ever users of postmenopausal hormones had an overall increased relative risk of breast cancer of 1.14.
- Current users for 5 or more years had a relative risk of 1.35 (CI = 1.21–1.49), and the risk increased with increasing duration of use.
- Current and recent users had evidence of having only localized disease (no metastatic disease) and ever users had less metastatic disease.
- There was no effect of a family history of breast cancer.
- There was no increase in relative risk in past users.
- The increase in relative risk in current and recent users was greatest in women with lower body weights.

The WHI has brought even greater attention to any relationship between breast cancer and HRT use. The estrogen-progestin versus placebo arm of the study was stopped early, due primarily to an increase in breast cancer risk with a HR of 1.2. No similar effect was noted in the estrogen-only arm of the study, which is ongoing. Whether or not women in this category will also have an increased risk of breast cancer is unknown at this time. There is other epidemiologic evidence to suggest combined, continuous HRT may confer a higher risk of breast cancer than either cyclic estrogen-progestin regimens or those with estrogen only.

The comparison between the collaborative epidemiologic analysis described above and the WHI is interesting (relative risk, 1.35 vs. 1.26). Another relevant point the authors from the collaborative reanalysis make is that the quantitative effect of their conclusion is similar to the impact of raising the age of menopause. According to their calculations, current and recent hormone use was associated with a 2.3% increase in breast cancer risk per year, and the effect of age of menopause was equivalent to a 2.8% increase in risk per year of delay.

The presence of only localized disease, in the collaborative study, raises concern regarding screening bias and whether ERT-HRT treatment simply accelerated the detection of tumors already present. All of these studies that have examined the mortality rates of women who were taking estrogen at the time of breast cancer diagnosis have documented improved survival rates. This reflects earlier diagnosis in users, because the greater survival rate in current users is associated with a lower frequency of late-stage disease. There has been a suggestion that estrogen users develop better differentiated tumors and the surveillance-detection bias is not the only explanation for better survival. This suggests that hormone treatment accelerated the growth of a malignant locus already in place, which appears clinically at a less virulent and aggressive stage.

Selective Estrogen Receptor Modulators

The controversy regarding HRT-ERT has heightened the call for alternatives. The term *hormone-estrogen replacement* implies the replacement of the beneficial aspects of premenopausal estrogen. SERMs make up a class of compounds that act like estrogen agonists on some tissues and estrogen antagonists on others. SERMs act by causing dimerization and conformational changes in the estrogen receptor, altering the interaction with the promoter regions on DNA. These conformational changes further impact function through their interactions with co-regulators and co-repressors. This is illustrated in cartoon form in Figure 41.5.

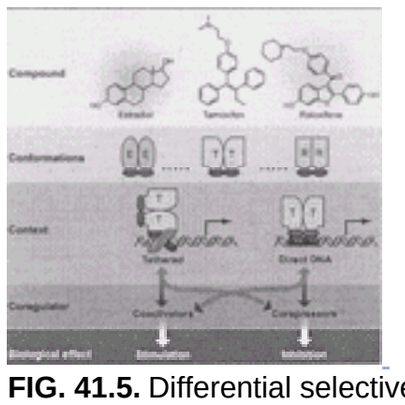

FIG. 41.5. Differential selective estrogen receptor modulator activity (stimulation and inhibition) is determined by the specific tissue, the endogenous milieu, and the impact of conformational changes on the interaction with regulatory sequences of DNA and co-regulatory proteins (co-activators and co-repressors). (From Katzenellenbogen BS, Katzenellenbogen JA. Defining the “S” in SERMs. Science 2002;295:2380–2381, with permission.)

The search for the “ideal” SERM, with positive (estrogenic) effects on the heart, bone, and brain and negative (antiestrogenic) effects on the breast and uterus, continues. Improved scientific knowledge regarding estrogen receptor function (more like a rheostat than an “on-off” switch), two receptor types (a and ß), more than 50 transcription factors, over 20 modifying proteins, and different response elements should enhance the development of therapeutic agents for selective clinical applications.

The beneficial aspects of raloxifene, the most studied SERM, with respect to osteoporosis, already have been discussed. There are evolving data with respect to CVD. Both raloxifene and tamoxifen decrease total cholesterol and low-density lipoprotein levels. Neither has an effect on high-density lipoprotein or triglyceride levels. Interestingly, raloxifene is either neutral or decreases two inflammatory markers (homocysteine and C-reactive protein), which might participate in the increase in cardiovascular events seen with the institution of HRT-ERT.

The available data about SERMs and CVD are, again, based on surrogate markers. A prospective study, Raloxifene Use in The Heart (RUTH), is ongoing. This study will evaluate 10,000 at-risk women and will add information to guide treatment strategies and, hopefully, increase our treatment options.

Limited data have suggested SERMs may have a beneficial effect on cognition. Although raloxifene is known not to improve (and potentially worsen) vasomotor symptoms, there is some preliminary evidence to suggest a neuroprotective effect. The extent and mechanism of this effect is not well characterized and awaits further study.

There is no doubt that the available SERMs are antiestrogenic at the breast. Tamoxifen is used primarily in the United States for cancer chemoprevention and treatment. Raloxifene also appears to decrease the incidence of estrogen receptor-positive cancer development. The Study of Tamoxifen and Raloxifene (STAR) should yield direct information regarding the benefit of raloxifene in women at risk for breast cancer as the available data are derived from osteoporosis trials. Lastly, it should be remembered that both tamoxifen and raloxifene increase the risk of thromboembolic phenomena, and this may have an impact on cardiovascular risk.

SUMMARY

The WHI did not address the effect of hormone treatment on hot flashes and vaginal atrophy. Clearly, there are alternatives for the treatment of osteoporosis and CVD that have less risk if CVD prevention is the sole reason for using HRT. Each woman should discuss with her health care provider the optimal treatment management to address her individual goals. This obviously would need to take into account medical and family history, as well as symptomatology.

If HRT-ERT is selected by the patient, progestin should be used only for those women with a uterus. Furthermore, in developing an overall treatment strategy, physicians should utilize the full armamentarium of medications (conjugated estrogens, estradiol, MPA, norethindrone, micronized progesterone, and androgens), routes of administration (oral, vaginal, transdermal), and cyclic patterns (continuous, intermittent, monthly, quarterly) available, including low-dose aspirin and statins. Duration of hormone therapy would also be an individual decision based on the original indication for treatment and its persistence. It can be recommended uniformly that menopausal women maintain appropriate nutrition, a healthy body weight, and regular exercise, including both weight-bearing aerobic exercise and muscle-strengthening exercise. This should be associated with moderation in alcohol intake and cessation of smoking.

SUMMARY POINTS

- Estrogen production in women is related to follicular maturation and the number of ovarian follicles is fixed, with declining numbers of follicles associated with hypoestrogenism.
- Declining ovarian estrogen production is associated with vasomotor instability, hot flashes, urogenital tract atrophy, and accelerated loss of BMD.
- Treatment of the symptoms associated with declining ovarian estrogen production is optimal with ERT in women without a uterus and estrogen with progestin regimens in women with a uterus.
- Although primary or secondary prevention of CVD has been suggested in observational studies, it has not been demonstrated in randomized treatment trials (HERS and WHI).
- A slight increase in the risk of breast cancer has been associated with HRT, albeit with a lower mortality likely secondary to earlier detection at a less aggressive stage of disease.
- Decisions regarding the use or ERT-HRT should be individualized, based on the woman's goals of therapy, and reevaluated periodically to ensure that the risk-benefit analysis continues to favor hormone use.

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Chapter 42

Laurie Jane McKenzie and Sandra Ann Carson

Human Sexuality and Female Sexual Dysfunction

ANATOMY
Erectile Tissues
Role of the Cervix/Uterus
Graefenberg Spot
SEXUAL RESPONSE CYCLE
The Masters and Johnson Hypothesis
The Kaplan Hypothesis
The Basson Hypothesis
NORMAL SEXUAL PHYSIOLOGY
SEXUAL DYSFUNCTION
Risk Factors
Evaluation
Classification
ETIOLOGY OF SEXUAL DYSFUNCTION
TREATMENT
Desire Disorders
Arousal Disorders
Orgasmic Disorders
Pain Disorders

SUGGESTED READINGS
Anatomy
Normal Female Sexual Response Cycle
Physiology
Sexual Dysfunction
Evaluation
Classification
Etiology
Treatment
Appendix A—Female Sexual Function Index (FSFI)a
Footnote

> “In view of the pervicacious gonadal urge in human beings, it is not a little curious that science develops its sole timidity about the pivotal point of the physiology of sex.”
>
> W. H. Masters and V.E. Johnson, *Human Sexual Response*, 1966

Sexuality and satisfying sexual functioning are important aspects of a woman's general health and feelings of well-being. However, the reluctance to engage in open discussions about sex extends even to physicians. Surveys of primary care physicians reveal that less than 50% ask new patients about sexual practices and concerns. Nevertheless, a thorough understanding of the normal sexual response and evaluation and treatment of common sexual dysfunctions is imperative to provide comprehensive gynecologic care.

ANATOMY

Female pelvic anatomy demonstrates pronounced changes during sexual arousal (Fig. 42.1). During sexual arousal there is a pronounced alteration of these anatomic structures. The vaginal walls assume a darker coloration due to vascular engorgement, the inner two-thirds of the vagina lengthen and distend, the labia minora increase in size, and the clitoris swells. Pelvic vasocongestion, swelling of external genitalia, and lubrication occurs. Contrary to findings by Masters and Johnson, magnetic resonance imaging (MRI) studies during either coitus or masturbation, revealed that the size of the uterus does not increase in size, but does elevate in the pelvis. The vagina lengthens by 1 cm, and after further arousal, the vaginal opening constricts secondary to vascular engorgement, called the “orgasmic platform”. The “orgasmic platform” undergoes a series of clonic contractions with the first three to six being strong and having an intercontractile interval of 0.8 seconds with subsequent periods lengthening before the strength of the contractions recede. However, the actual presence of a physical “orgasmic platform” has been questioned.

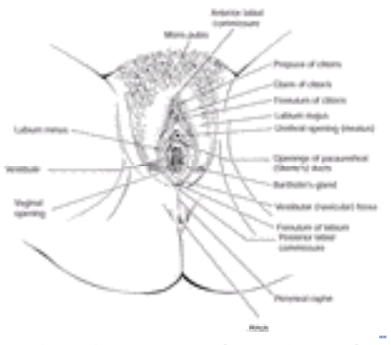

FIG. 42.1. Female external anatomy.

These anatomic changes noted in response to sexual arousal involve four functional groups of muscles. The first group consists of the ischiocavernous and bulbospongiosus. These muscles insert anteriorly on the shaft and crura of the clitoris which pulls the clitoris down to compress venous drainage and facilitate engorgement. The second group is the transverse perinea (superficial and transverse), which supports the perineum. The levator ani (the medial pubococcygeus and the lateral iliococcygeus) comprises the third set of musculature and forms the anterior pelvic diaphragm. The levator ani fixes the vesicular neck, anorectal junction, and vaginal fornices to the side wall of the pelvis. During sexual intercourse, vaginal distention from the penis evokes the vaginolevator and vaginal puborectalis reflex causing contraction of the levator ani muscles. This contraction leads to upper vaginal ballooning which acts as a receptacle for semen, elevates the uterus, and narrows and elongates the vagina. The development of the pubococcygeus muscle has been advocated to increase sexual pleasure and orgasm during coitus. Kegel proposed that underdevelopment of the pubococcygeus resulted in less pleasurable vaginal sensation during coitus and “every woman with a sexual complaint should be evaluated for possible pubococcygeal dysfunction.” The fourth set of muscles is the smooth muscle fibers of the upper two thirds of the vagina and the striated lower third. These four muscle groups vary considerably in size, strength, and volitional control among women. Although these muscle groups are well-defined anatomically, their exact impact on sexual functioning remains poorly understood.

Erectile Tissues

Erectile tissues, or cavernous bodies, are present in the clitoris and the vestibular bulbs. These areas become engorged with blood when successful sexual arousal occurs. The clitoris is comprised of three parts: the outermost glans, the midline corpus, and the innermost crura. The paired crura are called corpora cavernosa and are separated by a connective tissue septum. The clitoris is suspended to the anterior abdominal wall by a suspensory ligament, and is exquisitely sensitive to touch, temperature, and pressure. The autonomic innervation of the clitoris arises from the pelvic and hypogastric plexuses, employing both sympathetic and parasympathetic fibers. The clitoris has a dense concentration of pacinian corpuscles, as well as Merckles tactile discs, free nerve endings, and Meissner corpuscles. Sensory innervation to the clitoris travels from the skin via the dorsal nerve of the clitoris to the pudendal nerve, and subsequently to the spinal cord (Fig. 42.2.) Other erectile tissues are the paired vestibular bulbs. Located laterally to the vaginal orifice and directly beneath the skin of the labia, the vestibular bulbs are homologous to the corpus spongiosum of the penis.

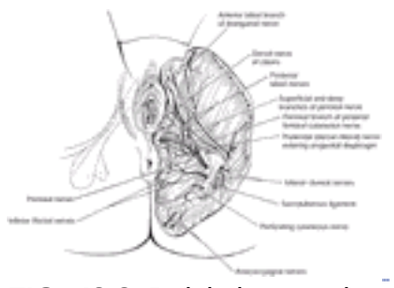

FIG. 42.2. Pelvic innervation.

Role of the Cervix/Uterus

The role of the cervix in sexual functioning has been widely debated. The cervix has a rich vascular and nerve supply, and it appears plausible that loss of the cervix may have an adverse effect on sexual arousal. In the widely reported Finnish cohort study from 1979, total abdominal hysterectomy was performed on 105 women and supracervical hysterectomy on 107. The only statistically significant finding was a decrease in orgasm frequency in the total hysterectomy group. The proportion of women that could not achieve orgasm in more than 75% of their coital encounters increased from 30% prior to the total abdominal hysterectomy to 47% at 1 year following the operation. Both groups had a statistically significant decrease in dyspareunia and no change in coital frequency. It is difficult to draw a definitive conclusion from this study as the treatment groups were not blinded and there were demographic differences between the two study groups. A subsequent study comparing 532 women after total abdominal hysterectomy with 146 women after supracervical hysterectomy found no differences. Attempting to define the role of the cervix and uterus in sexual functioning is a challenge, and the existing studies are methodologically flawed. A randomized, controlled trial will be necessary to further elucidate this issue.

Graefenberg Spot

The existence of a G-spot or Graefenberg spot refers to an allegedly highly erogenous region on the anterior vaginal wall, approximately one-third of the distance from the introitus. The concept of a G-spot is widely accepted among the public, however there is little objective evidence to support its existence.

The anterior vaginal wall has more innervation than the posterior wall, however this innervation is subepithelial; intraepithelial innervation would be expected if a sensitive region existed. Thus, sketchy clinical findings and no anatomic evidence exist to document the existence of a G-spot. Nonetheless, the reader is reminded that each woman is an individual and sexually unique and universal anatomic axioms should not dictate clinical care.

SEXUAL RESPONSE CYCLE

The Masters and Johnson Hypothesis

The classic approach to the female sexual response was proposed by William Masters and Virginia Johnson in 1966 when they arbitrarily divided the sexual response into four stages. These stages of excitement, plateau, orgasm, and resolution were presented as a continuum, with each stage progressing into the next.

The excitement phase was defined as sexual arousal or tension resulting from psychogenic or somatic stimuli. Pelvic vasocongestion and increased muscle tension is evident. Vaginal lubrication occurs, the vaginal walls assume a darker coloration due to engorgement, and the uterus elevates slightly. The inner two thirds of the vagina lengthen and distend, the labia minora increase in size, and the clitoris swells. Masters and Johnson noted a two- to three-fold increase in the labia minora diameter. Often the nipples become erect and a sex flush may occur.

During the plateau phase, the vaginal opening constricts due to vaginal engorgement. The clitoris often retracts, and if stimuli are adequate, orgasm occurs.

The orgasmic phase is described as the few seconds at climax in which sexual tension is relieved in a wave of intense pleasure, often accompanied by myotonia. This is an involuntary reflex that demonstrates uterine and vaginal contractions, and often varies in duration and intensity. Rhythmic pelvic thrusting may occur.

Following the release of sexual tension, there is often a feeling of well-being and satisfaction. This resolution stage follows orgasm and the body returns to its baseline state. Relaxation occurs, the sex flush disappears, and vasocongestion reverses. The clitoris and vagina resume their original size and shape.

The Kaplan Hypothesis

In 1974, Helen Kaplan became unsatisfied with the four stages of sexual response described by Masters and Johnson as she concluded that the sexual responses of patients did not appear to consist of an orderly sequence of separate events but consisted of two fundamentally separate components. The two distinct and relatively independent components are a genital vasoconstrictive reaction causing vaginal lubrication followed by the reflexive, clonic striated and nonstriated muscular contractions at orgasm. Kaplan also proposed a three-phase integrated model to include desire, arousal, and orgasm. She describes desire as an urge to seek out, initiate, or respond to sexual stimulation. Kaplan defines sexual desire as “a motivational or drive state that is generated by specific neurological processes in the brain—similar to other drives or appetites that subserve individual and species survival, not simply a subjective sensation or merely a mental event.” Kaplan's definitions of arousal and orgasm are similar to those proposed by Masters and Johnson; however, Kaplan focuses on the integration of these stages as opposed to occurring in a strict chronologic sequence.

The Basson Hypothesis

More recently, Basson has outlined an alternative sexual response cycle that emphasizes the role of sexual interaction with a partner in enhancing emotional closeness. The cycle begins with a state of “sexual neutrality” and if the woman seeks or is receptive to sexual stimuli, she will experience arousal and subsequent desire. Once desire is accessed, receptivity to sexual stimuli increases, which leads to further and more intense arousal. Emotional and physical satisfaction can then be attained, which facilitates emotional intimacy. The mental feedback of emotions, physical and genital arousal, mutual excitement, and cognition provide stimuli that modulate the ongoing sexual response. The focal point of this paradigm is “enhanced emotional intimacy,” and orgasm is not imperative for the experience to be satisfying.

NORMAL SEXUAL PHYSIOLOGY

Objective evidence of sexual arousal begins with increased clitoral length and diameter and vasocongestion of the vagina, vulva, clitoris, and uterus. The corpora cavernosa of the clitoris consists of a fibroelastic network and bundles of trabecular smooth muscle. Pelvic nerve stimulation results in clitoral smooth muscle relaxation and arterial smooth muscle dilation. With arousal there is an increase in the clitoral cavernosal artery inflow and an increase in the clitoral intercavernous pressure that leads to tumescence and extrusion of the clitoris. Engorgement of the genital vascular network increases pressure inside the vaginal capillaries and results in lubrication of the epithelial surface of the vaginal wall by a transudate of serum.

The vaginal fluid demonstrates significant changes in its ionic content before and after sexual arousal. Sodium and chloride levels increase significantly. Although most lubrication is from the transudate, which is passively transported through intraepithelial spaces, and appears on the surface of the vagina, a small amount of additional lubrication arises from the mucus secretions of the Bartholin glands.

These objective physiologic changes that occur with arousal are initiated by the medial preoptic, anterior hypothalamic region and related limbic-hippocampal structures within the central nervous system (CNS). Once activated, these centers transmit signals via the parasympathetic and sympathetic nervous systems to the clitoral and vaginal tissues. Serum concentrations of epinephrine and the norepinephrine metabolite, vanillylmandelic acid, increase prior to intercourse and remain elevated over baseline for up to 23 hours following sexual activity. Peripheral adrenergic stimuli may selectively “prepare” the body for genital responsiveness. Interestingly, anorgasmic women demonstrate an inhibition in physiologic sexual arousal under conditions of CNS activation. This may indicate that CNS activation may have a different influence on women with and without anorgasmia, and may have important implications for cardiac patients who take antihypertensive medications with high affinities for a-adrenergic receptors.

Another neuropeptide that impacts sexual function is serotonin (Table 42.1). Activation of the serotonin-2 receptor appears to impair sexual functioning and stimulation of the serotonin-1a receptor facilitates sexual functioning. Nefazodone (Serzone) is a selective serotonin reuptake inhibitor (SSRI) as well as a serotonin-2 receptor antagonist, and reportedly causes fewer sexual side effects than traditional SSRIs. The mechanism of action may be that nefazadone produces both a reduction in the number and activity of serotonin-2 receptors as well as an up-regulation in serotonin-1a receptors. The sexual side effects of SSRIs however, may be through a peripheral effect. Ninety-five percent of serotonin receptors are located in the periphery of the body, and peripheral serotonin acts on vascular smooth muscle to produce vasodilation and vasocongestion, acts on the smooth muscles of the genitals, and is active in peripheral nerve function.

Generic name	Trade name	Incidence of sexual dysfunction (%)
Sertraline	Zoloft	62.9
Fluvoxamine	Luvox	62.3
Fluoxetine	Prozac	57.7
Paroxetine	Paxil	70.7
Citalopram	Celexa	72
Venalafaxine	Effexor	67.3
Mirtazapine[b]	Remeron[b]	24.4
Nefazadone[b]	Serzone[b]	8

[a]All of the selective serotonin reuptake inhibitors are implicated in disorders of sexual arousal, desire, and anorgamia.
[b]Serotonin 2 (5HT2) receptor antagonists.
Source: Summarized data from a prospective multicenter study of 1,022 outpatients. *J Clin Psychiatry* 2001:62[Suppl 3]:10–21.

TABLE 42.1. *Selective serotonin reuptake inhibitors* [a] *and incidence of sexual dysfunction*

Dopamine is probably the most frequently studied of the neurochemicals that collectively regulate sexual activity, and while serotonin is generally inhibitory to sexual behavior, dopamine is regarded as facilitative. Dopamine generally enhances sensorimotor integration by removing tonic inhibition. Although steroid hormones increase the responsiveness of certain hormones, those neurons cannot fully respond to stimuli unless the tonic inhibition is removed. Therefore, dopamine does not directly affect sexual behavior; rather it allows hormonally primed output pathways to have access to sexually receptive stimuli. Dopamine agonists have been shown to increase mounting behavior and increase sexual behavior in sexually satiated male rats. Antiparkinsonian medications act as dopamine agonists and have been reported to increase sexual desire in human men. Bromocriptine, which decreases prolactin levels and is also a long-acting dopamine agonist, facilitates erectile functioning. Delayed or inhibited orgasm in women has been associated with antipsychotic medications that decrease dopamine activity. Cocaine enhances dopamine activity by blocking the presynaptic autoreceptor and, in low doses, is believed to enhance sexual pleasure. At higher doses, cocaine impairs sexual functioning and often leads to anorgasmia, perhaps a result of the vasoconstrictive effects of the drug.

Women with elevated prolactin levels frequently report a decrease in sexual interest that is often reversed with bromocriptine treatment. A significant two-fold increase in prolactin levels occurs in women following orgasm and prolactin remained elevated when measured 60 minutes after sexual arousal. Circulating oxytocin increases during sexual arousal and orgasm. In female animals, oxytocin injected either centrally or peripherally facilitates sexual behavior as measured by increases in a lordosis response. Blood cortisol levels appear unchanged during female sexual arousal or orgasm; however, hypercortisolism has been associated with decreased libido or erectile dysfunction in men.

Sexual stimuli involve a complex interplay between neurotransmitters and steroid hormones. The steroid hormones facilitate a sexual response by biasing sensorimotor integration so that a sexual stimulus is more likely to produce a sexual response. Testosterone administration to female-to-male transsexuals and androgen deprivation in male-to-female transsexuals support the theory that androgenic hormones play an important role in sexual desire. The androgens influence sexual desire, but are not sufficient alone as oral contraceptives and androgen antagonists do not consistently suppress libido, and patients with hypoactive sexual desire do not have lower androgen levels than women with normal sexual function. However, women report that their sexual desire diminishes following surgical menopause, and this desire can be restored with testosterone administration. Further evidence of androgen's effect on libido is illustrated when administration of dehydroepiandrosterone sulfate (DHEA-S) to postmenopausal women increases subjective ratings of sexual arousal when compared to placebo, although vaginal blood flow measures are unaffected. In premenopausal women, the effect of androgens is conflicting. There is a positive relationship between midcycle testosterone levels and coital frequency as well as testosterone levels and masturbation.

In contrast to the role of androgens, estrogens appear to have little direct effect on sexual desire and functioning. Exogenous estrogen, particularly when administered orally, increases sex hormone binding globulin which in turn reduces free testosterone and estradiol. No differences in estradiol levels have been found in women with or without hypoactive sexual desire, or as a function of coital frequency. Estradiol levels influence central and peripheral nerve transmission and exert a vasoprotective effect on pelvic vasculature. Estrogen is necessary to maintain the function of the vaginal epithelium, stromal cells, and smooth muscles of the muscularis as well as thickness of the vaginal rugae and vaginal lubrication. Estrogen deficiency may negatively impact sexual functioning by resulting in atrophy of the vaginal epithelium causing decreased lubrication and dyspareunia.

The role of progesterone on female sexual response still remains to be elucidated. Progesterone treatment does not appear to have a significant impact on sexual response, although there are some reports of diminished sexual desire with oral contraceptives or progestin implants.

Other chemical mediators have been proposed to augment and initiate sexual motivation. Pheromones are chemical substances released by one member of a species to communicate with another member, to their mutual benefit, and are secreted from the glands at the anus, breasts, urinary outlet, and mouth. Studies of these chemicals secreted by insects and animals have led to speculation that perhaps these substances would affect human sexual behavior. The main olfactory system in humans may respond to odor cues with behavior significance. There is a strong olfactory input to the prefrontal cortex and decision making in this region of the brain appears to be influenced by emotional signals. Investigation of the role of pheromones in humans has found no evidence of any change in sexual behavior.

It is apparent that the female sexual response is a complex integration of endocrine, neural, and neurochemical mediators. The steroid hormones appear to allow a permissive state to exist so that a sexually relevant stimulus can more likely elicit a sexual response. The long-term steroid effects may then induce a rapid physiologic change by altering levels of neurotransmitters. These chemical mediators are then communicated via multiple neural pathways which induce genital responses and sexual motivation. These complex interactions must be considered when attempting to define sexual functioning and to elucidate causes of sexual dysfunction.

SEXUAL DYSFUNCTION

Clearly, the complexity of the normal sexual response eschews a simple cause and effect, search and find, approach to human sexual dysfunction. Indeed, sexual dysfunction is a multicausal and multidimensional problem combining biological, interpersonal, and psychological components. It is not surprising that the prevalence is high. A 1992 study of adult sexual behavior in the United States (National Health and Social Life Survey) revealed 43% of women exhibit sexual dysfunction. Approximately 20% of women reported sex was not pleasurable, nearly one-fourth were consistently unable to achieve orgasm, and 8% to 21% experienced pain during intercourse. Often women will experience more than one sexual dysfunction, as marked overlap exists.

Risk Factors

Several risk factors are known to lead to sexual dysfunction. These include emotional or stress-related problems, deterioration in economic position, history of sexual trauma, and lower educational levels. Postmarital (divorced, separated, or widowed) status is associated with an elevated risk of orgasmic difficulties when compared to married women, and married women are one and a half times more likely to achieve orgasm than unmarried women. Black women tend to exhibit higher rates of hypoactive sexual desire compared to white women (44% vs. 29%) who report more sexual pain disorders (16% vs. 13%). Hispanic women, in contrast, consistently report lower rates of sexual dysfunction.

Evaluation

History Obtaining a thorough history for the evaluation of sexual dysfunction is imperative. The physician should ensure that the patient is comfortable and is assured of strict confidentiality. The interview can begin with open-ended questions and gender inclusive terminology should be used, so as not to assume heterosexuality. An introductory question such as “Most people experience sexual concerns or problems at times during their lives. What problems, if any, have you experienced?” can be helpful. The expectations and goals of the patient and her partner, the patient's degree of commitment to the relationship, and the presence or extent of extramarital relationships should be ascertained. Inquiring as to what the patient believes is the etiology of her sexual dysfunction may provide some insight, as the patient may simply admit that she is not attracted to her partner or has an underlying fear of pregnancy. The patient should be asked to define specifically what she perceives as the sexual difficulty. When she noted the onset of the problem, precipitating circumstances, the frequency and intensity, and whether she has experienced difficulty with other partners should be determined. Early sexual development and education should be discussed. Severely negative family attitudes toward sex (often associated with religious orthodoxy), traumatic prior sexual experience, or gender identity confusion are relevant. Relationship issues should be explored, such as whether the

couple has divergent sexual preferences or concerns of partner fidelity, and if there is any underlying hostility or abuse. Cognitive factors such as ignorance of sexual anatomy or sexual response and acceptance of cultural myths impact greatly upon therapy and should be addressed from the outset. The physician should inquire about ongoing illnesses, prior injuries, surgical and psychiatric history, and alcohol and recreational drug use. A thorough medication history is crucial, specifically the use of ß- adrenergic blockers, CNS depressants, anticholinergics, or antidepressants (Table 42.2). It should also be noted if the patient breast-feeding, or if she has recently undergone menopause.

Medications that Cause Disorders of Desire
Psychoactive medications
Antipsychotics
Barbiturates
Benzodiazepines
Selective serotonin reuptake inhibitors
Lithium
Tricyclic antidepressants
Cardiovascular and antihypertensive medications
Antilipid medications
Beta blockers
Clonidine (Catapres)
Digoxin
Spironolactone (Aldactone)
Hormonal preparations
Danazol (Danocrine)
GnRh agonists (e.g., Lupron, Synarel)
Oral contraceptives
Other
Histamine H_2-receptor blockers and promotility agents
Indomethacin (Indocin)
Ketoconazole (Nizoral)
Phenytoin sodium (Dilantin)
Medications that Cause Disorders of Arousal
Anticholinergics
Antihistamines
Antihypertensives
Psychoactive medications
Benzodiazepines
Selective serotonin reuptake inhibitors
Monoamine oxidase inhibitors
Tricyclic antidepressants
Medications that Cause Orgasmic Dysfunction
Methyldopa (Aldomet)
Amphetamines and related anorexic drugs
Antipsychotics
Benzodiazepines
Selective serotonin reuptake inhibitors
Narcotics
Trazodone (Desyrel)
Tricyclic antidepressants

Source: Adapted from Drugs that cause sexual dysfunction: an update. *Med Lett Drugs Ther* 1992;34:73–78, with permission.

TABLE 42.2. *Medications and female sexual dysfunction*

Assessment Scales Several self-report questionnaires are available for assessing sexual dysfunction, all with some advantages and limitations. The Sexual Evaluation Scale is a 16-item scale that pertains to global factors of sexual interest, arousal, and performance, but does not address the factors of sexual drive and satisfaction. The Brief Index of Sexual Functioning is lengthier and includes weekly assessment of sexual function. However, it contains sexually explicit questions that may contribute to patient noncompliance. The Arizona Sexual Experience Scale is a brief five-question scale designed to evaluate psychotropic drug-induced changes in sexual functioning, and is helpful in patients who have recently initiated antidepressant therapy. The Female Sexual Function Index (FSFI) is a brief, self-reported measure of sexual function with a high degree of internal consistency and construct validity. The FSFI evaluates desire, orgasm, arousal, sexual pain, lubrication, and sexual satisfaction (Appendix A).

Examination A detailed examination should be performed in the presence of a chaperone. The internal/external genitalia are examined closely and evidence of vaginal atrophy should be noted. A cotton swab can be used to elicit painful areas, particularly in patients reporting entry dyspareunia, and the vestibular areas, Bartholin ducts, Skene ducts, and the urethral meatus should be carefully checked. Areas of erythema or tenderness should be noted. Some women have minute papillae of the vestibular skin which is a normal variant that does not represent viral or other disease entities. A vaginal exam is performed using one finger prior to the bimanual exam to minimize confusion arising from abdominal tenderness. Vaginismus may be apparent during the exam, however approximately 25% of women who tolerate vaginal exams or tampon insertion experience involuntary spasms during coitus. The lateral walls of the vagina are palpated along the bladder anteriorly, the posterior wall, and vaginal fornices. The vagina is visually evaluated using a narrow, warmed, and well-lubricated speculum. The presence or absence of vaginal rugae, fissures, or friable tissue should be noted. Characteristics such as skin elasticity, pubic hair, labial fullness, and evaluation of the introital and vaginal depth offer an assessment of vaginal atrophy. Inspecting the cervix may detect dysplastic lesions or evidence of infection, which warrants further evaluation, including a Pap smear, cultures, or wet mounts. The vaginal fornices around the cervix are palpated for nodularity which is suggestive of endometriosis or may represent fixed adnexa from pelvic inflammatory disease. Muscle tone and Kegel strength are ascertained in addition to the bulbocavernosus reflex and genital/perineal sensation is assessed. With two examining fingers in the vagina, locate the levator muscles which are at the 5- and 7-o'clock positions just superior to the hymeneal ring. The patient is then instructed to contract these muscles. To assist in proper muscle group isolation, various verbal cues can be tried, such as “squeeze as if you are trying to stop your urine stream” or “squeeze as if you are trying to prevent flatus” or “pull my examining fingers up into the vagina.” A correctly performed pelvic floor contraction is demonstrated by cephalad retraction of the perineum and anus, posterior rotation of the clitoris, and anterior displacement of the examining fingers. Once the patient is able to contract the muscles properly, ask her to contract as strongly as possible for as long as possible in order to assess baseline pelvic floor function. This maximal effort is rated according to a pelvic muscle rating scale (Table 42.3).

	1	2	3	4
Pressure	None	Weak	Moderate	Strong
Duration	None	< 1 sec	1–5 sec	> 5 sec
Displacement	None	Slight anterior	Whole anterior	Gripped

TABLE 42.3. *Pelvic muscle rating scale*

The bulbocavernosus reflex is evaluated by squeezing the clitoris and feeling (or seeing) the anal sphincter and perineal muscles contract. Alternatively, the reflex may be initiated by suddenly pulling the balloon of a Foley catheter against the vesicle neck. The absence of this reflex in a man is almost always associated with a neurologic lesion, but the reflex is not detectable in up to 30% of otherwise normal women (Table 42.4).

Examination	Condition
External genitalia	
Assess muscle tone	Vaginismus
Assess skin color and texture	Vulvar dystrophy, dermatitis
Assess skin turgor and thickness	Atrophy
Assess pubic hair thickness and distribution	Atrophy
Expose clitoris	Clitoral adhesions
Assess for ulcers	Herpes simplex virus
Perform cotton swab test of vestibule	Vulvar vestibulitis
Palpate Bartholin glands	Bartholinitis
Assess posterior fourchette and hymenal ring	Episiotomy scars, strictures
Monomanual	
Palpate rectovaginal septum	Rectal disease, endometriosis
Palpate levator ani	Levator ani myalgia, vaginismus
Palpate bladder/urethra	Urethritis, interstitial cystitis, urinary tract infection
Assess for cervical motion tenderness	Infection, parametritis
Assess vaginal depth	Postoperative changes, postradiation changes, stricture
Bimanual	
Palpate uterus	Retroversion, leiomyomata, endometriosis
Palpate adnexa	Masses, cysts, endometriosis, tenderness
Perform rectovaginal examination	Rule out endometriosis
Obtain guaiac test	Bowel disease
Speculum	
Evaluate discharge, pH	Vaginitis, atrophy
Evaluate vaginal mucosa	Atrophy
Perform Pap smear	Human papillomavirus infection, dysplasia
Assess for prolapse	Cystocele, rectocele, uterine prolapse

Source: Adapted with permission from Phillips NA. The clinical evaluation of dyspareunia. *Int J Impot Res* 1998;10(suppl 2):S117–120.

TABLE 42.4. *Gynecologic causes of female sexual dysfunction and method of gynecologic examination*

More involved evaluation includes determination of vaginal pH, vaginal wall compliance, genital vibratory perception thresholds, and genital hemodynamics. The use of Semmes-Weinstein monofilaments to assess vulvar sensitivity to pressure and touch has been proposed. These 20 nylon monofilaments are all of equal length but varying diameters. The filament is pressed against the skin until it bends, providing a consistent reproducible application of force. The filaments are inexpensive, convenient, easy to use, and associated with a high degree of patient compliance. This technique reveals that women with sexual dysfunction have significant diminished vulvar sensitivity to pressure/touch compared to women without sexual dysfunction. Blood flow to the clitoral, labial, urethral, vaginal, and uterine arteries can be recorded and both blood velocity and venous pooling may be compared pre- and poststimulation. While it may be possible to demonstrate these differences objectively, in order for these assessments to be clinically relevant, a patient must be able to recognize these changes as sexual arousal, and their absence must be significant enough to interfere with sexual functioning (Fig. 42.3).

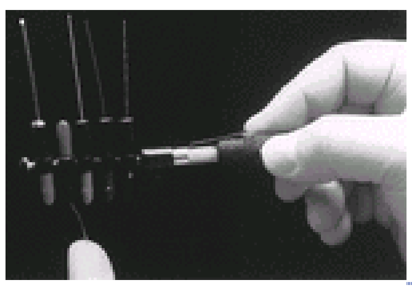

FIG. 42.3. Semmes-Weinstein monofilaments for detection of tactile neuropathy. (Photograph provided by Semmes-Weinstein Corp.)

Laboratory Evaluation Measurements of estradiol, follicle-stimulating hormone, prolactin, and testosterone are often obtained in patients with sexual dysfunction; however, there is little evidence to support a direct correlation between sexual dysfunction and hormonal parameters. Most researchers agree that estrogen plays only a minimal role in female sexual desire, yet estrogen deficiency does affect genital vasocongestion and lubrication and may induce atrophy of vaginal epithelium. Androgens and their role in sexual desire have yielded conflicting results (see Normal Sexual Physiology). With natural menopause, androgen levels (testosterone, DHEA-S) have been positively correlated with sexual interest; however, no significant differences in circulating testosterone levels have been demonstrated in normal women compared to women without hypoactive sexual desire.

Hemodynamic Testing Vaginal blood flow may be measured indirectly via vaginal photoplethysmography, pulsed wave Doppler ultrasonography, and measures of heat dissipation. Most of these techniques are reserved for the research setting. Vaginal photoplethysmography is the most studied technique in which a clear acrylic tampon is inserted into the vagina. This tampon contains either an incandescent light source or an infrared light-emitting diode as a light source and photosensitive light detector. The light source illuminates the capillary bed of the vaginal wall and the phototransistor detects the light that is reflected back from the vaginal wall and the

blood circulating within it. Disadvantages of this method are an inability to detect subtle changes in vaginal blood flow and often there is motion artifact. Measurement of tissue perfusion by measuring the cooling of a heated metal disk is another noninvasive technique that has been adapted for vaginal studies. A silver disk electrode is applied against the vaginal mucosa and maintained electrically at a temperature that exceeds body temperature. The electrical power needed to maintain this elevated temperature is then recorded. Increased blood perfusion under the disk will increase heat loss from the disk and require more power to maintain temperature. This power output therefore becomes an index of local blood perfusion. This technique is not affected by movement to the same degree as photoplethysmography.

Classification

The two primary classification systems for sexual dysfunction are the World Health Organization's *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition DSM-IV* (*DSM-IV*). The *ICD-10* definition of sexual dysfunction includes “the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish.” Categories are lack or loss of sexual desire (F52.0), sexual aversion disorder (F52.1), failure of genital response (F52.2), orgasmic dysfunction (F52.3), nonorganic vaginismus (F52.5), nonorganic dyspareunia (F52.6), and excessive sexual drive (F52.7).

The *DSM-IV* defines sexual dysfunction as a “disturbance in sexual desire and in the psychophysiologic changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty.” The described disorders include hypoactive sexual desire (302.71), sexual aversion (302.79), female arousal disorder (302.72), dyspareunia (302.76), vaginismus (306.51), and female orgasmic disorder (302.73).

An interdisciplinary consensus, known as the International Consensus Development Conference on Female Sexual Dysfunction: Definitions and Classification, was convened to address the shortcomings and problems associated with the *DSM-IV* and *ICD-10* classifications of sexual dysfunction. The panel consisted of representatives from a wide range of disciplinary backgrounds—endocrinology, family medicine, gynecology, pharmacology, psychiatry, psychology, physiology, urology, and rehabilitative medicine. The panel preserved the general structure of the *DSM-IV* and *International Classification of Diseases, Ninth Revision* (*ICD-9*) classifications and expanded/altered the traditional definitions of sexual disorders. A new category of sexual pain disorder was added to include noncoital sexual pain disorder. Diagnosis of these disorders requires the component of “personal distress”. The diagnoses were also subtyped as (a) lifelong versus acquired, (b) generalized versus situational, and (c) for etiology—organic, psychogenic, mixed, or unknown (Table 42.5).

Desire Disorders
Hypoactive sexual desire
Sexual aversion disorder
Arousal disorder
Orgasmic disorder
Pain disorders
Dyspareunia
Vaginismus
Noncoital pain
Subtypes
A. Lifelong vs. acquired
B. Generalized vs. situational
C. Etiology: organic, psychogenic, mixed, unknown

TABLE 42.5. *Classification of sexual dysfunction*

Desire Disorders Hypoactive sexual desire is the persistent or recurrent deficiency/absence of sexual fantasies/thoughts or desire for/receptivity to sexual activity which causes personal distress. Hypoactive sexual desire is the most commonly encountered dysfunction, seen in approximately 40% of patients in sexual counseling. Sexual desire is affected by many conditions such as medication use, life stages with accompanying hormonal changes, medical conditions, and interpersonal issues. Individuals with hypoactive sexual desire will also frequently exhibit difficulty with arousal and achieving orgasm. While obtaining a history, the physician should ask the patient how often she has felt sexual desire or interest, and inquire what she would rate her level of sexual interest on a scale from 1 to 5. The average population reports sexual desire approximately 3.4 times per month and a desire level of 3.5, as based on the FSFI control group. Hypoactive sexual desire is common in the female partners of men suffering from erectile dysfunction, and it is important to inquire regarding the partner's sexual functioning. Inquire regarding the presence of depression in the patient or partner, as decreased libido disproportionately affects patients with depression. In patients with major depression being evaluated for sexual dysfunction prior to the initiation of antidepressant therapy, only 50% of women and 75% of men reported sexual activity during the preceding month. Over 40% of men and 50% of women report decreased sexual interest. Reduced levels of arousal were more common in both depressed men and women (40% to 50%) than ejaculatory or orgasm difficulties. On physical exam the estrogen status of the external genitalia can carefully be evaluated by assessing the presence or absence of vaginal rugae, fissures, or friable tissue. Characteristics of skin elasticity, pubic hair, labial fullness, and evaluation of the introital and vaginal depth offer a further assessment of estrogen status. An extreme form of hypoactive sexual desire is sexual aversion disorder, which is the persistent or recurrent phobic aversion to and avoidance of sexual contact with a partner that causes personal distress. The etiology of sexual aversion disorder is often related to a history of traumatic sexual assault, such as a rape or child abuse.

Arousal Disorders Sexual arousal disorder is the persistent or recurrent inability to attain or maintain sufficient sexual excitement causing personal distress which may be expressed as a lack of subjective excitement or genital (lubrication, swelling) or other somatic responses. Arousal difficulties may be physiologic or psychological. Insufficient foreplay, emotional distraction, lack of vaginal lubrication, decreased clitoral or labial sensation or engorgement, lack of vaginal smooth muscle relaxation, pelvic trauma, medication use, and postsurgical changes may all contribute to diminished sexual arousal. Arousal disorder can be elucidated by inquiring how often the patient felt sexually aroused over the preceding 4 weeks, how she would rate her sexual arousal on a scale from 0 to 5, and how satisfied she is with her level of arousal during sexual intercourse. The physician should ascertain how often the patient was able to become lubricated during sexual activity (0 = never to 5 = always), and how difficult it was to maintain lubrication (0 = very difficult to 5 = not difficult). Most women without sexual difficulty will report an average score of approximately 4 on these questions. On physical exam, careful attention should be paid to the estrogen status of the external genitalia and the degree of vulvar sensation and muscle tone.

Orgasmic Disorders Orgasmic disorder is the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient stimulation and arousal, which causes personal distress. Fifty percent of women report intermittent or situational difficulties in achieving orgasm and nearly 10% of sexually active women are incapable of attaining orgasm. There appears to be both physical and psychological components; as compared to orgasmic women, anorgasmic women report (a) greater discomfort in communicating with a partner regarding sexual activities involving direct clitoral stimulation, (b) more negative attitudes toward masturbation, (c) greater endorsement of sex myths, and (d) greater sexual guilt. Orgasmic disorders may be primary (never experiencing an orgasm) or secondary. The physician should inquire as to how often the patient was able to attain orgasm during the preceding 4 weeks (0 = never to 5 = always), and how difficult it was to achieve orgasm (0 = impossible to 5 = not difficult). Women without sexual difficulty report a score assessment of approximately 4 for each question. Inquire as to the ability of the patient's partner to maintain an erection, or if there is difficulty with premature ejaculation. Assess if there is a history of alcohol or drug abuse, and what prescription medications the patient is taking. On physical exam specifically evaluate muscle tone and review clitoral anatomy with the patient.

Pain Disorders Sexual pain disorders encompass dyspareunia, vaginismus, and nonsexual pain categories. Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse, and may result from genital stimulation, attempted entry, deep thrusting, or occur immediately after intercourse. Endometriosis, vestibulitis, hypoestrogenism, ovaries adherent in the cul-de-sac, and pelvic or urinary infections may be etiologic factors. Often women with chronic pelvic pain that were scheduled for laparoscopy are evaluated for interstitial cystitis by cystoscopy with hydrodistention and biopsy. Interstitial cystitis is diagnosed in approximately one third of women with a combination of urgency, frequency or nocturia, and positive cystoscopic findings. If sensation is impaired, neurologic referral may be indicated as disorders such as multiple sclerosis, spinal cord, or peripheral nerve injury may lead to sexual dysfunction. There is also a psychological component associated with these disorders as the anticipation of pain leads to decreased arousal and subsequent lack of desire. Vaginismus, the recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, is another sexual pain disorder leading to personal distress. The diagnosis of vaginismus however, does not require the presence of pain. Spasm of the pubococcygeus and levator ani muscle render vaginal penetration difficult, if not impossible. Frequently, this disorder is situational in that the patient may tolerate speculum or digital exams, but is unable to tolerate vaginal penetration during intercourse. This may be the function of either a psychological component or a conditioned response to painful stimuli. The final subgroup under the pain disorders is noncoital pain which includes such diagnoses as noncoital sexual pain that is recurrent or persistent genital pain induced by nonpenetrating sexual stimuli. To determine the degree of pain being experienced, the physician should inquire as to how often the patient has pain with and immediately following intercourse (1 = always to 5 = never). Most women on the FSFI report an average score of 4.6. Inquire if the pain is noted with entry or deep penetration, and if it varies with position. Ask if the patient experiences difficulty with lubrication or experiences discomfort with tampon insertion? Determine if the pain is localized specifically to the introitus or more pronounced during micturation? In addition to the general pelvic exam, the anterior vaginal wall should be carefully palpated to examine for the presence of a urethral diverticulum. The pathognomonic finding is a tender cystic swelling on the anterior vaginal wall. Patients in whom urethral diverticulum is strongly suspected may undergo voiding cytourethrography, followed by possible positive pressure urethrography, ultrasound, or MRI. Determine if the pain is superficial, deep, or vaginal, and attempt to reproduce the pain. Look for evidence of a poorly healed episiotomy scar or evidence of friable tissue at the vaginal cuff in a hysterectomy patient. A prolapsed fallopian tube into the cuff often results in significant dyspareunia. A biopsy and pathologic analysis of the tissue would be diagnostic. Aggressively seek the diagnosis of an underlying etiology, even if laparoscopy is required. Davis and Telinde state that “the most important single diagnostic instrument for the discovery of a suburethral diverticulum is a high index of clinical suspicion.”

ETIOLOGY OF SEXUAL DYSFUNCTION

The interplay of vasogenic, musculogenic, neurogenic, hormonal, and psychogenic factors influences the female sexual response, and a disruption in any of these components may cause sexual dysfunction.

Neurogenic sexual dysfunction may result from spinal cord trauma or disease. In a complete transection of the spinal cord, no afferent impulses from the genitals can occur, however sexual fantasy and erotica have induced orgasm in some patients. Complete upper motor neuron injuries preclude vaginal lubrication, however women with incomplete injuries still maintain lubricating ability. Peripheral nervous system disease such as diabetes may impact nerve endings in the external genitalia precluding adequate arousal and the ability to achieve orgasm.

Hormonal alterations have a significant impact upon sexual functioning. Surgical or medical menopause, premature ovarian failure, hormonal contraceptive use, hypothalamic–pituitary–axis dysfunction, and postpartum states may induce marked hormonal fluctuations and result in vaginal dryness, altered arousal, and decreased desire. Hypoestrogenism, from any cause, results in atrophy of the vaginal epithelium and a decrease in genital vasocongestion and lubrication. Administration of both androgen and estrogen to medically or surgically menopausal women has been shown to restore sexual desire; however estrogen treatment alone has not been shown to be successful. The role of exogenous androgens is still debated, as several studies have rendered somewhat mixed results. With natural menopause, androgen levels have been positively correlated with sexual interest, and there is a small but positive correlation between midcycle testosterone levels and intercourse frequency. These results are contrary to the lack of difference in testosterone levels between women with and without clinically diagnosed hypoactive sexual desire, and from studies that show oral contraceptives and androgen antagonists do not consistently suppress libido. There is a subset of women with hypoactive sexual desire in which testosterone treatment appears to be useful. Elevated levels of prolactin appear to suppress libido in women, and restoration of libido is noted with dopamine agonist therapy.

Vascular-mediated effects are noted on sexual arousal in patients with high blood pressure, smoking, elevated cholesterol, and cardiac disease. Aortoiliac or atherosclerotic disease diminish pelvic blood flow and may reduce lubrication and clitoral engorgement. Cardiovascular disease may interfere with intercourse secondary to dyspnea. Traumatic injury to the arterial bed from fractures, surgical disruption, blunt trauma, or chronic perineal pressure from bicycle riding can result in diminished blood flow and subsequently sexual dysfunction.

Impairments in pelvic floor musculature contribute to sexual dysfunction. When the levator ani muscles are hypertonic, vaginismus may result leading to dyspareunia and other sexual pain disorders. If hypotonic, urinary incontinence or anorgasmia can result. A poorly healed episiotomy site or vaginal delivery of a macrosomic infant may contribute to muscular dysfunction.

The psychogenic component of sexual response is a critical one. Body image, self-esteem, and relational issues impact sexual arousal, as does emotional conflict such as anxiety, fear, anger, or guilt. An existing mood disorder is further compounded by the effects of psychotropic medications, which tend to inhibit sexual functioning in up to 75% of patients. SSRIs have been associated with decreased arousal, decreased genital sensation, and anorgasmia. Tranquilizers such as diazepam inhibit sexual function secondary to antidopaminergic action. Previous unresolved negative experiences such as sexual assault or domestic abuse will impact desire and arousal, and may manifest as a sexual aversion disorder or vaginismus.

TREATMENT

A multidisciplinary approach is imperative in thorough evaluation and treatment of sexual dysfunction. Psychiatric consultation is necessary for patients with a suspected assault history or evidence of depressive symptomatology. Urologic referral, particularly in patients with pelvic pain may reveal the presence of interstitial cystitis or a urethral disorder such as a urethral diverticulum. After arriving at a working diagnosis, diagnosis-specific treatment is most efficacious.

Desire Disorders

Pharmacologic Treatment

Hormone Replacement Therapy Indicated for use in postmenopausal women, estrogen replacement therapy results in improved clitoral sensitivity, increased libido, and decreased pain during sexual intercourse. Estrogen creams or the vaginal estradiol ring (Estring) may reduce complaints of vaginal irritation, pain, or dryness secondary to atrophy. Long-term use of estrogen vaginal creams is considered an unopposed estrogen treatment in women with an intact uterus and requires progesterone opposition. An oral progesterone, such as medroxyprogesterone 5 mg daily for 10 days a month (or equivalent), may be used initially, with frequency or dose adjustment if breakthrough bleeding occurs. The estradiol ring has little systemic absorption and does not require the addition of progesterone. Patients who are uncomfortable wearing the ring during the day often achieve relief with night use only.

Testosterone Testosterone replacement therapy has been prescribed for menopausal woman with symptoms of inhibited sexual desire, dyspareunia, and decreased lubricating ability. In women in whom menopause had been surgically induced, supraphysiologic doses of testosterone enanthate given by injection alone or in conjunction with estrogen increase arousal, desire, sexual activity, orgasm frequency, and fantasies more than estrogen alone. Transdermal testosterone (300 µg) given to women following hysterectomy and oophorectomy results in increased sexual frequency and orgasm despite an appreciable placebo response. The percentage of women with sexual fantasies, masturbation, or coitus at least once per week increases two to three times above baseline. Transdermal testosterone has no significant effects on the serum concentration of high-density lipoprotein, total cholesterol, low-density lipoprotein, triglycerides, liver function tests, or fasting insulin/glucose levels. Serum free and bioavailable testosterone increase to normal values. Dihydrotestosterone and total testosterone increase to above normal with treatment. This is not a treatment approved by the Food and Drug Administration (FDA), and no treatment guidelines for testosterone replacement therapy exist. Many physicians are concerned about the lack of safety data on the role of testosterone in breast cancer and hepatic side effects; however hepatocellular damage or carcinoma is rare at prescribed dosages, and the development of breast cancer has not been reported clinically. Potential side effects of testosterone, which may occur in 5% to 35% of patients, include lipoprotein alterations, acne, hirsutism, clitoromegaly, and voice deepening. Before initiating testosterone treatment, physicians should discuss the potential and theoretic risks as well as the individual risk and benefit assessments with the patient. In general, patients with current or previous breast cancer, uncontrolled hyperlipidemia, liver disease, acne, or hirsutism should not receive testosterone therapy (Table 42.6).

TABLE 42.6. *Dosages for testosterone administration* [a]

Arousal Disorders

Pharmacologic Treatment

Sildenafil Citrate Sildenafil citrate (Viagra) is a selective inhibitor of phosphodiesterase-5 and therefore enhances and prolongs the cellular effects of the second messenger substrate cyclic guanosine monophosphate (cGMP), the specific substrate for this enzyme. The guanylyl cyclase/cGMP pathway is the signal transduction mechanism activated by nitric oxide (NO). NO is released by the endothelial cells and the postsynaptic parasympathetic cavernosa neurons in males and leads to a cascade of chemical reactions that ultimately relaxes smooth muscle, dilates arteries, and engorges the corpora cavernosa. Therefore, once the psychological and physical arousal set in motion these chemical events in the corpora cavernosa, sildenafil, when taken 1 hour prior to sexual activity, helps maintain erections in men. Research has also identified phosphodiesterase-5 in human clitoral tissue. In women, there is the potential that sildenafil may be useful in treating orgasm delay and anorgasmia by facilitating lubrication, clitoral perfusion and engorgement, and the swelling and engorgement of the female genitalia. The role of sildenafil in treating sexual dysfunction in women, however, remains to be determined. In women experiencing psychotropic medication-induced sexual dysfunction, there may be a role for sildenafil. There may be some improvement in sexual functioning in women who reported sexual dysfunction since initiating antidepressant or antipsychotic medication therapy. Further clinical studies evaluating the safety and efficacy of sildenafil for treatment of female sexual dysfunction are needed.

Nonpharmacologic Treatment The EROS-CTD (Clitoral Therapy Device, Urometrics, Inc. St Paul, MN) is the first FDA-approved therapy for female sexual dysfunction. This small, battery-powered vacuum device is designed to enhance clitoral enlargement, increase blood flow to the clitoris, and improve sexual arousal. Women with sexual arousal disorder noted improvement in all symptoms of female sexual arousal disorder, and patients without such disorder also report similar changes in sensation, lubrication, ability to orgasm, and overall satisfaction.

Orgasmic Disorders

Anorgasmia treatment relies on maximizing stimulation and minimizing inhibition. Stimulation may include masturbation with prolonged stimulation (initially up to 1 hour) with the use of a vibrator as needed. Surveys of young women reveal that the most effective techniques for triggering orgasm are manual and oral stimulation of the clitoris, and that joining the male's thrusting pattern without additional clitoral stimulation was one of the least effective methods. Muscular control of sexual tension such as alternating contraction and relaxation of the pelvic musculature during high sexual arousal has proven helpful. The volitional muscle control is similar to Kegel exercises (Table 42.7). Methods to minimize inhibition include distraction by fantasy or listening to music. Past failure to achieve orgasm can elicit self-defeating and distracting thoughts about whether the patient will be able to achieve orgasm. The patient mentally monitors her own and her partner's physical response, unable to relax and enjoy the sexual stimulation for its own sake. Such behavior makes the patient more a spectator than a participant in her own sexual pleasure. Masters and Johnson coined the term “spectatoring,” which they describe as a major deterrent to effective sexual functioning. Kaplan suggests this obsessive self-observation

arising out of fear of failure to be the single most immediate cause of female orgasmic dysfunction.

Teaching Kegel exercises
Instructional examination with examiner's finger in vagina
Initial patient home exercise with the patient's finger in the vagina
Slow count to 10, with movement directed "in and up"
Hold for count of 3
Slow release to count of 10
Repeat 10–15 times daily
Consider vaginal weights, biofeedback clinics
Maintaining Kegel exercises
Advise repetitions during routine activities (standing in line, at stop lights, etc.)
Schedule follow-up appointments to discuss progress

TABLE 42.7. *Kegel exercises*

Masters and Johnson's approach to anorgasmia used a temporary ban on orgasm and sexual intercourse until permitted by their sensate focus program. Their exercises focused on “non-demand pleasuring” and attempted to improve sexual skills while avoiding goal-oriented behavior. Their program also included assertiveness training, modeling, behavioral reversal, and education. Although widely accepted among sex therapists, their “success” rates of 80% could not be reproduced by other therapists. Group therapy and erotic fantasy have also been proposed.

Pain Disorders

Vestibulitis Several treatment modalities have been employed in the treatment of pain disorders. The most common type of premenopausal dyspareunia is vulvar vestibulitis. The most commonly used treatments are cognitive-behavioral therapy, biofeedback, and vestibulectomy. Typical cognitive–behavioral interventions aim at reducing pain and improving sexual functioning and include Kegel exercises, vaginal dilation, and relaxation techniques. Surface electromyographic biofeedback has been applied to dyspareunia. Vestibulectomy, in which the painful tissue of the vulvar vestibule is excised, has variable success rates, ranging from 43% to 100%.
Vaginismus Treatment of vaginismus consists of smooth muscle relaxation and vaginal dilation. Muscle relaxation can be taught during an exam by having the patient isolate and alternatively contract and relax the pelvic musculature around the examiner's finger. Commercial dilators or tampons of increasing diameter may be placed in the vagina for 15 minutes twice daily to facilitate muscle relaxation and dilation (Fig. 42.4).

FIG. 42.4. Vaginal dilators. (Photograph provided by Milex Products Inc.)

Interstitial Cystitis Mild symptoms of interstitial cystitis may respond to dietary modifications, stress reduction, biofeedback, and bladder retraining. Avoiding acidic, alcoholic, or carbonated beverages or spicy foods and artificial sweeteners have been reported by some patients to reduce their interstitial cystitis pain. The only oral medication currently FDA-approved to treat interstitial cystitis is pentosan polysulfate sodium (Elmiron), and other medications such as tricyclic antidepressants that have analgesic properties, antiinflammatory drugs, antihistamines, antispasmodics, and muscle relaxants may offer relief. More invasive treatments include hydrodistention of the bladder done at time of cystoscopy, bladder instillation with dimethyl sulfoxide (DSMO), or an implantable sacral nerve stimulator. Surgical procedures such as bladder augmentation or urinary diversion are used as a last resort.

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Appendix A—Female Sexual Function Index (FSFI) [a]

Questions

Q1: Over the past 4 weeks, how *often* did you feel sexual desire or interest?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

Q2: Over the past 4 weeks, how would you rate your *level* (degree) of sexual desire or interest?

5 = Very high

4 = High

3 = Moderate

2 = Low

1 = Very low or none at all

0 = No sexual activity

Q3: Over the past 4 weeks, how *often* did you feel sexually aroused (“turned on”) during sexual activity or intercourse?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

0 = No sexual activity

Q4: Over the past 4 weeks, how would you rate your *level* of sexual arousal (“turn on”) during sexual activity or intercourse?

5 = Very high

4 = High

3 = Moderate

2 = Low

1 = Very low or none at all

0 = No sexual activity

Q5: Over the past 4 weeks, how *confident* were you about becoming sexually aroused during sexual activity or intercourse?

5 = Very high confidence

4 = High confidence

3 = Moderate confidence

2 = Low confidence

1 = Very low or no confidence

0 = No sexual activity

Q6: Over the past 4 weeks, how *often* have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

0 = No sexual activity

Q7: Over the past 4 weeks, how *often* did you become lubricated ("wet") during sexual activity or intercourse?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

0 = No sexual activity

Q8: Over the past 4 weeks, how *difficult* was it to become lubricated ("wet") during sexual activity or intercourse?

0 = No sexual activity

1 = Extremely difficult or impossible

2 = Very difficult

3 = Difficult

4 = Slightly difficult

5 = Not difficult

Q9: Over the past 4 weeks, how often did you *maintain* your lubrication ("wetness") until completion of sexual activity or intercourse?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

0 = No sexual activity

Q10: Over the past 4 weeks, how *difficult* was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

0 = No sexual activity

1 = Extremely difficult or impossible

2 = Very difficult

3 = Difficult

4 = Slightly difficult

5 = Not difficult

Q11: Over the past 4 weeks, when you had sexual stimulation or intercourse, how *often* did you reach orgasm (climax)?

5 = Almost always or always

4 = Most times (more than half the time)

3 = Sometimes (about half the time)

2 = A few times (less than half the time)

1 = Almost never or never

0 = No sexual activity

Q12: Over the past 4 weeks, when you had sexual stimulation or intercourse, how *difficult* was it for you to reach orgasm (climax)?

0 = No sexual activity

1 = Extremely difficult or impossible

2 = Very difficult

3 = Difficult

4 = Slightly difficult

5 = Not difficult

Q13: Over the past 4 weeks, how *satisfied* were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

5 = Very satisfied

4 = Moderately satisfied

3 = About equally satisfied and dissatisfied

2 = Moderately dissatisfied

1= Very dissatisfied

0 = No sexual activity

Q14: Over the past 4 weeks, how *satisfied* have you been with the amount of emotional closeness during sexual activity between you and your partner?

5 = Very satisfied

4 = Moderately satisfied

3 = About equally satisfied and dissatisfied

2 = Moderately dissatisfied

1= Very dissatisfied

0 = No sexual activity

Q15: Over the past 4 weeks, how *satisfied* have you been with your sexual relationship with your partner?

5 = Very satisfied

4 = Moderately satisfied

3 = About equally satisfied and dissatisfied

2 = Moderately dissatisfied

1= Very dissatisfied

Q16: Over the past 4 weeks, how *satisfied* have you been with your overall sexual life?

5 = Very satisfied

4 = Moderately satisfied

3 = About equally satisfied and dissatisfied

2 = Moderately dissatisfied

1= Very dissatisfied

Q17: Over the past 4 weeks, how *often* did you experience discomfort or pain during vaginal penetration?

0 = Did not attempt intercourse

1 = Almost always or always

2 = Most times (more than half the time)

3 = Sometimes (about half the time)

4 = A few times (less than half the time)

5 = Almost never or never

Q18: Over the past 4 weeks, how *often* did you experience discomfort or pain following vaginal penetration?

0 = Did not attempt intercourse

1 = Almost always or always

2 = Most times (more than half the time)

3 = Sometimes (about half the time)

4 = A few times (less than half the time)

5 = Almost never or never

Q19: Over the past 4 weeks, how would you rate your *level* (degree) of discomfort or pain during or following vaginal penetration?

0 = Did not attempt intercourse

1 = Very high

2 = High

3 = Moderate

4 = Low

5 = Very low or none at all

Scoring System

The individual domain scores and full scale score of the FSFI are derived by the computational formula outlined in the table below. Individual domain scores are obtained by adding the scores of the individual items that comprise the domain and multiplying the sum by the domain factor (see below).

The full scale score is obtained by adding the six domain scores. It should be noted that within the individual domains, a domain score of zero indicates that no sexual activity was reported during the past month.

Domain	Questions	Range	Factor	Min Score	Max Score
Desire	1,2	1–5	0.6	1.2	6.0
Arousal	3,4,5,6	0–5	0.3	0	6.0
Lubrication	7,8,9,10	0–5	0.3	0	6.0
Orgasm	11,12,13	0–5	0.4	0	6.0
Satisfaction	14,15,16	0 (or 1)–5	0.4	0	6.0
Pain	17,18,19	0–5	0.4	0	6.0

Footnote

[a]For the complete FSFI questionnaire, instructions, and scoring algorithm, please go to http://www.fsfiquestionnaire.com/, or contact Raymond Rosen, Ph.D., Department of Psychiatry, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854.

Chapter 43

Howard T. Sharp

Chronic Pelvic Pain

GLOSSARY
CONTEMPORARY PAIN THEORIES
PUTATIVE PELVIC PAIN STATES
- Adhesions
- Endometriosis
- Pelvic Inflammatory Disease
- Myofascial Pain
- Pelvic Congestion
- Irritable Bowel Syndrome
- Ovarian Remnant Syndrome
- Residual Ovary Syndrome
- Pain of Uterine Origin

PSYCHOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN
PATIENT HISTORY
PHYSICAL EXAMINATION
PAIN MANAGEMENT
NSAIDs
- Neurolytic Agents
- Narcotics
- Narcotic Agreements

SUMMARY POINTS

SUGGESTED READINGS
- Glossary and Contemporary Pain Theories
- Putative Pain States
- Endometriosis
- Pelvic Inflammatory Disease and Myofascial Pain
- Pelvic Congestion Syndrome

OVARIAN REMNANT SYNDROME
- Pain of Uterine Origin

Science has produced many drugs, therapies, and surgeries in attempts to relieve the suffering associated with chronic pelvic pain (CPP). Unfortunately, only modest success has been achieved. This likely is due, in part, to the heterogeneity that exists in this ill-defined population of patients, as well as our limited understanding of pain modulation. Often, when standard therapies fail, or when no visible pathology can be identified, other specialties such as gastroenterology, urology, neurology, or psychiatry are consulted. Patients eventually may be referred to centers specializing in CPP or empiric pain management, wherein neurolytic or opioid therapy may be commenced without finding a specific cause for pain.

Along the course of therapy and referral, frustration is often a byproduct of treating a supposedly remediable pain state only to have pain persist. Furthermore, a confusing aspect of CPP is that its definition implies that no etiology can be found; however, most textbooks list several causes for CPP (adhesions, endometriosis, pelvic inflammatory disease [PID], etc.). Therefore, the clinical challenge is to decipher which of the following is most likely:

1. A defined pain state exists but has been improperly diagnosed and treated.
2. A defined pain state exists, has been correctly identified, but happens to be present in an incidental form.
3. A neuropathic pain processing state is present.

GLOSSARY

Allodynia: pain due to a stimulus which does not normally provoke pain.
Central pain: pain initiated or caused by a primary lesion of dysfunction in the central nervous system.
CPP: nonmenstrual pain of 6 months' duration or greater, localized to the pelvis, anterior abdominal wall below the pelvis, or lower back, severe enough to result in functional disability or require medical or surgical treatment.
Dysesthesia: an unpleasant abnormal sensation, whether spontaneous or evoked.
Endometriosis: the existence of two or more of the following outside of the endometrium: (a) endometrial epithelium, (b) endometrial stroma, (c) endometrial glands, (d) hemosiderin-laden macrophages.
Hyperalgesia: an increased response to a stimulus which is normally painful.
Myofascial pain syndrome: a heterogeneous pain-producing disorder characterized by localized, reproducible, hyperirritable trigger points within a muscle or its investing fascia.
Neuropathic pain: pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system.
Neuralgia: pain in the distribution of a nerve or nerves.
Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage.

CONTEMPORARY PAIN THEORIES

Until the 1960s, pain was considered a sensory response to tissue damage. It is now widely accepted that pain has a reactive or emotional as well as sensory component, which is influenced by genetic differences, experiences, gender, anxiety, or expectation. The perception of and response to pain are believed to be determined by four simultaneous processes which include: transduction (depolarization of a peripheral sensory nerve ending to generate an impulse), transmission (neural events to carry the impulse), modulation (neural events that control transmission neurons), and perception (event processing influenced by behavioral and emotional factors).

The theory most widely accepted to explain the mechanism whereby pain transmission occurs was described by Melzak and Wall as the gate-control theory. This theory suggests that the modulation of nociception at the spinal cord is mediated by descending signals for high centers within the brain through neurotransmitters. It describes a bidirectional gate at the level of the spinal cord, rather than merely unidirectional pain transmission as previously held by the Cartesian theory.

PUTATIVE PELVIC PAIN STATES

Adhesions

Pelvic inflammatory disease, endometriosis, inflammatory bowel disease, or surgery may cause adhesions; yet, in up to 50% of cases there may be no significant antecedent event. Although adhesions commonly are found in patients with CPP, it may be difficult to assess whether they are contributing to pelvic pain or are merely incidental findings.

Several studies have raised questions about the surgical treatment of adhesions. First, in a prospective study which involved second-look laparoscopy following laparotomy for reproductive surgery, 51% of patients developed de novo adhesions. Therefore, the possibility exists that treating adhesions may lead to more adhesions. Secondly, there is evidence to suggest that the lysis of adhesions may not result in significant pain relief. A randomized, prospective study of patients with CPP and known stage II to IV (moderate to severe) pelvic adhesions assessed the efficacy of surgical adhesiolysis on patients with CPP. Patients either underwent minilaparotomy adhesiolysis or no treatment. At 9- to 12-month follow-up, using the McGill Pain Scale to compare outcomes, there was no difference in the treatment group (n = 24) compared with controls (n = 24). After stratification, the authors acknowledged a trend toward a benefit in patients with well-vascularized or thick adhesions involving the intestinal tract, the pain hypothesis being symptoms of intermittent small bowel subileus. This small study lacks the power to answer definitively

the question as to whether treatment of adhesions is beneficial.

In a case-control study of 100 consecutive laparoscopies in patients with CPP and 88 laparoscopies for infertility, pelvic adhesions were found more often in the control group (26% versus 39%). Trimbos and others studied 200 asymptomatic women undergoing laparoscopic sterilization and found a 14% incidence of pelvic adhesions. In a prospective cohort study of 102 women undergoing laparoscopy, wherein the surgeons were blinded as to the indications, which were pain (64%), infertility (35%), previous abnormal findings (19%), and sterilization (15%), adhesion scores were no different in the CPP group compared with controls.

In an uncontrolled, prospective study of 30 women undergoing laparoscopic adhesiolysis for CPP with a mean follow-up interval of 8.2 months, there was an overall improvement of pain in 63%. There was a trend toward greater improvement in the group with CPP, compared with the group exhibiting CPP syndrome. CPP syndrome was defined as having at least four of the following (a) pain longer than 6 months' duration, (b) previous treatments unsuccessful in relieving pain, (c) diminished physical activity (work, exercise, sex), (d) at least one vegetative sign of depression (sleep dysfunction, decreased appetite, psychomotor retardation), (e) altered family role.

Laparoscopic pain mapping under conscious sedation provides additional information to better define whether a patient's adhesions are associated with pain. This technique employs local anesthesia at trocar sites in combination with intravenous opioids and benzodiazepines to enable the conscious patient to tolerate laparoscopic surgery. Pelvic structures can be mapped using a verbal analog pain scale (VAPS) from 0 to 10 to determine whether pain can be generalized to the pelvic viscera or to a focal point or adhesion. It is important to distinguish between surgically induced pain and pain which truly mimics the patient's chronic pain.

Taking these studies into consideration we can learn some valuable lessons. (a) The more surgery that is performed, the more likely adhesions are to occur. (b) Adhesions may be present in asymptomatic patients. (c) Adhesions may be incidental in symptomatic patients. (d) Although some case series have shown some benefit to adhesiolysis, the only randomized clinical trial of adhesiolysis in patients with CPP showed no treatment benefit. (e) Conscious sedation pain mapping surgery may better enable us to determine which adhesions are painful. (f) Judgment is critical as to whether or not to perform surgery in patients who have had multiple laparoscopic procedures, weighing the risks and benefits.

Endometriosis

Endometriosis is one of the most enigmatic of gynecologic disorders. Not only is there little correlation between the extent of disease and the degree of pain, but it often is found in asymptomatic women. The noted exception is deep, infiltrating endometriosis in the rectovaginal septum, which has been shown to have a direct correlation to pain.

Endometriosis may have several appearances, ranging from the more typical “powder burn,” blue-gray lesions, to atypical lesions which may be clear, red, or white. Various explanations have been proposed to account for endometriosis-related pain including inflammation, prostaglandin production, neuronal involvement, and adhesions. Data from conscious sedation laparoscopic pain mapping have demonstrated areas of pain well beyond the visible endometriosis.

Symptoms associated with endometriosis include cyclic pelvic pain or dysmenorrhea. The pain associated with endometriosis may precede the menses, occur with menses, and continue after menses. Tenesmus may be associated with involvement of the rectosigmoid colon. Other clinical manifestations may include dyspareunia or ovarian mass (endometrioma).

Conservative medical treatment is recommended as the initial therapy for endometriosis or presumed endometriosis. This may include nonsteroidal antiinflammatory drugs (NSAIDs), oral contraceptive pills (OCPs), danazol, progestins, or gonadotropin-releasing hormone (GnRH) agonists. These medications have been shown to reduce the size of endometriotic lesions and, thus, the stage; however, they have not been shown to eliminate disease. There are no convincing data to suggest that one form of medical suppressive therapy is superior to another. Usually, the agent with the lowest side effect profile, such as an NSAID or OCP, is selected as first-line therapy.

Oral contraceptive pills may be used in a cyclic (standard) or continuous fashion. Continuous use refers to the ingestion of active pills every day for 3 to 6 months, rather than allowing menses to occur during placebo administration. This usually allows the patient to avoid the dysmenorrhea which may occur with the cyclic regimen. If OCPs are not effective after 3 months, danazol (600–800 mg/d) or GnRH agonists may be used.

The use of danazol for endometriosis-associated pain was evaluated by Cochrane Database reviewers, wherein four trials were found to have study design adequate for inclusion. The reviewers concluded that danazol is effective in treating the symptoms and signs of endometriosis; however, its use is limited by the occurrence of androgenic side effects. GnRH agonists such as leuprolide or goserelin generally are used for 6 months if a favorable response is noted. The main concern about prolonged use of these agents is the loss of bone mineral density. The treatment window may be extended to 12 months with the use of add-back therapy (addition of norethindrone acetate with or without conjugated equine estrogens).

Surgery generally is reserved for refractory cases. If surgery is to be performed, it should be tailored toward the patient's reproductive wishes. If the patient desires to preserve her childbearing capacity, endometriotic lesions may be destroyed or removed by vaporization or excision laparoscopically or by laparotomy. It is argued by some that vaporization may treat only the “tip of the iceberg,” with the potential to leave deep, infiltrating endometriosis behind. To date, there are no convincing data to recommend one laparoscopic therapy over the other. Unfortunately, a significant number of patients treated conservatively (without hysterectomy and bilateral salpingo-oophorectomy) will develop recurrent symptoms 12 months after surgery.

Laparoscopic surgery for the treatment of endometriosis-associated pain was reviewed in the Cochrane Database. Only one study was deemed adequate for evaluation; therefore, most of our understanding stems from level 3 data (case series and opinions of experts). The review concluded that laparoscopic laser treatment of endometriosis was more effective than expectant treatment of endometriosis, but the reviewers included a caution about the interpretation of results due to the lack of any corroborating studies.

Hysterectomy with or without adnexectomy may be appropriate in cases in which childbearing is no longer an issue.

Pelvic Inflammatory Disease

PID is a significant health problem (approximately 1 million cases per year), resulting in an expense of $3.5 billion annually in the United States alone. It clearly can be a cause of acute pain, yet it also may be asymptomatic. The most likely mechanism for pain is from inflammation and distension of the fallopian tubes. A distended, fluid-filled fallopian tube or hydrosalpinx will sometimes persist for months or years and may cause CPP. It is less clear why pain persists in patients with treated PID, who subsequently have normal-appearing reproductive organs and whose culture results are negative for causative microorganisms. It is theorized that the initial inflammatory insult may have started a cascade of signals within the pelvis, spinal cord, and brain, resulting in visceral neuropathic pain.

One study estimated that as many as 15% to 25% of patients with PID will go on to have CPP (relative risk = 3.0–5.0). There are no good studies addressing how to treat patients with laparoscopy-negative, culture-negative presumed persistent PID. They, therefore, often are treated with NSAIDs, neurolytic agents, or opioids. The patient's partner should be treated, also, to avoid reinfection. Persistent hydrosalpinx usually is treated surgically by salpingectomy.

Myofascial Pain

Myofascial pain is common in patients with a history of abdominal trauma or multiple surgeries and often is overlooked as a cause for CPP. Myofascial pain syndrome is a heterogeneous pain-producing disorder characterized by localized, reproducible, hyperirritable trigger points within a muscle or its investing fascia. The clinical sign of the trigger point is that it is tender when compressed, and has characteristic referred pain patterns, referred tenderness, motor dysfunction, or autonomic dysfunction.

Abdominal wall myofascial pain is detected best by isolating the rectus abdominus muscles, by having the patient flex her abdomen by lifting her feet or head and shoulders off the examination table while in the supine position. A one-finger search along the anterior abdominal wall is performed to identify painful trigger points. When localized, trigger points can be treated successfully with icing, stretching exercises, and with local anesthetic injection. One to two milliliters of a 50:50 mixture of 1% lidocaine and 0.25% bupivacaine may be injected into the muscle and fascia with a 22- or 25-gauge needle to achieve a diagnostic and therapeutic block. Slocumb reported on the successful treatment of 89% of 131 patients with CPP who had trigger point injections. Most patients obtained relief within five injections. Physical therapy also has been successful in treating myofascial pain syndrome.

Pelvic Congestion

Patients with pelvic congestion syndrome typically complain of pelvic pain and aching which becomes progressively worse throughout the day, and they also may complain of dyspareunia or postcoital aching. Pelvic congestion syndrome as a cause for CPP has been a controversial entity since it was first described by Taylor in 1949. One reason for skepticism is the observation that some women who demonstrate dilated vessels at the time of surgery or during pregnancy are asymptomatic.

Beard and co-workers proposed a more objective method of diagnosing pelvic varicosities using transcervical pelvic venography to measure vessel diameter, vessel tortuosity, and dye transit time, suggesting that vein diameter alone is not the only significant finding of pelvic congestion syndrome. Subsequent studies by these authors propose diagnostic criteria for pelvic congestion syndrome and pathophysiologic mechanisms for pain production. It has been postulated that pain from vascular congestion is caused by vasoactive nociceptive peptides, such as substance P and calcitonin gene-related peptide. In a study by Reginald and colleagues of patients with venographically diagnosed pelvic congestion syndrome injected with a potent vasoconstrictor (dihydroergotamine), a 35% reduction in vein diameter, decreased dye transit time, and up to 4 days of pain relief was demonstrated when compared with patients injected with placebo. They hypothesized that vasoconstriction allows clearance of nociceptive vasoactive peptides.

Conservative treatment of pelvic congestion includes medroxyprogesterone acetate in 30- to 50-mg daily doses. Ultimately, surgery may be necessary. In Beard's series of 36 patients treated with hysterectomy and bilateral salpingo-oophorectomy, 67% obtained complete relief of pelvic pain. Only 1 of the remaining 12 patients had significant pain.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder affecting approximately 15% of adults in the United States, yet only 25% of persons with questionnaire-detected IBS actually seek health care. It has been defined as lower abdominal pain, which is present for at least 12 weeks (not necessarily consecutive) out of the past year, that cannot be explained by structural or biochemical abnormalities. At least two of the following clinical features are needed for diagnosis: (a) pain relief with defecation, and onset associated with a change in (b) frequency or (c) consistency of stools.

Theories to explain a putative mechanism for IBS include visceral hyperalgesia, infection, an imbalance of neurotransmitters, and psychological factors. More recently, growing evidence suggests that these patients have a gastrointestinal sensory-reflex dysfunction as a common pathophysiologic mechanism, which may be manifested by different forms depending upon specific pathways involved. This may explain why some individuals are more pain prone, while others may be more prone to have diarrhea or constipation.

Rectal and sigmoid balloon distension studies have shown a lower threshold for pain, referred to as *visceral hypersensitivity*, in patients with IBS compared with controls. However, when balloon testing is performed, only 40% to 60% of patients with IBS report pain at levels of distension below the range of normal values; therefore, gut wall distension my not be the only stimulus to cause IBS.

Therapy for IBS involves treating symptoms, whether one is diarrhea prone or constipation prone. Diarrhea-prone patients respond to loperamide, hyoscyamine, and desipramine, whereas constipation-prone patients respond to fiber therapy or cisapride. Patients with a pain predominance may be treated with tricyclic antidepressants, NSAIDs, anticholinergic agents, calcium channel blockers and, in some cases, opioid analgesics. Newer agents are under development, such as visceral antinociceptive agents, ?-opioid agonists, and 5HT3 and 5HT4 receptor antagonists.

Patients who have rectal bleeding, persistent occult fecal blood, or failure of medical therapy should be referred to a gastroenterologist to rule out malignancy or inflammatory bowel disease.

Ovarian Remnant Syndrome

Ovarian remnant syndrome may result from incomplete removal of ovarian tissue at the time of oophorectomy and can be associated with CPP in premenopausal women. Patients with this syndrome usually have a history of extensive endometriosis or pelvic inflammatory processes, resulting in a technically difficult oophorectomy. Cyclic pelvic pain caused by ovarian remnant syndrome most commonly is associated with the development of ovarian follicles within hormonally active ovarian tissue. This diagnosis is suspected when serum levels of follicle-stimulating hormone and luteinizing hormone are normal. Hormone replacement therapy should be discontinued at least 10 days before assessing serum gonadotropin levels. Clomiphene citrate and GnRH agonists have been used to stimulate ovarian tissue, which assists in making an ultrasonographic diagnosis of ovarian remnant syndrome.

Surgical treatment usually requires extensive intraperitoneal adhesiolysis and retroperitoneal dissection to remove all ovarian tissue. In a series of eight patients treated surgically for ovarian remnant syndrome, three required large bowel resection, cystotomy was performed in three and a ureteroneocystostomy in one, and one required a small bowel resection. Outcome data regarding postoperative pain relief after surgical resection are limited to small case series, but cure rates as high as 90% are reported.

Residual Ovary Syndrome

Residual ovary syndrome originally was described by Grogen in 1958. It is characterized by the development of pain in one or both ovaries conserved at the time of hysterectomy, theoretically caused by perioophoritis with a thickened ovarian capsule. It has been postulated that pain is produced by the cyclic expansion of the ovary encased in adhesions.

The most common complaint in women with residual ovary syndrome is chronic lower abdominal pain, dyspareunia, and radiation of pain to the back or anterior thigh. A tender mass may be palpated on bimanual examination. This syndrome may occur in as many as 3% of women who have undergone hysterectomy with ovarian conservation. Treatment typically has been oophorectomy rather than lysis of adhesions, to avoid recurrent adhesion formation. Care should be taken to avoid ureteral damage, because retained ovaries often are near the ureter. Outcome data are limited regarding pain relief after surgery for retained ovaries (level 3 data). Postoperative pain relief has been reported in over 80% of patients after oophorectomy.

Pain of Uterine Origin

In the United States, approximately 18% of hysterectomies are performed for CPP, with endometriosis cited as the most common indication. Carlson and co-workers demonstrated significant reduction in pain following hysterectomy for CPP of all causes. In patients with pelvic pain who underwent hysterectomy, 85% complained of frequently occurring pain preoperatively, compared with 13% at 12 months postoperatively. In a prospective cohort study comparing surgical to nonsurgical treatment, 49% of medically managed patients with CPP had continued symptoms compared with 3% treated by hysterectomy. Moreover, 25% of patients in the nonsurgical group underwent hysterectomy within 1 year.

Stovall and others reported a 78% success rate in patients undergoing hysterectomy for pelvic pain of presumed uterine origin. In this retrospective study, patients were excluded for nonuterine pain such as endometriosis. A prospective multicenter cohort of 308 women undergoing hysterectomy for CPP reported resolution of pain in 74% and improvement in 21%. Risk factors for continued pain included age 30 or younger, history of pelvic inflammatory disease, and use of public assistance. These studies are helpful because they underscore the importance of investigating other, nongynecologic causes for CPP, and they provide guidelines for preoperative counseling.

Hysterectomy may be indicated in the absence of significant pathology, as long as a diagnostic laparoscopy has been performed, and the patient's pain has persisted for longer than 6 months with a serious negative impact on the quality of life. Prior to undergoing a hysterectomy the patient should be treated medically (oral contraceptives, NSAIDs, and induced amenorrhea) and should be evaluated for urinary, gastrointestinal, musculoskeletal, and psychological causes for pain. Possible causes of pain of uterine origin are listed in Table 43.1.

Adenomyosis
Chronic endometritis
Degenerating leiomyomata
Pelvic congestion

TABLE 43.1. *Possible causes of pain of uterine origin*

PSYCHOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

Patients sometimes get the message “your pain is all in your head.” Whether patients are actually told this or whether they hear this is irrelevant. This concept reflects what physicians were taught historically as the somatic model of pain, wherein there was a direct relationship between tissue damage and pain intensity. This model does not account adequately for the discrepancy between objective physical findings and the perception of pain severity. A more contemporary approach recognizes the central models of pain, which include the effect of peripheral nociception and central pathways that determine disability and distress.

The psychological aspects of CPP can be significant. It is, therefore, worthwhile to distinguish among co-morbid states such as depression, anxiety, and panic attacks. It often is helpful to obtain consultation from an interested psychiatric health care professional. However, some screening tests can be done by primary care physicians, such as the Beck Depression Inventory or Zung Depression Index.

Clinical depression associated with CPP usually is manifested by sleep disturbance (insomnia or hypersomnia), loss of interest in pleasurable activities, guilt feelings, loss of energy, diminished concentration, appetite changes (decreased or increased), psychomotor changes, and possible suicidal ideation. The mainstays of therapy include the use of serotonin reuptake inhibitors, tricyclic antidepressants, and psychotherapy. Clinicians who prescribe these medications should be aware of diagnostic criteria for depression and be familiar with the side effects and contraindications of these medications.

PATIENT HISTORY

A thorough patient history is one of the most helpful tools in the evaluation of patients with CPP. The COLDERR acronym may be used to gain a general understanding of the patient's history of present illness.

Character—What does the pain feel like? (sharp, dull, crampy)
Onset—Does the pain come on suddenly or gradually? Is it cyclic or constant?
Location—Is the pain localized or diffuse?
Duration—How long has the pain been present and how has it changed over time?
Exacerbation—What activities or movements make it worse?
Relief—What medication, activities, and positions make it better?
Radiation—Does the pain radiate anywhere (back, groin, flank)?

There are several important aspects of taking a detailed pain history and reviewing organ systems. Comprehensive history and physical examination forms are available through the International Pelvic Pain Society Web site and can be downloaded at http://www.pelvicpain.org/. Establishing whether the pain is cyclic or not is helpful is narrowing the list of possible causes (Table 43.2). If the patient has poor insight into the nature of her pain, a pain calendar may be used prospectively to chart her symptoms during the month.

Adenomyosis
Endometriosis
Irritable bowel syndrome
Mittelschmerz
Ovarian remnant syndrome
Pelvic congestion syndrome

[a] Not necessarily limited to being cyclic.

TABLE 43.2. *Cyclic causes for chronic pelvic pain* [a]

Reviewing past surgeries is helpful for gaining information about which organs can be eliminated from consideration and what effect surgery had on their pain. It may help establish a causal relationship between surgery and pain, which is common among patients with myofascial pain syndrome.

A thorough review of systems is important to exclude nongynecologic causes for CPP. Gastrointestinal complaints should be explored with specific questions about bowel frequency, consistency, associated pain, and to exclude a history of blood in the stool, which would alert the clinician to rule out neoplasm (Table 43.3). Likewise, urinary complaints such as dysuria, hematuria, nocturia, enuresis, and increased frequency should be probed for urologic causes of CPP (Table 43.4).

Cholecystitis
Chronic appendicitis
Constipation
Diverticulitis
Irritable bowel disease
Inflammatory bowel disease
Neoplasm
Pseudomembranous enterocolitis
Ulcer (duodenal, gastric)

TABLE 43.3. *Gastrointestinal causes for chronic pelvic pain*

Bacterial cystitis
Detrusor dyssynergia
Interstitial cystitis
Neoplasm
Urethral caruncle
Urethral diverticulum
Urethral syndrome
Urolithiasis

TABLE 43.4. *Urologic causes for chronic pelvic pain*

PHYSICAL EXAMINATION

Observing a patient's gait, body language, and facial expression can provide valuable information. Myofascial pain syndrome can result in or be a result of musculoskeletal dysfunction as seen with abnormalities in gait, body posture, leg lengths, or sacroiliac joint mobility. Such abnormalities warrant evaluation by a physiatrist or physical therapist.

A one-finger abdominal examination is performed on the anterior abdominal wall to detect trigger points, as described in the myofascial pain section. In addition, abdominal wall hernias may be diagnosed using this technique. Trigger points should be marked on the patient's skin with a soft pen tip and then mapped in the patient's chart for future comparison. Trigger points also may be found within the muscles of the back and buttocks.

A cotton-tipped applicator is useful in the examination of the vulvar vestibule to elicit painful areas or sites of vulvar vestibulitis. Special attention should be given to Bartholin ducts and Skene glands. On speculum examination, the vaginal fornices, or vaginal cuff in the posthysterectomy patient, can also be examined for tenderness using a cotton-tipped applicator. Any cervical discharge should be noted, examined by microscopy, and cultured. The posterior vaginal fornix should also be inspected visually to identify endometriosis. This sometimes is possible only with the aid of a tenaculum.

It is helpful to perform a “unimanual” examination prior to the bimanual examination to avoid “cross-contamination” from anterior abdominal wall pain signals. This consists of examining the vagina, cervix, and pelvic floor muscles with the hand in the vagina, without using the hand on the abdomen. The pelvic floor muscles should be examined individually to include the levator ani group, coccygeus, obturator internus, and the piriformis muscles. The uterus, tubes, and ovaries should be examined for localized pain. The pelvis should then be examined using the bimanual technique.

The rectovaginal examination is particularly useful to evaluate nodular or infiltrating endometriosis. If there is no tenderness in the cul-de-sac or along the uterosacral ligaments, yet endometriosis is strongly suspected, the patient should be reexamined during the menses.

PAIN MANAGEMENT

Pain management may include the use of NSAIDs, neurolytic agents, and narcotics. Knowledge of drug interactions, contraindications, and side effects are important aspects of successful pain management.

NSAIDs

NSAIDs are usually a safe category to start with, realizing there are several contraindications to these drugs, especially in patients with gastrointestinal disorders. The newer COX-2 (cyclooxygenase inhibitor-2) drugs have the advantage of fewer adverse effects on the gastrointestinal tract (Table 43.5).

Ibuprofen 400–800 mg qlth, maximum dosage = 2,400 mg/d
Naproxen sodium 250–500 mg qlth, maximum dosage = 1,500 mg/d
Mefenamic acid 500 mg initially, then 250 mg q6h
Rofecoxib 50 mg/d
Celecoxib 100–200 mg b.i.d.
Ketorolac 10 mg q6h, not to exceed 5 days
Tramadol 50–100 mg q6h

NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 43.5. *Oral NSAIDs*

Neurolytic Agents

Neurolytic agents encompass a number of drug categories used in the treatment of neuropathic pain, which include tricyclic antidepressants, serotonin reuptake inhibitors, and ion channel blockers. Table 43.6 lists some of these drugs which have been studied in patients with chronic pain.

Drug class	Drug dosage
Antidepressants	
Tricyclic	
Amitriptyline	65–100 mg/d
Imipramine	100–200 mg/d
Desipramine	100–200 mg/d
Selective Serotonin Reuptake Inhibitors	
Paroxetine	20–40 mg/d
Fluoxetine	20–60 mg/d
Citalopram	10–40 mg/d
Ion Channel Blockers	
Mexiletine	150–600 mg/d
Carbamazepine	200–1,000 mg/d
Phenytoin	300 mg/d
Lamotrigine	400 mg/d
Gabapentin	1,200–3,600 mg/d

TABLE 43.6. *Oral Neurolytic Agents*

Narcotics

Narcotics often are thought of as appropriate for acute pain only; however, in some instances under careful supervision, patients with chronic pain may be candidates for narcotic therapy (Table 43.7). When narcotics are used, narcotic contracts are often helpful. Patients who demonstrate drug abuse behavior are not candidates for narcotic therapy. A patient who repetitively loses her prescription, uses multiple physicians for obtaining narcotic prescriptions, or routinely runs out of narcotics early is not considered a narcotic candidate. Patients who use narcotics over the long term should regularly report the symptoms on a VAPS and should report their degree of functionality. They should be encouraged regularly to wean from these agents.

Drug	Dosage
Intermediate Potency	
Propoxyphene	65 mg q3–4h p.r.n.
Codeine	15–60 mg q4–6h p.r.n.
High Potency	
Hydrocodone	5–30 mg q4–6h p.r.n.
Oxycodone	5–30 mg q4–6h p.r.n.
High Potency—Long Acting	
Methadone	5–20 mg q12h
Oxycodone SR	10–80 mg q12h

SR, sustained release.

TABLE 43.7. *Oral narcotics*

Narcotic Agreements

When long-term narcotic therapy is used for pain management, it is useful to have the patient enter into a pain agreement to prevent misunderstandings and to help both the physician and patient comply with the federal laws regarding controlled substances.

When the agreement is entered, it is understood that if the patient terminates the agreement, the physician will discontinue narcotic therapy but will taper the medicine over a period of several days, as necessary, to avoid withdrawal symptoms. Also, a drug-dependence treatment program should be recommended. The patient agrees to describe the pain character and intensity, the effect of the pain on her daily life, and how well the narcotic is helping to relieve the pain. The patient also agrees not to use any illegally obtained controlled substances, and not share, sell, or trade medication with anyone.

Opioids, controlled stimulants, or antianxiety medication must not be obtained from any other doctor. The patient must agree to safeguard her pain medicine from loss or theft with knowledge that lost or stolen medicines will not be replaced. She should understand that prescriptions will be made only at the time of an office visit or during regular office hours and that no refills will be available during evenings or on weekends. This is helpful for covering physicians who receive calls from patients asking for narcotics. The pharmacy name, location, and telephone number are recorded and a log of the dosage, quantity, and prescription date is recorded in the patient's chart.

SUMMARY POINTS

- CPP is a complex entity, often without obvious, visible pathology.
- A distinction must be made between putative causes of CPP, which will respond to specific treatment, versus CPP associated with incidental pathology.
- Treatment of CPP with incidental pathology may result in failure and, in some cases, removal of otherwise normal organs. In such cases, treatment may take a more general and empiric course, resulting in the use of neurolytic medications and possibly the judicious use of narcotics.

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Chapter 44

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Perioperative Evaluation

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INTRODUCTION

> “One important key to success is self-confidence. An important key to self-confidence is preparation.”
>
> Arthur Ashe

In this country, obstetrician-gynecologists are the primary surgeons in over 3.6 million pelvic operative procedures completed on an annual basis (Table 44.1). These procedural volumes, when combined with the many thousand minor office and obstetric procedures, are testimony to the enormous potential physical, psychological, and economic impact of surgery and potentially preventable adverse events on women's health care. Importantly, nearly 50% of all adverse perioperative events are preventable. The sheer numbers undeniably suggest that risk prevention should be the ultimate goal of every surgeon. Assuming the role of primary care physician and surgical subspecialist for women, obstetrician-gynecologists should accept responsibility for developing, instituting, and completing all aspects of perioperative management. As an important step to improve quality of care, we should be cognizant of the potential role and benefits that allow objective discussion of nonsurgical options, as well as understand appropriate surgical indications for pelvic disease processes.

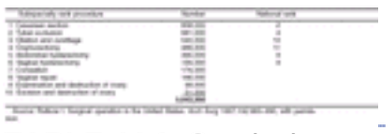

TABLE 44.1. *Surgical procedures in obstetrics and gynecology*

Our primary goals should consist of prospective preoperative recognition, evaluation, and management of the significant clinical aspects of existing medical comorbidities and development of operative techniques to form a flexible multifaceted surgical skill set that increases the opportunity for safe completion of the procedure, regardless of inherent technical difficulty. Finally, pelvic surgeons should be capable of devising a postoperative care plan that further minimizes the risk of an adverse perioperative outcome, enhances the early recognition of acute perioperative problems, and lessens the risk and the intensity of potentially catastrophic perioperative complications. This care plan should be formalized prior to entering the preanesthetic area or the operating suite, and its execution should contain enough clinical alternatives to ensure a successful result, regardless of the intraoperative findings or postoperative complications encountered. The volumes of existing published literature on surgical alternatives and indications establish a clear message: “optimal” perioperative care is a moving target. Every treatment plan and intervention requires careful aim if the goals of improved quality and optimal patient outcome are to be attained. Mastery of these perioperative planning processes only serves to improve the individual and collective quality of patient care. Proper implementation should result in decreased individual, regional, and national health care expenditures.

SURGICAL INDICATIONS AND CONSENT FOR SURGERY

It is the ultimate responsibility of every obstetrician-gynecologist to evaluate thoroughly the patient's reproductive tract complaints prior to entering the possibility of surgical management. In addition to evaluating the pelvic condition, it is vital to conduct a preoperative search for physical or psychological comorbidities. Only when armed with this global information can the surgeon objectively present the risks and realistically relate the expected outcome of the entire spectrum of accepted medical and surgical options. This information should be processed and presented to the patient (and other support persons when appropriate) in a manner that is not demeaning, using understandable language that allows and facilitates an informed decision and consent process. Although the preoperative diagnostic period may be deemed routine by the surgeon and staff, many women consider the prediagnostic interval to be the most stressful time of treatment. This psychological stress contributes to difficulty in understanding the importance and results of diagnostic studies or results and potentially clouds the information discussed during preoperative discussions. Decisions, options, and alternatives, as they relate to the potential need for postoperative therapy, can be lost. The preoperative use of illustrative drawings, pamphlets, videos, or other visual educational materials often can be of assistance in improving patient (and family) comprehension of medical alternatives, operative indications, associated risks, and expected treatment outcomes. Typically, this preoperative encounter (or encounters) to discuss surgical options and obtain consent is best undertaken in a private setting, completed in a manner that is conducive of a two-way flow of communication. Eye contact, a caring touch, an unhurried approach, and other “soft” physician behaviors lower communication barriers and facilitate patient and “significant other” comprehension. The complexity of preoperative discussion and necessary time expenditure may vary dramatically with the surgical indications, as well as with the medical alternatives to the proposed

procedure. Regardless, the algorithm of care, surgical risks and outcome expectations should be detailed, recognizing that modification may be required secondary to important or imperative patient desires (e.g., a patient desiring retention of ovaries or fertility). Regardless of the extent of preparation and best surgical technique, any unexpected or adverse intraoperative or postoperative event can alter dramatically the final surgical procedure and ultimate result. The apparently “simple” laparoscopic salpingo-oophorectomy may be complicated by uncontrolled abdominal wall, intraperitoneal, or retroperitoneal bleeding, intestinal injury, or the finding of an ovarian malignancy. Postoperative myocardial infarction (MI), infection, or thromboembolism may occur. A good rule of thumb is to discuss during the explanation of surgical risks adverse events that occur at a frequency of 1% or more. Any preoperative consent discussion should include the risk of death or permanent disability. Failure to address any or all of these risks can result in misunderstanding, fear, and anxiety and fosters mistrust. As important as the consent process, the resultant preoperative patient education decreases the need for postoperative analgesia and is associated with less anxiety and earlier ambulation. Unless the clinical situation is emergent or life-threatening, these discussions are best undertaken at a time remote from the day of surgery. Timely entered, legible chart documentation should follow any and all of these discussions.

Following the mutual decision to bypass medical management, the surgeon is faced with a number of other important procedural questions including the route (i.e., vaginal versus abdominal versus laparoscopic approach), as well as who should perform the procedure. It is intuitive and reported data confirm that, even among subspecialists, individual surgical skills and outcomes of specific procedures differ dramatically. These differences may relate to the surgeon's innate technical ability, the specifics of the individual's previous training, patient selection, or factors unrelated to the physician. Without placing blame, the training demands of our subspecialty have altered the overall extent of residency surgical experience, resulting in fewer major operative procedures being completed per trainee. These educational changes have resulted in a noticeable decrease in resident surgical skill acquisition. Importantly, these relative deficiencies noted by senior observers may not be perceived or recognized by the individual trainees. Coupled with the increasing ratio of postresidency physicians to annual operative procedures and the increasing technical procedural subspecialization, it is easily understood how difficult it is for the pelvic surgeon to obtain, maintain, or refine new surgical skills, even in our restricted subspecialty where the surgical focus is entirely on reproductive tract procedures. These factors lend credence to the adage, “no one can be all things to all people,” and each physician must individualize the decision to operate, consult, or refer. Specific referral guidelines citing evidence-based data have been created to assist practicing obstetrician-gynecologists in the care of women with selective diagnoses. Additionally, a favorable outcome of many procedures is related to increasing surgical experience, surgical volume, and expertise. Although disease-specific guidelines may not relate to “routine procedures,” it is logical and scientific that improved perioperative outcomes should follow increased surgical case volume. Although these effects may be surgeon or program related, arguments against consultation or referral have little scientific merit and may not be in the patient's best interest. Although circumstances may prohibit actual patient referral, the ready availability of curbside, personal, telephone, and internet consultation should encourage information dissemination, and utilization of available resources should improve patient care.

HISTORY AND PHYSICAL EXAMINATION

> “Listen to women and they will tell you what's wrong with them.”
>
> Charles E. Flowers

Every operative procedure requiring anesthesia should be viewed as a physiologic stress test. The intensity of the stress response varies in direct proportion to the extent of the actual surgical procedure and is associated with a clinically and biochemically measurable adverse effect. Nearly every organ system is affected adversely by general anesthesia. The associated 20% reduction in resting heat production and increased surface heat loss predispose patients to hypothermia, increasing the risk of an adverse cardiac event, altered pulmonary response to hypercarbia and hypoxemia, impaired coagulation, and poor wound healing. The untoward anesthesia-related pulmonary effects of impaired oxygenation and altered lung mechanics are likely well tolerated by the 40 year old, but they may have catastrophic consequences in the elderly or in those with coexisting pulmonary disease. Most inhalational drugs directly create increased cardiac risk by altering myocardial oxygen supply and demand kinetics. Myocardial depression, increased arrhythmogenicity (as high as 27% incidence), and altered neural tone form the triad for predisposing women to adverse cardiovascular effects. Importantly, these risks are not lessened with regional anesthesia use. Reduction in renal blood supply (decreased by 30 to 70%), suppression of the immune system, ileus, and stress-related gastric ulceration represent but a few of the other quantitative adverse effects of anesthesia. Many of these effects can be correlated with the duration of operation, and every effort should be made to increase operative efficiency in an attempt to safely shorten the procedure and minimize risks.

Despite these anesthesia-enhanced risks, only a small percentage of operative deaths are attributable solely to anesthesia. Less than 18% of surgical mortality is directly attributable to the surgical procedure. The vast majority of surgical mortality (79%) can be related directly to problems created in great part from the patient's coexisting medical disease. This mortality risk further illustrates the need to undertake a diligent preoperative search to identify and potentially modify the adverse effects of any significant coexisting medical condition.

The literature is inundated with articles espousing the proposed benefits of preoperative radiologic testing and laboratory evaluation; however, the diagnostic power contained in a carefully obtained history and a thorough physical examination is enormous. The reproducible validity of this simple, easily obtainable evaluation is underscored when recognizing that as many as 98% of abnormalities found with preoperative laboratory and radiologic screening can be predicted by historical or physical findings.

Although studies relating to the pelvic process (i.e., urodynamics) frequently are necessary to delineate the need for surgery, attempts to obtain important historical information regarding diagnosed medical comorbidities and clinically silent medical disease are vital to direct additional preoperative evaluation. Review of pertinent medical records combined with initial direct questioning about previous hospitalizations, current treating physicians, concurrent diagnoses, use of prescribed and over-the-counter medications, and allergies will assist in the detection of coexisting medical disease. This information may be vital to the preoperative plan regarding the continuation (e.g., cardiac, hypertensive) or discontinuation (e.g., aspirin, oral contraceptives, anticoagulant) of medications. Over-the-counter and herbal medication usage can create the potential for additional untoward complications and should be evaluated (Table 44.2). Conducting a pointed review of systems allows the determination of performance status and aids in the diagnosis of significant but previously undetected medical disease. Although intended to cover multiple systems, simple questions as to the patient's ability to walk a mile, climb two flights of stairs, or blow out a match from 12 inches away may suffice as a screen for significant cardiopulmonary disease. Historical information obtained by questionnaire can be considered valid; however, the presence or absence of important symptoms should be confirmed during the office visit.

Sympathomimetic Effects
Ephedra sinica (ma-huang)
Panax ginseng (ginseng)
Glycyrrhiza glabra (licorice)
Hydrastis canadensis (goldenseal)
Potentiate Bleeding
Tanacetum parthenium (feverfew)
Allium sativum (garlic)
Ginkgo biloba (ginkgo)
Zingiber officinale (ginger)
Prolong Sedative Effects
Valeriana officinalis (valerian)
Piper methysticum (kava-kava)
Hypericum perforatum (St. John's wort)

Source: American Society of Anesthesiologists Web pages at www.asahq.org. Accessed January 13, 2003. Leak JA. Herbal medicine: What do you need to know? *ASA Newsletter* 2000; 64:6–7, with permission.

TABLE 44.2. *Herbal medicines: possible adverse effects*

A thorough multisystem physical examination is an essential part of every preoperative evaluation. Specific attention to the cardiopulmonary system assists in the detection of important coexisting disease that may alter outcome adversely and directs additional investigation. Every system carries some import, and abnormal findings allow for appropriate morbidity-reducing, cost-effective adjustments in the perioperative plan.

LABORATORY INVESTIGATION

The primary goal of preoperative laboratory preparation is to obtain results that allow reduction of those inherent risks related to the proposed procedural component, as well as those risks associated with occult or recognized coexisting medical morbidities. It has become apparent that a “broadly cast net” preoperative laboratory screening strategy confers little patient benefit for the following reasons. (a) The majority of laboratory abnormalities can be predicted by findings noted in the history and physical examination. It is rare to detect an unexpected abnormality. (b) The physiologic, psychological, and economic costs associated with the evaluation of abnormal laboratory (including false-positive) studies brings little value, and it rarely influences clinical care. (c) As many as 60% of abnormal preoperative test results are not known or evaluated preoperatively, creating potential liability. Multiple reports suggest that nearly 70% of ordered preoperative laboratory tests are not indicated by facts obtained in the history and physical examination.

This information reiterates the importance of the history and physical examination and suggests that a directed preoperative laboratory testing strategy (Table 44.3) for routine procedures is both safe and cost effective. Obviously, special studies such as tumor markers (e.g., CA-125) are appropriate during evaluation and management

of women with pelvic malignancies, because they offer diagnostic assistance, facilitate decisions regarding patient triage, are potentially prognostic, and are of significant value during postoperative management. Although care should be individualized, it has become apparent that directed preoperative laboratory testing forms a firm foundation for quality preoperative care for patients undergoing elective procedures.

TABLE 44.3. *Preoperative testing strategy*

Although advances in blood banking technology have lessened the risk of transfusion and favorably affected the outcomes of many surgical procedures, it is apparent that women do not need to have a type and crossmatch performed prior to the majority of obstetric or gynecologic surgical procedures. Although maximal surgical blood order schedules have been established, they should be validated at each institution. When deemed necessary, a type and screen allows for identification of specific antibodies and assures rapid availability (=20 min) of red blood cell products. Individual decisions regarding blood bank strategies should be related to the patient's preoperative status (i.e., hemoglobin and hematocrit, blood volume), anticipated losses, and existing comorbidities that might carry an early transfusion trigger. Anemia is not uncommon among women undergoing pelvic surgery. Although it may constitute an indication (menorrhagia, associated with leiomyomas) or result from an indication (cervical cancer), its presence should prompt an evaluation. As deemed appropriate, a preoperative search for other causes or losses should be undertaken. Additionally, preoperative discussions regarding procedure-associated blood loss and its attendant risks represent an important aspect of informed consent.

Critically ill patients may benefit from having their serum hemoglobin levels maintained at about 10 g/dL, but data suggest little effect of transfusion on survival in patients whose hemoglobin levels are between 8 and 10 g/dL. The majority of women can safely undergo elective procedures without a type and screen.

RADIOLOGIC INVESTIGATION

Routine imaging studies can be obtained safely as directed by findings of the history and physical examination. The indications for a preoperative chest radiograph are relatively straightforward, and abnormalities are associated with an increased risk of perioperative pulmonary complications. Unfortunately, unnecessary chest radiographs and many additional, sometimes unnecessary, undirected diagnostic preoperative imaging studies are obtained frequently.

Diagnostic ultrasonographic examination, pelvic and abdominal computed tomography (CT), and magnetic resonance imaging studies are performed in patients with suspected or known gynecologic malignancies. These studies may suggest the benefit of preoperative triage to a subspecialist but rarely influence the surgical approach. Their results should not be considered binding, typically contribute little to clinical care, and often add significantly to health care costs. Although the radiologist's suggestions for additional studies are noted frequently, the astute pelvic surgeon should combine physical findings, patient symptoms, and laboratory results to develop the perioperative care plan, based on necessity and benefit of histologic confirmation of a radiologic abnormality.

Although proponents of preoperative “radiologic staging studies” suggest relative accuracy, the pelvic surgeon must recognize the subjective aspects of interpretation. In general, their routine use has not been associated with an alteration in perioperative clinical care. Although findings may alter approach, negative results do not exclude the finding of significant pathology. Not to condone or condemn, the value and use of other noncardiac imaging studies have not been evaluated adequately. However, it appears that in specific situations CT scans have a significant false-negative result rate (e.g., for the evaluation of extraovarian disease). Radiologic investigation adds little to clinical care in patients with endometrial cancer in the absence of physical findings. There is little clinical value for intravenous pyelography (IVP) to evaluate ureteral location or displacement, because it is not a substitute for intraoperative ureteral identification. In the absence of malignancy, hydronephrosis is likely related to displacement and is easily corrected or managed during the operative procedure.

The exception is an abnormal finding on a clinically indicated routine cancer screening study (e.g., mammography), in which test results may have a significant impact on clinical care, particularly in those women undergoing “elective pelvic procedures.”

ENDOSCOPIC EVALUATION

There is little evidence to suggest the value of multiple endoscopic procedures prior to most routine gynecologic procedures. However, it is certainly appropriate to consider obtaining history-directed or disease-specific (e.g., inflammatory bowel disease, previous colon cancer) or recommended cancer screening endoscopic procedures prior to elective procedures. For example, endoscopy performed prior to rectovaginal or vesicovaginal fistula repair may render significant and important information and cause the physician to alter the surgical approach or initiate referral.

CARDIAC DISEASE

Preoperative assessment to detect undiagnosed heart disease and direct appropriate perioperative treatment of women with longstanding or newly diagnosed cardiac disease is of vital importance. The majority of inhalational anesthetics are myocardial depressants, modify neural tone, and are arrhythmogenic, creating risk even in the healthy patient. Nearly 50,000 perioperative MIs occur annually. Approximately 20,000 are fatal, and hundreds of thousands of related serious extracardiac complications occur, resulting in poor outcome. The prevalence of cardiovascular disease increases directly with increasing age, and within the aging population serous cardiac events occur regularly. Although no age group is risk free, gynecologic procedures in the aging population are estimated to result in a 25% increase in the incidence of necessary major intraabdominal procedures, potentially increasing the absolute risk of cardiac morbidity. Although heart disease may not be readily apparent, the answers to carefully framed historical questions can assist in unmasking occult cardiac risk factors. Gynecologists should feel compelled to become familiar with the important aspects of perioperative cardiac care, to improve individual patient outcome as well as the overall health of the entire female population.

Proper preoperative cardiac assessment requires a systematic approach, typically undertaken in close coordination with qualified consultants. Attention to history, physical findings, and the effects of comorbid diseases forms the foundation for initial evaluation. These findings assist in the direction of ordering ancillary cardiac studies, which can clarify risk and improve predictive power for perioperative morbidity associated with the proposed gynecologic surgery. They also allow institution of a sound plan for perioperative monitoring and management A disease-specific approach is important, specifically addressing signs, current symptoms, and management of coronary artery disease (CAD), hypertension, heart failure, valvular heart disease, arrhythmias, pacemakers, pulmonary vascular disease, and type and extent of surgery.

General Considerations

Particular energy should be directed preoperatively to elicit historical or physical evidence of cardiac ischemia. Important elements include angina, a history of MI, past or current signs or symptoms suggesting congestive heart failure, unexplained palpitations, evidence of previous cardiac intervention, and renal impairment. Important aspects of noncardiac diseases that increase the incidence of cardiac risk factors, including diabetes mellitus, hypertension, hypercholesterolemia, family history of CAD, and obesity, should be evaluated. Age greater than 70 years, MI within the preceding 12 months, and evidence of congestive heart failure significantly increase postoperative cardiac complications in patients undergoing gastrointestinal, urologic, and gynecologic surgery. Concurrently, the pelvic surgeon should attempt to determine the patient's “functional capacity.” The simple inability to walk three blocks or climb two flights of stairs portends a poor functional status. Physical examination evaluating the patient's overall status is mandatory. This evaluation, coupled with laboratory and radiologic information and an electrocardiogram (ECG), provides a baseline estimate as to actual perioperative cardiac risk. Numerous schema from Goldman and others intended to quantify cardiac risks have been designed, reported, and verified in an attempt to quantitate perioperative cardiac risk. The American College of Cardiology-American Heart Association (ACC-AHA) published revised practice guidelines based on qualitative analysis. Specific risk categories include ischemic heart disease, congestive heart failure, high-risk surgery, diabetes mellitus, renal insufficiency, and poor functional status (Table 44.4). They define clinical risk stratification for noncardiac surgical procedures. Noncardiac procedures with high (>5%), intermediate (<5%), and low (<1%) risk of cardiac morbidity or mortality have been categorized (Table 44.5).

TABLE 44.4. *Factors that increase the risk of perioperative cardiac complications in patients undergoing noncardiac surgery and indications for the use of perioperative ß-blocker therapy*

High (Reported Cardiac Risk Often >5%)
Emergent major operations, particularly in the elderly
Aortic and other major vascular
Peripheral vascular
Anticipated prolonged surgical procedures associated with large fluid shifts or blood loss or both
Intermediate (Reported Cardiac Risk Generally <5%)
Carotid endarterectomy, head and neck
Intraperitoneal and intrathoracic
Orthopedic
Low (Reported Cardiac Risk Generally <1%)
Endoscopic procedures
Superficial procedure (i.e., dilation and curettage)
Breast

From: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;105:1257–1267, with permission.

TABLE 44.5. *Cardiac risk stratification for noncardiac surgical procedures*

Data prompting development of these guidelines suggest that coronary artery bypass surgery or other invasive interventions (i.e., coronary angioplasty) are appropriate only in an effort to reduce cardiac risks following the stress of noncardiac surgery when they would be indicated for symptoms or to manage test-related cardiac disease nonsurgically. Specific disease states requiring strong consideration of presurgical revascularization include poorly controlled angina pectoris (despite maximal medical therapy), high-risk left main coronary artery stenosis (>50%), severe two- or three-vessel CAD (with involvement of the proximal left anterior descending artery) with greater than 70% stenosis, easily induced myocardial ischemia on preoperative stress testing, and left ventricular systolic dysfunction at rest.

Cardiac Disease–Specific Approach

Coronary Artery Disease CAD commonly occurs at a lower incidence in females than in males; however, diabetic women are risk equivalent to men. The mortality of an acute MI is greater for women and increases dramatically in the aged patient. Importantly, MIs occurring during the perioperative period carry a higher mortality risk than those occurring otherwise. Many surgical patients have diagnosed CAD or risk factors for CAD. Women who are potential candidates for attempts at preoperative myocardial revascularization may benefit from noninvasive cardiac testing performed to determine the amount of myocardium in jeopardy, the patient's ischemic threshold, and the objective determination of ventricular function. Test results should be used to assist in stratifying prognostic information and determining the extent and benefit of perioperative surgical or medical intervention and postoperative monitoring.

Hypertension As the training and practice of obstetricians-gynecologists increasingly stresses the importance of primary care, the preoperative evaluation and the management of hypertension has become a major focus on the gynecologic patient's problem list. Although the identification of early-stage hypertension should lead to the institution of appropriate medical therapy, the ACC-AHA guidelines suggest that those with stage II or milder hypertension (systolic blood pressure below 180 mm Hg and diastolic blood pressure below 110 mm Hg) are not at increased risk for perioperative cardiovascular complications. Surgical delay for medical treatment of women with stage I or II hypertension is not necessary or beneficial. However, elevated blood pressure in patients with stage III hypertension (systolic blood pressure 180 mm Hg or higher and a diastolic blood pressure 110 mm Hg or higher) should be controlled prior to surgery. The administration of ß-adrenergic blockers in this clinical situation results in rapid, effective control of severe blood pressure elevation and perioperative hypo- or hypertension, either of which is associated with an increased risk of coronary ischemia. Regardless of actual measured systemic pressures, the ACC-AHA guidelines suggest that the blood pressure of patients with significant hypertension who require urgent surgery be controlled. The goal is to avoid the ischemic complications associated with perioperative blood pressure fluctuations that commonly occur in the surgical patient who has uncontrolled hypertension.

Heart Failure Ventricular failure is an important predictor of and prognostic factor for perioperative cardiac morbidity. The initial attempt to identify women with ventricular dysfunction begins with a detailed history and organ-specific physical examination. Determination of ventricular status is mandatory in those with evidence or history of congestive heart failure, because the physiology of perioperative ventricular failure portends an ominous situation. Perioperative subspecialty consultation, pharmacologic manipulation to maximize cardiac oxygen supply–demand ratio, careful administration of intravenous fluids, and cardiac monitoring may benefit these patients. During preoperative investigation, gynecologic surgeons should not exclude the possibility of rare causes of cardiomyopathy, including hypertrophic obstructive cardiomyopathy, because their appropriate medical management decreases morbidity. Echocardiography, to obtain an estimate of ventricular function and to rule out anatomic abnormalities, should be considered and may be necessary for the perioperative assessment for those women with suspected, known, or history of heart failure or cardiomyopathy.

Valvular Heart Disease Although interpretation of the physical findings can be challenging, the gynecologic surgeon should attempt to identify significant heart murmurs. Echocardiography aids in defining the anatomic abnormality and in detailing the need and benefit of antibiotic endocarditis prophylaxis (Table 44.6). Failure to diagnose any significant valvular dysfunction or to administer appropriate antimicrobial prophylaxis increases the risk of a catastrophic perioperative consequence.

Endocarditis Prophylaxis Recommended
High-risk Category
Prosthetic cardiac valves, including bioprosthetic and homograft valves
Previous bacterial endocarditis
Complex cyanotic congenital heart disease (e.g., single-ventricle states, transposition of the great arteries, tetralogy of Fallot)
Surgically constructed systemic pulmonary shunts or conduits
Moderate-risk Category
Most other genital cardiac malformations (other than those listed above and below)
Acquired valve dysfunction (e.g., rheumatic heart disease)
Hypertrophic cardiomyopathy
Mitral valve prolapse with valvular regurgitation, thickened leaflets, or both
Endocarditis Prophylaxis Not Recommended
Negligible-risk Category (Risk No Greater Than That of the General Population)
Isolated secundum atrial septum defect
Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residual beyond 6 months)
Previous coronary artery bypass graft surgery
Mitral valve prolapse without valve regurgitation
Physiologic, functional, or innocent heart murmurs
Previous Kawasaki syndrome without valve dysfunction
Previous rheumatic fever without valve dysfunction
Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

Source: Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;277:1795, with permission.

TABLE 44.6. *Cardiac conditions associated with endocarditis*

Aortic stenosis poses the greatest valvular risk for poor postoperative cardiac outcome. Cardiac morbidity in women with untreated aortic stenosis undergoing noncardiac surgery approaches 10%, sufficient to persuade every pelvic surgeon to diagnosis this condition. ACC-AHA practice guidelines advise postponement of elective surgery in women with severe or symptomatic aortic stenosis until valve replacement, the accepted standard intervention, can be performed. In emergent situations, aortic valvuloplasty may be employed but has less certain success. In general, surgical correction of mitral stenosis is not indicated prior to noncardiac surgery unless the severity would warrant treatment in a nonsurgical setting. If deemed necessary, balloon valvuloplasty is an appropriate corrective option for those with severe mitral stenosis. Mild to moderate mitral stenosis requires control of perioperative heart rate to reduce the risk of heart failure. Significant aortic regurgitation requires attention to intravascular volume control and attempts at medical afterload reduction. In contrast to mitral stenosis, bradycardia should be avoided or aggressively treated to avoid left ventricular backfill. Mitral regurgitation most commonly is associated with papillary muscle dysfunction and mitral valve prolapse. Prior to surgical procedures, antimicrobial prophylaxis may be indicated for those with mitral valve prolapse and demonstrable clinical evidence of regurgitation or echocardiographic evidence of anatomic mitral valve leaflet abnormalities. Women with significant mitral regurgitation murmurs require careful monitoring of the left ventricular ejection fraction, because the low-resistance regurgitant valve predisposes perioperative patients to retrograde cardiac flow, resulting in pulmonary edema and high pulmonary artery pressures. Invasive perioperative cardiac monitoring may be necessary, because echocardiography tends to overestimate ejection fraction in patients with mitral regurgitation. Patients with prosthetic mitral valves receiving systemic anticoagulants require intervention to lessen the risk of endocarditis and intracardiac coagulation. The fifth consensus conference on anticoagulation suggests:

1. For minimally invasive surgical procedures, reduce the international normalized ratio to subtherapeutic range and resume the normal dosage of oral anticoagulation immediately postprocedure.
2. Perioperative heparin is recommended for patients when significant bleeding is anticipated or the risk of thromboembolism is high. These clinical situations include women with a mechanical valve in the mitral position (low flow rate), a Bjork-Shiley valve, or history of thrombosis or embolus associated with valvular replacement during the past year. Systemic anticoagulation is appropriate if three risk factors are present, including atrial fibrillation, previous embolus, hypercoagulable condition, or mechanical prosthesis with left ventricular function of less than 30%.

3. For patients whose clinical condition falls between these extremes, the risk–benefit ratio of anticoagulation should be considered individually.

Arrhythmias Every gynecologic surgeon will encounter perioperative cardiac arrhythmias. The majority are considered benign, but their underlying etiology should be sought aggressively, because undiagnosed cardiac ischemia may initially become clinically evident as a perioperative arrhythmia. Perioperative arrhythmias may worsen existing ischemia by increasing myocardial demand or decreasing cardiac efficiency. Pulmonary disease, metabolic derangements, or drug toxicities are common causes. Monitoring and treatment is important, because an unstable arrhythmia such as atrial fibrillation occasionally may deteriorate into a life-threatening rhythm (i.e., ventricular fibrillation). In addition to conferring a therapeutic cardiac morbidity risk reduction in patients with CAD, ß-blockers may reduce arrhythmia-related perioperative morbidity and mortality. Premature ventricular contractions occurring at a rate of fewer than 6 per minute are presumably “benign.” Even short and spontaneously converting runs of ventricular tachycardia may not predispose patients to perioperative death from MI. However, underlying coronary ischemia may be unmasked by the occurrence of these rhythms, making it imperative that the underlying etiology of a perioperative arrhythmia be ascertained, even if these are not treated by antiarrhythmic agents other than ß-blockade. Atrioventricular (AV) block, especially Mobitz type II or third-degree heart block, may increase operative risk. Patients with type I second-degree AV block, first-degree AV block, and left and right bundle branch blocks are usually asymptomatic and their arrhythmias rarely contribute to postoperative morbidity and mortality. It is reasonable to consider early subspecialty consultation to diagnose and treat women who develop perioperative cardiac arrhythmias. Patients with known or previously treated or untreated congenital heart disease or pulmonary vascular disease deserve close evaluation. Individuals with previous surgical correction of a ventricular septal defect, patent ductus arteriosis, or tetralogy of Fallot may be at increased operative cardiac risk, possibly due to decreased pulmonary vasculature reactivity to hypoxia.

Risk Stratification According to Type of Surgery

Although individually weighted, existing patient risk factors, the type and extent of operation, and the operative circumstances are important to delineate the risk of perioperative cardiac morbidity. Intuitively, the decision to operate and the choice of operation or operative approach should be made in an attempt to offer the most effective treatment while minimizing patient cardiac risk. Other medical conditions should be addressed to lessen any indirect impact or perioperative cardiac outcome.

Every surgical intervention should be biased by or based on acute or chronic patient-specific factors. Although emergent surgical indications lessen available evaluation time, urgency does not absolve the responsibility to search diligently for significant risk factors. The young woman in shock with a ruptured ectopic pregnancy may provide the physician with only a brief opportunity for cardiac evaluation; however, cardiac risk factors are uncommon in this population, minimizing the necessity for or benefit of an extensive evaluation. The elderly patient with acute intestinal obstruction and strangulated bowel related to ovarian carcinoma may harbor significant cardiac risk factors but may require life-saving surgery despite significant coronary risk and a high potential for morbidity.

Perhaps more problematic is evaluation of those patients who require diagnostic or therapeutic surgery for pelvic malignant neoplasms and who are discovered to have cardiac disease during the presurgical evaluation. The clinical situation surrounding this or semi-urgent gynecologic procedures may preclude the benefit of extensive intervention (i.e., coronary artery bypass grafting [CABG]). In this situation, consultation and maximal medical therapy can improve the patient's perioperative cardiac condition and lessen risks.

Perioperative evaluation of women undergoing elective pelvic surgery should consider the risk of an adverse cardiac event in relation to the extent of the necessary surgical procedure. The benefit of medical management of the gynecologic condition should always be considered carefully. A minimally invasive or a vaginal surgical approach carries less physiologic stress and less risk of associated cardiac morbidity when compared with more extensive intervention (e.g., an abdominal approach). Although it requires planning and technical flexibility, matching the patient's gynecologic and medical conditions to a proper surgical approach should be every surgeon's goal. Good matches most frequently result in good outcomes.

Risk Assessment and Treatment

The ultimate objective of preoperative cardiac risk assessment is to rule out serious CAD that requires cardiac intervention remote from the need for noncardiac surgery. Preoperative evaluation should be designed to recognize existing disease, expose occult underlying heart disease, and provide an opportunity for appropriate cardiac assessment.

Noninvasive Testing ACC-AHA recommendations for those undergoing noncardiac surgery provide a short-cut to the appropriate application of noninvasive cardiac testing, which is indicated by two of three listed risk factors. This testing schema assumes that the identification of a high-risk patient will identify those who would benefit from preoperative coronary revascularization or maximization of medical therapy. Either would contribute to improving the patient's long-term quantity and quality of life. Noninvasive studies include the 12-lead electrocardiogram, echocardiography, contrast ventriculography, radionuclide angiography, exercise stress testing, nonexercise stress testing, myocardial perfusion imaging, and dobutamine stress echocardiography. The ACC-AHA evaluation guidelines algorithm can be applied to all patients. In general, the gynecologic surgeon should consider the role of noninvasive testing after consultation with qualified specialists to assist in the evaluation, interpret the results of noninvasive testing, and recommend intervention for those patients with cardiac risk factors.

Coronary Artery Bypass Graft-Specific Interventions The decision to perform CABG prior to noncardiac surgery should be based on potential risks versus the short- and long-term benefits of coronary revascularization. Eagle and colleagues reporting on 3,368 patients (Coronary Artery Surgery Study database) with CAD, found that patients undergoing minimally invasive procedures have a cardiac-related mortality rate of less than 1%, regardless of previous CABG. In contrast, major procedures including abdominal surgery carried a significantly higher risk of cardiac morbidity and mortality. The risk of death (1.7 vs. 3.3%, $P = .03$) and nonfatal MI (0.8% vs. 2.7%, $P = .002$) was significantly lower after CABG. The ACC-AHA task force has recommended that preoperative coronary revascularization be employed in specific clinical situations: in those women with acceptable risks of coronary revascularization and a suitable amount of viable myocardium, those with left main coronary artery stenosis, those with three-vessel CAD in conjunction with left ventricular dysfunction, those with two-vessel disease involving severe proximal left anterior descending artery obstruction, and when intractable coronary ischemia persists despite maximal medical therapy. These practice guidelines also suggest that the timing of coronary revascularization be weighed against the clinical urgency and extent of noncardiac surgical intervention. Patients requiring elective noncardiac procedures of intermediate or high surgical risk who have significantly abnormal coronary anatomy should be referred for surgical revascularization prior to noncardiac surgery. Those same patients undergoing low-risk noncardiac surgical procedures or patients with less severe coronary artery lesions should not undergo preoperative coronary artery revascularization.

Preoperative Prophylactic Coronary Intervention The ACC-AHA task force has recommended that percutaneous transluminal coronary angioplasty (PTCA) be used in the perioperative setting in a manner identical to that proposed outside of the perioperative setting. Although debate exists as to the most appropriate interval from PTCA to the pelvic surgical procedure, delay for at least 2 to 4 weeks should be allowed to ensure healing and exclude restenosis of the treated vessel. However, extended delays of more than 6 to 8 weeks after PTCA may allow restenosis of the treated vessel and further increase the risk of perioperative ischemia. If a coronary artery stent is placed, ACC-AHA recommendations suggest postponing surgery for to 2 to 4 weeks to allow stabilization and to exclude the risks of stent site stenosis. The 2-week delay allows completion of a full course of thienopyridine and aspirin therapy and lessens the risk of subsequent stent thrombosis. There is little evidence available to describe the perioperative effect of prophylactic coronary intervention months to years before noncardiac surgery; however, coronary restenosis is unlikely to occur within 8 to 12 months after prophylactic coronary intervention, with or without stent placement. Obviously, patients with previous cardiac intervention remain at risk to develop subsequent additional coronary artery lesions. The Bypass Angioplasty Revascularization Investigation (BARI) compared the outcomes of noncardiac surgical procedures following CABG (250 patients) versus PTCA (251 patients) in 1,049 surgeries. The median time interval between the most recent coronary revascularization procedure and noncardiac surgery was 29 months. There were no significantly different outcomes when evaluating morbidity, in-hospital morbidity, and hospitalization costs, suggesting equivalence of revascularization procedures. However, the risk of cardiac death or MI was lower (0.8% vs. 3.6%) when noncardiac surgery was performed less than 4 years after revascularization, emphasizing the need for thoughtful preoperative cardiac evaluation in this patient population.

Perioperative Medical Therapy Several prospective randomized trials have evaluated the effects of perioperative ß-blocker administration. Poldermans and others administered bisoprolol to the 146 patients with high cardiac risk. The risks of both cardiac death (17% vs. 3.4%) and nonfatal MI (0 vs. 17%) were lowered significantly with treatment. Oral atenolol has been compared with placebo for 7 perioperative days. Although there was no significant decrease in MI or cardiac death, a significant decrease in ischemia (24% vs. 39%) was apparent in those receiving atenolol. This report also detailed a significant decrease in the subsequent 6-month death rate (1% vs. 10%) in those treated with atenolol. Ace inhibitors were also evaluated in two studies which showed no demonstrable benefit. Although randomized prospective clinical trials of ß-blockade in a gynecologic population are not available, it seems reasonable to extrapolate the benefits of these interventions to those discovered to have a high cardiac risk during preoperative evaluation prior to a pelvic operation. ACC-AHA practice guidelines recommend perioperative ß-blocker treatment for patients with angina, symptomatic arrhythmias, untreated hypertension, known CAD, or major risk factors for CAD. The potential effect of a-antagonist perioperative cardiac protection has also been evaluated. A randomized placebo-controlled multicenter trial study of mivazerol use during the perioperative period in 2,854 patients with known CAD or significant risk factors reported no difference in MI incidence; however, the cardiac death rate was reduced by nearly 50% ($P = .04$). The Perioperative Ischemia Research Group also reported a significant reduction in perioperative cardiac ischemia in patients given high-dose perioperative mivazerol. This new information suggests that the perioperative administration of a-antagonists may have a future role in cardiac protection.

Arrhythmias The perioperative goal of cardiac arrhythmia or conduction disturbance management relates to the desire and need to prevent the deterioration of a given rhythm into one that is incompatible with life, to prevent cardiac ischemia, and to prevent thrombosis and endocarditis. Electrophysiology studies with ablation of aberrant conduction foci may be necessary for women with demonstrable supraventricular arrhythmias. Advanced Cardiac Life Support (ACLS) guidelines can be used for the pharmacologic treatment of perioperative supraventricular arrhythmias. Electrical or pharmacologic cardioversion may be necessary if patients are symptomatic or hemodynamic compromise is present. Beta adrenergic or calcium channel blockade also may be indicated for rate control in the absence of successful electrical cardioversion. Depending on the extent of surgery, patients with atrial fibrillation receiving systemic anticoagulation require evaluation and, perhaps, presurgical reversal. Simple discontinuation of the oral anticoagulant (72 hours prior) usually will suffice. However, fresh frozen plasma or parenteral vitamin K may be necessary

to reverse anticoagulation and ensure hemostasis. Frequent asymptomatic premature ventricular contractions or short runs of ventricular tachycardia may not require antiarrhythmic treatment because they do not, in general, increase perioperative cardiac risk. Although other lesser arrhythmias do not require treatment, the gynecologist should be diligent in pursuing causes of new arrhythmias to rule out myocardial ischemia. Sustained ventricular tachycardia should be treated following ACLS guidelines using lidocaine, procainamide, or other agents such as amiodarone. Care of perioperative arrhythmias is likely optimized with close communication and consultation with appropriate internal medicine, cardiac, or critical care consultants.

Other Situations

Implanted Pacemakers and Implantable Cardiac Defibrillators Occasionally the gynecologic surgeon will encounter a surgical candidate with a pacemaker or implantable cardiac defibrillator. Lack of familiarity with the device and its function can cause perioperative anxiety, particularly when combined with the intraoperative use of electrocautery. General ACC-AHA recommendations include the following. (a) Patients should have the implanted device evaluated before and after surgical procedures to determine the underlying rhythm, program settings, and battery status. If the pacemaker is programmed in a rate-responsive mode, the device should be inactivated during surgery. (b) If patient is pacemaker dependent, the pacing threshold should be determined and evaluated appropriately. (c) Implantable cardiac defibrillators should be turned off during surgery and on again after recovery from anesthesia.

Pulmonary Artery Catheters Invasive cardiac monitoring, including the use of a pulmonary artery catheter, provides instantaneous information, which may contribute to successful postoperative decision making. Unfortunately, the risks of catheter insertion and malfunction are significant and the rate of complications are operator dependent. Additionally, information generated from pulmonary artery catheterization is sometimes esoteric, and decisions based on the cardiac function data are limited by some degree of observer subjectivity. Evidence does not support the routine perioperative use of a pulmonary artery catheter; however, placement should be considered in specific high-risk patient subsets. It may have particular benefit in those in whom the gynecologic disease (e.g., ovarian cancer) or the surgical procedure (e.g., exenteration) is associated with large fluid shifts in those with a compromised medical condition.

Surveillance for Perioperative Myocardial Infarction A significant proportion of perioperative MIs are silent but carry a higher mortality rate (40%–70%) than those occurring in a nonsurgical setting. Electrocardiography, cardiac-specific biomarkers, echocardiography, and radioisotope studies have all been proposed and used for detection of postoperative MIs. Although many of these studies used alone or in combination are effective, false-positive findings are common. The measurement of creatinine phosphokinase myocardial bands alone is less diagnostic of MI than the evaluation of serum troponin levels. Guidelines call for standard surveillance in low-risk patients without documented CAD and normal preoperative ECG or serum biomarker findings. However, patients with high or intermediate clinical risks who have known or suspected CAD and are undergoing high- or intermediate-risk procedures are followed appropriately with an ECG obtained in the recovery room and on the first two postoperative mornings, combined with a cardiac troponin level obtained 24 hours postoperatively and on day 4 or at hospital discharge, whichever comes first. If infarction occurs, rapid reperfusion of the myocardium is the cornerstone of therapy. Unfortunately, thromboembolic therapy cannot be used in the immediate postoperative setting, leaving medical therapy (to maximize cardiac oxygen supply–demand ratio), angiography, and revascularization as the only available therapeutic interventions.

Arrhythmia and Conduction Disorders An arrhythmia should be addressed immediately to determine its etiology and managed according to ACLS guidelines. Tachyarrhythmias should prompt the immediate assessment of potential contributing factors including hypotension, hypoxia, or metabolic derangements. An ECG with rhythm strip should assist in identifying the exact features of the arrhythmia. Narrow-complex regular arrhythmias are likely due to AV node reentry tachycardia or supraventricular tachycardia. Vagal maneuvers should be employed initially. Pharmacologic management consists of administering adenosine or AV nodal blockade using ß-blockers, calcium channel blockers, or class I-A or I-C antiarrhythmic agents. Atrial fibrillation and flutter are unstable rhythms, which often produce a rapid ventricular response. Initial management should be aimed at control of ventricular rate by AV node blockade. Evaluation of the underlying etiology is paramount, and the use of cardioversion should not be entertained until the underlying etiology (e.g., hypothyroidism hypokalemia, hypomagnesemia) has been found and corrected. Infrequent premature ventricular contractions do not require treatment; however, long runs of ventricular tachycardia may require antiarrhythmic therapy, particularly if symptoms or hemodynamic compromise occurs. In general, ventricular arrhythmias should be treated according to ACLS guidelines in conjunction with appropriate cardiology or internal medicine consultation. Cardiac pacing should be considered when warranted by hemodynamic compromise, symptoms including chest pain, or pulmonary edema. The pelvic surgeon assumes great responsibility for perioperative care of the patient with cardiac risks. Although performing the best-suited procedure for the gynecologic condition is imperative, an understanding of the factors that influence overall results, the appropriate intervention, and the timely use of consultants can only improve operative outcome.

PERIOPERATIVE PULMONARY EVALUATION

Postoperative pulmonary complications (PPC) commonly occur following abdominal or pelvic surgery. Pulmonary dysfunction occurs in as many as 80% of patients, and clinically significant PPCs include atelectasis, bronchospasm, the need for prolonged ventilatory support, pneumonia, and worsening pulmonary function due to exacerbation of an underlying problem. The combination of general anesthesia and abdominal surgery results in a morbid alteration of pulmonary physiology, with effects that are compounded by postoperative immobilization, narcotics, or inadequate pain relief.

Patient-related Risk Factors

All patients, even those without underlying known pulmonary disease, remain at significant risk following general endotracheal anesthesia and abdominal surgery. Numerous comorbidities have been linked to the risk of developing PPC (Table 44.7). Although the physiologic and economic costs are significant, unfortunately, the ability to qualitatively or quantitatively evaluate or modulate pulmonary risks is not that of cardiac risks.

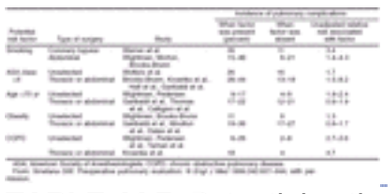

TABLE 44.7. *Potential patient-related risk factors for postoperative pulmonary complications*

Tobacco abuse is a risk factor for PPC, even without clinically apparent pulmonary disease. When compared with nonsmokers, the relative risk of PPC for smokers increases as much as four-fold following abdominal surgery. Although difficult at best, prolonged smoking cessation reduces the risk of PPC by nearly 50% Unfortunately, many of the physiologic effects of smoking are long lasting, and little benefit is gained unless smoking is stopped at least 8 weeks prior to surgery.

A patient who is unable to exercise is at increased risk for PPC following abdominal surgery. The inability to climb a flight of stairs or blow out a match at 6 inches (equals an FEV <1.76 L) suggests a very high pulmonary risk. The Goldman cardiac risk index and the American Society of Anesthesiologists classification reasonably predict pulmonary risk but not necessarily the severity of PPC. Clinically evident chronic obstructive pulmonary disease has been associated with four- to five-fold relative risk of PPC in patients undergoing surgery. Despite common belief, age and obesity, when controlling for other existing comorbidities, do not contribute significantly to the development of PPC.

Active asthma, when severe, can be among the most difficult respiratory conditions to manage, although its presence does not necessarily herald an increase in perioperative bronchospasm if appropriate prophylaxis is administered. Preoperative improvement of small airway patency, as evidenced by freedom from wheezing and a peak flow greater than 80% of predicted value, may minimize pulmonary risk in these patients. A short course of oral steroids may assist in achieving this preoperative goal. Even though history and physical examination may detect those at risk for PPC, no spirometric or other test detects those patients whose abdominal surgery should be canceled. Most patients can undergo surgery even if at high risk.

Although the optimal reduction regimen is unknown, the realization that postoperative pneumonia is extremely morbid and occasionally lethal in even a healthy patient demands adequate attention to perioperative pulmonary management.

Procedure-related Pulmonary Risk Factors

Limitation of surgery to the lower abdomen greatly reduces the extent of pulmonary dysfunction and the risk of developing PPC. Upper abdominal incisions increase this risk by as much as 40% in general surgery patients. A laparoscopic approach significantly reduces the risk of PPC by as much as 33%

The type of anesthesia, anesthetic pharmaceutical agent, and length of surgery play important roles in patient risk. Although reports have shown mixed results, spinal conduction anesthesia (spinal or epidural anesthesia) offers pain relief, improves pulmonary mechanics, and may significantly reduce the chance of PPC when compared with general endotracheal anesthesia.

Preoperative Evaluation

Using findings from the history and physical examination, one can select the majority of patients who are at risk for developing PPC. Although not considered a standard part of routine preoperative evaluation, preoperative pulmonary function testing may be indicated in specific patient subsets. The American College of Physicians has recommended spirometry to determine forced expiratory volume (FEV) in patients who have significant pulmonary risk factors or in those undergoing high-risk surgical procedures, particularly if requiring abdominal or thoracic incisions. Others have suggested minimal benefit of this intervention. These studies may delineate the etiology of pulmonary dysfunction; however, they rarely add value in terms of altering clinical management. Some have recommended that perioperative P_aCO_2 monitoring can assist in the management of those who are chronic CO_2 retainers. Although hypercarbia is a significant risk for PPC, no validated published studies suggest a CO_2 threshold which prohibits surgery. Baseline CO_2 determination may be useful for postoperative ventilator management.

Although individual risk factors are important, several risk indices have been developed. Unfortunately, none has been validated scientifically to quantitate actual pulmonary risks. Included in these indices are abnormal findings during examination, risks related to Goldman cardiac risk assessment, and the Charleston comorbidity index. The time expenditure and expense of any invalidated algorithm are not justified in clinical practice.

Risk Reduction Strategies

The inability to quantify pulmonary risk highlights the importance for the gynecologist to develop clinical acumen in an effort to reduce pulmonary complications. Several risk-reduction strategies have been proposed (Table 44.8). Attention to maneuvers that enhance postsurgical lung expansion combined with adequate pain control to reduce splinting and subsequent atelectasis are the vital components of good postoperative pulmonary care. Preoperative education engages the patient in her care, increases her willingness and active participation, and assists in overcoming a major psychological obstacle to postoperative pulmonary health. The potential benefits of incentive spirometry, chest physiotherapy, and inhalational nebulizer treatments can be explained and understood preoperatively.

Preoperative
Encourage cessation of cigarette smoking for at least 8 weeks prior to surgery.
Treat airflow obstruction in patient with chronic obstructive pulmonary disease or asthma.
Administer antibiotics and delay surgery if respiratory infection is present.
Begin patient education regarding lung expansion maneuvers.
Intraoperative
Limit duration of surgery to less than 3 hours.
Use spinal or epidural anesthesia.[a]
Avoid use of pancuronium.
Use laparoscopic procedures when possible.
Substitute less ambitious procedure for upper abdominal or thoracic surgery when possible.
Postoperative
Use deep breathing exercises or incentive spirometry.
Use continuous positive airway pressure.
Use epidural analgesia.[a]
Use intercostal nerve blocks.[a]

[a]This strategy is recommended, although variable efficacy has been reported in the literature.

TABLE 44.8. *Postoperative pulmonary complication risk-reduction strategies*

RENAL DISEASE

The anatomic relation of the urinary tract to the reproductive organs places it at risk for extrinsic (disease-related) or iatrogenic complications. Although intraoperative technique should be designed to decrease injury risk, perioperative renal insufficiency or failure is among the most foreboding postoperative complications faced by the gynecologic surgeon. The overall risk of urinary tract injury is procedure related and is not uncommon (=2%). Preoperative urologic studies may reveal congenital anatomic or other abnormalities and a rare renal cancer. Importantly, radiographic evidence of ureteral deviation, displacement, or hydronephrosis should not be considered a substitute for good operative technique and cannot be equated with lessening the risk of injury. The 3% incidence of serious adverse events associated with IVP and its lack of cost effectiveness (approximately 833 IVPs necessary to potentially prevent 1 ureteral injury) draw attention to its routine use.

Total cessation of renal function (i.e., bilateral ureteral obstruction) results in a daily increase of 1 to 2 mg/dL in serum creatinine. Although the postoperative dynamics of measured serum creatinine are complex, lesser degrees of elevation (i.e., > 0.3 mg/dL per day) should raise suspicion for a unilateral ureteral injury.

Although overt oliguric renal failure rapidly becomes clinically obvious, lesser degrees of renal insufficiency may occur silently. Although all patients are at risk, the geriatric patient is at particular risk of perioperative renal insufficiency secondary to an age-related decrease in glomerular filtration rate, a decrease in urinary concentrating ability, and narrowed limits for sodium, potassium, and acid excretion. This population should be monitored carefully to maintain euvolemia and minimize the electrolyte load found in many medications.

Research has detailed the predominant biochemical and physiologic changes occurring in the patient with acute renal failure. Recognizing the important effects of medullary hypoxia, tubular cell injury, and alterations associated with diuretics and electrolytes assists in understanding the mechanisms of disease; however, the clinical usefulness of this new information has yet to make a significant impact on daily practice. Thus, the classic approach of evaluating intrinsic renal, prerenal, or postrenal etiologies of perioperative renal failure remains useful. Prerenal azotemia results from any condition which prevents adequate blood flow to the renal unit. Hypovolemia, renal artery atherosclerotic disease, and pharmacologic etiologies (e.g., a combination of ace inhibitors and diuretics) interfere with normal renal perfusion. Hypovolemia may occur as a result of intrinsic cardiac failure, general anesthesia, excessive blood loss, pre-, intra- or postoperative volume contraction, or physiologic vasodilation (e.g., as in septic shock). Most postoperative causes of prerenal azotemia are reversible with the correction of intravascular volume deficits, minimizing the effect of left ventricular dysfunction or the reversal of anesthesia.

Postrenal failure, which can be related to outflow tract obstruction at any level of the renal collecting system, carries significant importance following pelvic surgery. Functional obstruction due to a neurogenic bladder or the inability to void spontaneously may be related to existing deficits or postsurgical changes. Urethral catheterization typically reverses this problem. Postobstructive oliguria related to causes proximal to the bladder requires significant ureteral obstruction. Although this situation can occur with bilateral renal calculi, bilateral or unilateral obstruction can occur after prolapse surgery and it is most frequently encountered with advanced carcinoma of the cervix or in idiopathic retroperitoneal fibrosis. Renal ultrasonography is an easily obtained diagnostic study. Acute management of most causes of postrenal failure involve appropriate diversion of the urinary units, either by transvesical ureteral stenting or percutaneous nephrostomy, to preserve existing renal function.

Lastly, intrinsic renal dysfunction may be due to acute tubular necrosis, interstitial nephritis, and acute glomerulonephritis. Intrinsic renal failure most often is due to renal parenchymal ischemia or the effects of nephrotoxic agents, including aminoglycoside antibiotics, vancomycin, amphotericin B, and cisplatin. Radiocontrast agents and heme pigments are two agents commonly associated with acute tubular necrosis. The former may have intrinsic parenchymal effects and create a diuresis that aggravates existing volume deficits. Interstitial nephritis associated with an allergic drug reaction, autoimmune diseases, infiltrative diseases, and infectious agents represents another form of intrinsic renal failure. When present, withdrawal of the offending agent usually results in reversal; however, glucocorticoid administration may hasten recovery. Finally, acute glomerular nephritis, rare in the gynecologic patient, may also be responsible for intrinsic renal failure and should be entertained in the differential diagnosis of postoperative renal insufficiency, particularly in the absence of other causes.

Diagnosis, Morbidity, and Mortality

The initial diagnostic evaluation of women with perioperative renal insufficiency requires a systematic method of investigation. Intraoperative suspicion and assessment with cystoscopy (or cystotomy) and methylene blue or indigo carmine dye injection is an important initial step. Postoperative hypovolemia may be obvious. However, volume status determination may be difficult when based on history, physical examination, and quantitation of perioperative input and output data. The urinalysis in those with prerenal azotemia shows a high osmolality (>500 milliosmoles per kilogram), a fractional sodium excretion of less than 1%, and proteinuria. Elevated serum blood urea nitrogen out of proportion to creatinine (greater than 20:1 ratio) is strongly indicative of prerenal azotemia. Renal azotemia often is associated with minimal proteinuria; however, urine osmolality will be less than 350 milliosmoles per kilogram and fractional excretion of sodium will be greater than 1. The surgeon's degree of suspicion based on operative findings and events is an important aspect of assessment to exclude postrenal azotemia, particularly when the procedure required a difficult pelvic dissection, repair of a prolapse, or treatment of a malignancy. Renal ultrasonography can determine quickly the extent of unilateral or bilateral hydronephrosis and eliminate the possibility of clinically significant ureteral ligation or kinking. If an ultrasonograph is not diagnostic, an IVP may answer important questions, although the administration of contract may worsen the clinical condition of a patient with intrinsic renal insufficiency.

Nonoliguric and oliguric renal insufficiency can occur in the postoperative patient, and physicians should not assume that “adequate” urine production indicates intact renal function. Importantly, oliguric renal failure portends a worse prognosis than nonoliguric renal failure. Using low-dose dopamine to increase renal perfusion (and convert an oliguric problem to a nonoliguric situation) has no proven efficacy and, if unsuccessful, should be discontinued, because it creates a propensity for cardiac

arrhythmias and alters blood supply to other vital organs.

The morbidity and mortality (fivefold) of renal failure in the postoperative patient is higher than that of individuals treated medically. These adverse outcomes probably are related to many factors, from perioperative ischemic insults to the volume depletion and other changes associated with contrast used for preoperative testing (i.e., IVP, CT) or mechanical bowel preparation. Common predisposing comorbid illnesses, including diabetes mellitus, hypertension, and cardiopulmonary insufficiency, carry their own inherent risks for causing renal insufficiency. Medications such as ace inhibitors and nonsteroidal antiinflammatory drugs, used frequently in the perioperative patient, also increase risk.

Methods to promote perioperative renal protection include practicing good surgical technique, limiting the use of nephrotoxic drugs, maximizing cardiopulmonary function by paying attention to intraoperative blood and volume losses, and replacing intravascular losses. Although invasive monitoring to guide fluid replacement may be helpful, its use and the administration of pharmacologic agents (dopamine, mannitol, furosemide) or other interventions has not been conclusively proven beneficial. Hopefully, continued research on adenosine and prostaglandin administration will prove fruitful.

Women with chronic renal insufficiency are at risk for acute renal insufficiency during the perioperative period. Preoperative internal medicine or nephrology consultation should be considered in an attempt to optimize volume, use dialysis strategically, and manage coexisting morbidities.

Management

Dialysis is the cornerstone of perioperative management of renal insufficiency once postrenal obstructions are relieved. Specialists should be consulted to treat acidemia, recalcitrant hyperkalemia, symptomatic volume overload, or impending cardiovascular failure. All medication dosages and schedules should be reviewed regularly to maximize efficacy and minimize toxicity.

In conclusion, although perioperative renal failure represents a significant danger to the operative patient, insufficient scientific data exist to identify patients at risk and to develop guidelines for postoperative renal surveillance and management. The surgical community awaits a more specific definition of renal failure, additional research regarding renal protection strategies, and better, less invasive treatments for patients with perioperative renal insufficiency.

WOUNDS AND INCISIONS

Once surgery has been deemed appropriate therapy, selecting the operative approach is possibly the most important initial surgical decision. Choice of approach is related primarily to physician bias and comfort, related to previous teaching and experience. However, surgical indications, disease process, previous abdominal incision (and resultant adhesions), patient preference, and existing medical comorbidity should be considered carefully prior to solving this sometimes complex problem. Adequate intraoperative exposure must be a primary consideration. Although a vertical lower midline incision should be the first consideration, some, particularly those with a large body mass index, may be best managed with an upper abdominal incision, avoiding trauma to the infection-prone panniculus. A panniculectomy may be necessary or appropriate. It is evident that many, if not most, gynecologic (even oncologic) and obstetric procedures can be completed safely through a more cosmetic transverse lower abdominal approach. The transverse approach may offer the additional advantage of less pain and diminished postoperative pulmonary dysfunction. Although the Pfannenstiel incision, when combined with a table-stabilized self-retaining retractor, will often suffice, preoperative consideration of a Maylard (rectus muscle splitting) incision or intraoperative conversion to a Cherney (rectus splitting–incision at pubic insertion) may be necessary. Regardless of the initial approach, to avoid hernia risks the incision should not be placed perpendicular to a previous incision. Placing the long axis of the incision in the direction of maximal skin tension creates the most aesthetically pleasing scar.

A more contemporary approach to numerous gynecologic procedures involves laparoscopy. Many, if not most, routine procedures and a significant proportion of complex procedures used for the management of benign or malignant disease can be safely completed laparoscopically, with less physiologic stress, less pain, and a more rapid return to normal activity. Although there are many correct answers to surgical incision placement, performing an incomplete procedure because of a compromised incision is an unacceptable alternative and should be avoided by immediate conversion to a more accommodating approach (e.g., hand-assisted laparoscopy or an open operation).

Operative laparoscopy and abdominal approach are associated with additional inherent surgical risks, so they should not replace vaginal surgery. Although laparoscopy may be complementary to “convert” abdominal procedures and to complete (extensive) operations, stand-alone vaginal surgery should remain an important arm of the obstetrician-gynecologist's surgical repertoire, because it results in less morbidity. Vaginal surgery will suffice for many, if not most, gynecologic procedures. Although lesser invasive (laparoscopic or vaginal) surgical approaches are associated with diminished physiologic stress, their use does not negate the need for appropriate preoperative evaluation, preparation, and management.

Wound Preparation

Although many rituals of preoperative skin preparation exist, only a few add documented value to patient care. Preoperative hair removal is not deemed necessary; however; if performed, clipper removal at a time close to surgery avoids microinjury and is associated with a lower risk of wound infection than is razor preparation.

Routine preoperative skin antisepsis is necessary to minimize the infectious potential of normal flora, as well as of pathogens. Bacterial concentrations in moist body areas (i.e., perineum) reach $10^{6}/cm^{2}$ of tissue and are greater than those in drier (abdomen) areas, reaching $10^{3}/cm^{2}$ of tissue. These areas also harbor different ratios of aerobic to anaerobic bacteria. Preparation solutions differ significantly in the immediate or late (>3 hours) mean bacterial reduction. Regardless of solution used, the preparation should be allowed to “set” for no less than 5 minutes to attain its maximal activity and bacterial reduction.

Surgical Technique

Creating an abdominal incision with a single bold knife stroke through the skin and subcutaneous tissue avoids a stairstep effect in the subcutaneous tissues. The use of multiple knife blades to create the incision offers little benefit and contributes to expense. Avoiding the creation of subcutaneous dead space is important because dead space increases the risk of wound infection and poor wound outcome, even when closed. The use of electrical or laser coagulation techniques to create an incision saves little time and adds little value. Their use creates “devitalized” tissue, which may contribute to an adverse wound environment and increase the risk of surgical site infection, resulting in acute or late poor wound outcome. Surgical technique may be of specific impact in those already at high risk because of thick (=3.0 cm) subcutaneous tissues.

The rationale for proper suture selection rests on the need for tensile strength, the duration of retained tensile strength, and the biologic effects on the involved tissue (Table 44.9). In general, the suture's chemical composition is more important than the physical configuration, although braided and multifilament sutures may potentiate infection. When compared with other absorbable materials, polyglycolic acid suture is associated with less inflammation and decreased pain, and in animal models it lessens the risk of infection. The incorporation of permanent suture material creates an increased risk of (˜10%) chronic wound problems (i.e., pain, wound sinus); however, their use is associated with a lessened risk of developing a fascial hernia. Vascular pedicle ligation can be accomplished safely using short-term absorbable sutures, because the risk of bleeding (1.5-mm vessels) is minimal 96 hours after ligation. There is little clinical benefit to be gained from peritoneal closure.

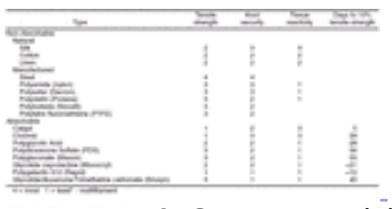

TABLE 44.9. *Suture material*

Suture size selection should be based on specific needs. Excluding fascial closure, there is little rationale for using suture larger than 2-0. Additional wound suture material increases the inflammatory response and may predispose to infection, and the tensile strength of a 2-0 absorbable suture is adequate for nearly all pedicle ligations.

Although it seems basic, correct suture-tying techniques can contribute to surgical outcome. Complex knots (e.g., surgeon's) impart greater tensile strength than multiple simple square knots. Avoiding excess knots minimizes the amount of suture material, lessens inflammatory volume, and potentially decreases the risk of poor

wound outcome. Although all knots should be secure, tightly tied fascial sutures strangulate the incorporated tissues, increase ischemia, and lessen wound strength. Although good surgical technique always has been tied to attempts to prevent adhesion formation, the development of hyaluronic acid products for adhesion prevention has opened new avenues.

The astute surgeon recognizes the different tissue-related healing curves and selects a suture designed to promote good outcome. Although short-term wound results are important, the risk of late problems (e.g., hernia) can be minimized with appropriate closure technique. A suture length–to–wound length ratio of greater than 4 decreases the risk of hernia formation and can be accomplished by placing sutures at least 1.5 cm from the fascial edge and 1.5 cm apart.

Subcutaneous tissue closure is typically unnecessary. If required to lessen tension on wound edges, small minimally reactive sutures should be chosen. Closed suction and subcutaneous drain placement are of little apparent benefit, and drains increase the risk of surgical site infection.

The best method or material for epithelial approximation should be related to the potential time, cost, need for return visits, and cosmetic results.

GASTROINTESTINAL CARE

Perioperative management of the gastrointestinal tract during pelvic surgery focuses on the following three aspects: (a) avoidance of operative injury and reduction of subsequent complications, (b) the role of early feeding, and (c) the appropriate diagnosis and management of patients with liver disease.

Excluding the need to address important aspects of coexisting intestinal diseases (e.g., inflammatory bowel disease) and issues related to cancer screening, gastrointestinal preparation values the decisions related to the incorporation of bowel preparation. Mechanical intestinal preparation offers a number of potential benefits (Table 44.10). Although suboptimal preparation may increase the risk of contamination, most pelvic surgeons are inclined to use a mechanical bowel preparation when the risk of manipulation or injury is substantial. Several regimens are used. Fleets Phospho-Soda (90 mL) is cost effective, well tolerated, and gives excellent results.

Remove fecal material.
Lower bacterial load.
Improve handling.
Reduce spillage, contamination.
Lessens risk of mechanical disruption.
Facilitates intraoperative palpation.
Allows intraoperative colonoscopy.
Aids laparoscopic handling.

TABLE 44.10. *Mechanical bowel preparation potential benefits*

Intestinal bacterial flora colony counts are high in the colon and distal ileum, decreasing dramatically in the more proximal small intestine unless obstructed. Classically the mechanical regimen is combined with oral antibiotics, typically including erythromycin or neomycin or both, to reduce luminal bacterial content. Although debate persists, the benefit of oral antibiotics over intravenous antibiotics is apparently small, and oral use is associated with significant gastrointestinal symptoms.

Early Oral Feeding and Nasogastric Suction

Nasogastric suction often has been incorporated into the postoperative care of women undergoing difficult pelvic operations. Reports not only question its use but deny its benefit as it relates to symptomatic relief, lessened risk of ileus, need for reinsertion, and protection of intestinal anastomosis. Regardless of procedure, fewer than 10% of patients require nasogastric suction, and it appears to be of little benefit to the other 90%. As importantly, early oral feeding is well tolerated, does not increase the risk of ileus or symptoms, and may shorten hospital stay.

Liver Disease

The preoperative detection of liver disease may not be easy, because serum enzymes (transaminase) may not be elevated in patients with late-stage disease. However, the historical and physical findings of significant alcohol intake or exposure to hepatotoxins should raise suspicion. Physical evidence of malnutrition, signs of hepatic encephalopathy, or jaundice usually signify advanced disease. Laboratory evidence of hepatic dysfunction includes an elevated (10-fold) increase in serum transaminase levels, abnormal coagulation study results, elevated total bilirubin values, and low serum albumin levels. Classic surgical risk indices have been based on the Child classification, initially detailed in the 1960s to determine risks associated with surgical management of those with esophageal varices. These indices have been applied to the risks in those with liver disease who are undergoing abdominal surgery.

Perioperative management of women with hepatic disease requires particular attention to drugs (and to their dosing and scheduling) which are metabolized by the liver. For example, patients receiving benzodiazepines and narcotics are at risk for drug accumulation and overdosage due to poor hepatic clearance.

Patients with acute liver disease (vital or other) should not undergo elective surgery until stabilization of liver dysfunction has been secured. Those with chronic liver disease and hepatic encephalopathy in an attempt to stabilize liver function may benefit from subspecialty consultation.

INFECTION

Perioperative surgical site infection occurs in the practice of every gynecologic surgeon. Knowledge of prophylactic measures and the optimal treatment regimen for those with active or acquired infection are expected of every pelvic surgeon. Numerous factors including obesity, diabetes, use of steroids, and even length of preoperative hospitalization are all risk factors for infectious perioperative morbidity (Table 44.11). Although addressing each of them is beyond the scope of this chapter, numerous technical methods can modulate these risks. Proper use of prophylactic antibiotics lessens infectious risks in many pelvic procedures. Numerous antibiotics and regimens are efficacious. In most situations a single dose, administered properly, is as effective as most multiple regimens. However, in longer procedures (i.e., =3 hours) when the duration of the procedure is longer than the half-life of the chosen drug or if blood loss exceeds 1,500 milliliters, repeat dosing improves its benefit. The use of antibiotics prophylactically can result in patient hypersensitivity and the development of resistant strains of bacteria. Although careful thought is never to be discouraged, the potential benefit of controlling operative site infection with antibiotic prophylaxis usually outweighs other patient risks. The authors use a second-generation cephalosporin, which has better anaerobic coverage than first-generation cephalosporins and minimizes the loss of Gram-positive coverage that typically occurs with third-generation cephalosporins, recognizing the lack of enterococcus coverage. Patients allergic to penicillin have an 8% risk of cross-reactivity with cephalosporins, but anaphylaxis risk is estimated at 0.0001% to 0.1% in non–penicillin-allergic patients to 0.02% in penicillin-allergic patients. Doxycycline or metronidazole represents an excellent alternative in patients undergoing abdominal or vaginal hysterectomy. Although the benefit of antibiotic prophylaxis has not been demonstrated in patients undergoing laparoscopy-assisted hysterectomy, it would seem prudent to use these drugs. The recommendation of prophylaxis for other procedures varies (Table 44.12). Specific prophylaxis for those women at risk for endocarditis is imperative (Table 44.13).

Surgeon Related	Patient Related
Preoperative Stay	Age
Preparation	Nutritional Status
Patient	Diabetes
Staff	Renal Insufficiency
Incision	Hepatic Insufficiency
Placement	Radiation Therapy
Method	Chemotherapy
Hemostasis	Hypoxemia
Suture Material	Sepsis
Vasoconstrictors	Immunocompetence
Drains	Obesity
Closure Technique	
Dressing	
Antibiotic Prophylaxis	
Experience	

TABLE 44.11. *Infection risk factors*

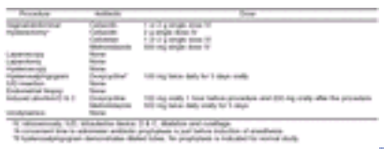

TABLE 44.12. *Antimicrobial prophylactic regimens by procedure*

TABLE 44.13. *Prophylactic regimens for prevention of endocarditis in susceptible patients undergoing genitourinary or gastrointestinal procedures.*

Treatment for Existing Infection

Prophylactic drugs are administered to patients in the absence of preoperative evidence of active infection. However, gynecologic patients with an obvious infection prior to surgery should receive an antibiotic treatment regimen appropriate for the type of infection. For example, patients with tuboovarian abscess should be treated with a broad-spectrum antibiotic regimen covering Gram-positive, Gram-negative, and anaerobic bacteria with a single or multiple drug regimen, according to patient acuity.

Postoperatively, antibiotics should be given for documented infection. It is clear that most postoperative febrile illness is not related to a documented infection. When postoperative fever, leukocytosis, and clinical picture suggest postoperative infection, an examination to identify potential sources should be performed. Source-directed therapy is appropriate. Adjunctive procedures, including CT or ultrasonographically guided drainage, may hasten recovery in patients with fluid collections or abscesses. In general, patients should receive adequate, broad-spectrum antibiotic treatment prior to surgical intervention.

THROMBOEMBOLISM

Thromboembolic phenomena, including deep venous thrombosis (DVT) and pulmonary embolism (PE), are inevitable following gynecologic surgery. A 1988 meta-analysis estimated a 6% to 7% proximal DVT risk and a 0.5% to 0.8% fatal PE risk in unprotected patients over 40 years of age undergoing abdominal surgery. This risk makes surgeons anxious because of the difficulty of diagnosing venous thromboemboli and the potential catastrophic outcome of fatal PE.

The impact and importance of postoperative thromboembolic prophylaxis is no longer a question. In a survey by the American College of Surgeons, approximately 96% of surgeons claimed they regularly used antiembolic prophylaxis. However, patient poll and chart review suggest that only one third of patients received adequate prophylaxis.

Despite the perception that venous emboli are a rare and unimportant event, all gynecologic patients should be considered at risk. The misconception regarding incidence is fostered by the high occurrence (˜50%) of DVT and PE postdischarge. Additionally, surgeons have been anxious about the potential side effects of prophylaxis, because low-dose unfractionated heparin or low-molecular-weight heparin administration has been associated with postoperative bleeding and wound hematomas. The infrequent occurrence of heparin-induced thrombocytopenia also has created some anxiety regarding prophylaxis. Finally, the initial or primary cost of thromboprophylaxis has deterred some from its use, although some have agreed that prophylaxis is cost effective. Thromboembolic phenomena can be clinically silent, whereas complications related to prophylaxis are not easily missed by the gynecologic surgeon or the patient. Furthermore, according to the Rochester Epidemiology Project and other studies, the incidence of PE and DVT is increasing as women age. Prophylaxis in the gynecologic practice will become more important during the next decade.

Despite these common misperceptions, principles of good gynecologic perioperative care demand careful attention to the role and benefit of thromboprophylaxis. The American College of Chest Physicians published guidelines regarding perioperative thromboprophylaxis. Risk factor stratification (Table 44.14) allows delineation of low risk, moderate risk, high risk, and highest risk categories, with coincident risk of developing DVT, clinical PE, and fatal PE. Proposed recommendations for thromboprophylaxis strategies ranged from aggressive mobilization in the lowest risk patients, to the use of pneumatic compression hose, elastic stockings, or pharmaceutical methods with heparin (unfractionated or low-molecular- weight). Patients at highest risk are deemed candidates for combined mechanical and heparin prophylaxis.

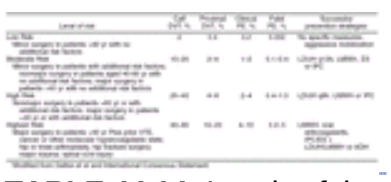

TABLE 44.14. *Levels of thromboembolism risk in surgical patients without prophylaxis*

A report suggested that the frequency of DVT following gynecologic procedures was approximately 16% (a range of 4%–38%). Fatal PE was reported in only 0.4% of the pooled sample. The cited risks for postoperative thromboembolic event included age greater than 40, history of venous embolism, surgery for cancer, and an abdominal surgical procedure. It was suggested that gynecologic oncology patients were at particularly high risk, fulfilling Virchow's triad of advanced age, cancer, and the hypocoagulable state; venostasis related to pelvic mass compression; vascular injury due to lymph node dissection; postoperative immobility; and the thrombogenic effect of chemotherapy. Importantly, the authors noted a 75% reduction in fatal PE (from 0.4% to 0.1%) with the use of appropriate thromboprophylaxis. The strongest evidence presented for thromboprophylaxis was a relative risk reduction of 64% with use of low-dose unfractionated heparin (reductive from 20% of patients to 7%). A dose response was suggested. Gynecologic cancer patients derived less protection than the noncardiac patients from the twice daily administration of low-dose unfractionated heparin. It would appear that dosing 3 times a day is more appropriate. Although of concern, the potential risk of bleeding complications was not reproducible. Importantly, aspirin use was deemed insufficient for thromboprophylaxis. Low-molecular-weight heparin has been associated with fewer bleeding complications and is being studied in comparison with low-dose unfractionated heparin. However, low-molecular-weight heparin, although extensively studied, did not meet the criteria for study inclusion by the American College of Chest Physicians, so it was not included in their recommendations.

In general, patients undergoing brief procedures require no prophylaxis except early mobilization. Patients having major gynecologic procedures for benign disease without additional risk factors should receive low-dose unfractionated heparin twice daily, low-molecular-weight heparin, or perioperative external pneumatic compression hose. For the highest risk patients, dual prophylaxis with either low-dose unfractionated heparin plus elastic stockings or external compression hose, low-dose unfractionated heparin 3 times daily, or low-molecular-weight heparin given in daily doses of at least 3,400 anti-Xa units may be useful for DVT/PE prevention. The duration of antithrombotic therapy in the highest risk patients is being studied, because there is some speculation that anticoagulation continued beyond the intermediate postoperative period may reduce the risk of thromboembolic phenomena as well as the risk of death.

NEUROLOGIC COMPLICATIONS

Avoiding serous perioperative neurologic sequelae, including stroke, seizure, altered mental status, and operation-associated nerve injury, is a vital aspect of perioperative management. Most general anesthetics adversely affect central nervous system function. Even short-term anesthetic use impairs psychomotor performance for 5 hours and sleep patterns for 24 hours or more. Women at risk for cerebrovascular disease (as evidenced by transient ischemic attacks, peripheral vascular disease, or other events) may require specific preoperative evaluation and neurologic consultation. Although an asymptomatic carotid bruit may signal the need for imaging studies or consultation, it does not, by itself, increase perioperative risk. Presurgical neurologic and radiologic evaluation, extracranial carotid endarterectomy, systemic anticoagulation, and platelet inhibition are some of the potential perioperative risk-sparing procedures to be considered. Central nervous system function is important for those women with arterial disease who are at risk for other thrombotic events and, regardless of risk, the adverse effect of perioperative hypotension (even of short duration) should be avoided. The overall risk of recurrent stroke approaches 3.0% but, fortunately, the risk of stroke is 0.2% to 0.7% in those with no such history.

Cerebral blood flow is unstable and brain metabolism is depressed for 6 to 8 weeks following a completed stroke, making it prudent to avoid any significant elective

operations during this interval. The risk of a second infarct may approach 20%, and the mortality rate is high (˜25%). Preoperative central nervous system (CNS) scanning may assist in determining the time of resolution of the initial infarct, when operative procedures are less likely to result in repeated infarct. Emergency procedures in those at risk for CNS infarct should completed in a perioperative environment that maintains an elevated blood pressure and avoids events that may increase the risk of CNS hypoperfusion.

Vertebral basilar ischemic episodes are associated with a lower perioperative stroke risk than is carotid ischemia. Although perioperative neurologic evaluation may be appropriate, these patients usually are managed medically, with minimal surgical risks.

Operative Neurologic Deficits

Nearly 2.0% of gynecologic procedures are associated with postoperative lower extremity neurologic deficits, regardless of attention paid to preoperative care or positioning. Multiple nerves are at risk, regardless of positioning, surgical duration, or approach. Mechanisms of nerve injury include prolonged compression (e.g., femoral nerve), excessive traction, stretch (e.g., sciatic nerve) or transection (e.g., lateral femoral cutaneous nerve). Regardless of the extent of injury, attention to positioning, or retractor placement, these problems occur and are managed by evaluation and rehabilitation. Fortunately, most resolve. Attention to minimizing hip flexion and external rotation potentially lessens the risk of traction injury. Ilioinguinal and iliohypogastric nerve injuries can be diagnosed with relief after local infiltration of nerve block or excision.

SUMMARY POINTS

- The primary goal of the pelvic surgeon involves prospective preoperative recognition, evaluation, and management of existing medical comorbidities. Every pelvic surgeon should commit to the development of operative techniques that form a surgical skill set geared to the safe completion of indicated surgical procedures.
- Appropriate consultation should be sought if the level of qualification does not fit the necessary procedure.
- A thorough, multisystem physical examination is an essential part of the preoperative evaluation to detect important coexisting disease. The suspicion or diagnosis of coexistent morbidities which have not been diagnosed previously requires preoperative investigation. Laboratory and radiologic investigation should be conducted patiently and procedures directed in a safe, cost-effective manner.
- Coexisting or occult cardiac disease represents a significant contributor to perioperative morbidity. Particular attention to the detection, evaluation, and management of cardiac risk factors including CAD, hypertension, congestive heart failure, valvular disease, arrhythmias, and hypercholesterolemia is imperative. Particular attention to ACLS guidelines is important. Perioperative assistance by personnel experienced in cardiac care should be invoked when necessary.
- Perioperative pulmonary care is an important concern. The procedure should be designed to minimize pulmonary risks when possible. Postoperative attention to pulmonary toilet may render the best possible outcome.
- Perioperative renal failure is associated with high morbidity and mortality. No intervention, including prophylactic low-dose dopamine, mannitol, or furosemide therapy, has been shown to be of any benefit in reducing the incidence of perioperative renal insufficiency.
- The optimal surgical incision is chosen according to the procedure done, existing comorbidity, disease process, and patient preference. Appropriate preoperative skin antisepsis is necessary and, in combination with intravenous antimicrobial agents, will decrease the incidence of wound infection. Good surgical technique is mandatory for wound health and maximizing patient outcome.
- Classically, bowel preparation (mechanical, with or without antibiotic) is undertaken prior to many gynecologic procedures. Nasogastric suction has not been shown to lessen the risk of ileus, and only 10% of patients require insertion of a nasogastric tube postoperatively. Most patients can be managed without nasogastric suction.
- Proper use of prophylactic antibiotics lessens infectious risks in many pelvic procedures. Single-agent broad-spectrum antibiotic use, such as cephalosporin, doxycycline, or metronidazole, appears to be safe and effective for women undergoing abdominal or vaginal hysterectomy.
- The American College of Chest Physicians published guidelines regarding perioperative thromboprophylaxis. Patients at low risk should be mobilized aggressively postoperatively. Those at moderate and high risk should use pneumatic compression hose, elastic stockings, or pharmaceutical methods. Patients at highest risk may also benefit from combined mechanical and pharmaceutical prophylaxis.
- Approximately 2% of gynecologic procedures are associated with postoperative lower extremity neurologic deficits. Special attention should be paid to patient positioning, surgical duration, proper use of surgical retractors to prevent excessive traction and stretch, and careful operative techniques.

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Chapter 45

John O.L. DeLancey and Kris Strohbehn

Pelvic Organ Prolapse

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INTRODUCTION

Pelvic organ prolapse is a condition unique to the field of obstetrics and gynecology. It has helped define our specialty and continues to lie in the exclusive province of the obstetrician-gynecologist. Although often discussed as a purely mechanical phenomenon, prolapse is associated with significant functional problems. Stress urinary incontinence, micturition difficulties, and problems with defecation are all associated with prolapse. These functional derangements are not simply results of altered support of the bladder and rectum but have to do with the innervation and musculature of the urinary and intestinal tracts, as well. This chapter reviews the structural and functional aspects of prolapse necessary to understand and manage these conditions.

PELVIC FLOOR AND THE NATURE OF GENITAL PROLAPSE

The pelvis lies at the bottom of the abdominopelvic cavity, and the pelvic floor closes the canal within the bony pelvis (Fig. 45.1). The pelvic floor forms a supportive layer that prevents the abdominal and pelvic organs from falling through the opening within the pelvic bones. Its structural role can best be appreciated by considering a surgeon's hand placed through a transabdominal incision that pushes caudally on the pelvic organs. All of the structures that prevent this hand from passing through the pelvic canal constitute the pelvic floor. In addition to this supportive role, the pelvic floor must accommodate conception and parturition, while also controlling storage and evacuation of urine and feces. To understand the pelvic floor and genital prolapse, it is necessary to understand the mechanical strategies that evolution has put in place to prevent downward descent of the pelvic organs, as well as the process by which genital prolapse occurs. As Victory Bonney pointed out, the phenomenon of prolapse is similar to the maneuver that a scrub nurse uses to evert the in-turned finger of a surgical glove (Fig. 45.2). Compressing the air within the glove drives the invaginated finger outward in much the same way that increases in intraabdominal pressure force the vagina and the uterus to prolapse. It is not the weight of the uterus that is important in the development of prolapse, but rather the forces placed on the pelvic floor by increases in intraabdominal pressure.

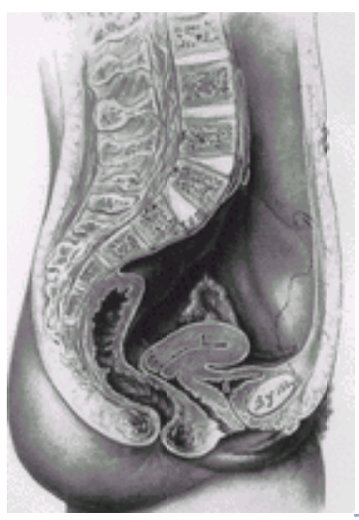

FIG. 45.1. Sagittal section of the abdomen and pelvis shows the relation of the pelvic floor to the abdominal cavity. (From Kelly HA. *Gynecology.* Baltimore: Appleton

and Co, 1928:64, with permission.)

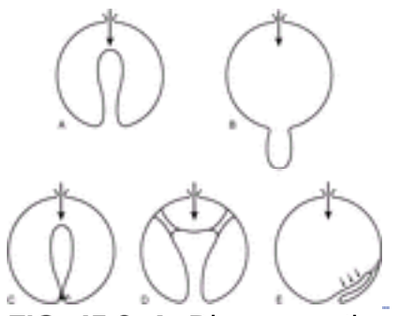

FIG. 45.2. A: Diagrammatic representation of the vagina within the abdomen shows how increases in abdominal pressure *(arrow)* force the vagina to prolapse. **B:** This prolapse may be prevented by **(C)** constricting the lower portion of the vagina, **(D)** suspending the vagina from the pelvic walls, and **(E)** forming a flap-valve closure, wherein the vagina is pinned against surrounding structures.

Two mechanical principles explain how the pelvic floor prevents prolapse (see Fig. 45.2). First, the uterus and vagina are attached to the walls of the pelvis by a series of ligaments and fascial structures that suspend the organs from the pelvic sidewalls. Second, the levator ani muscles constrict the lumina of these organs, forming an occlusive layer on which the pelvic organs may rest. It is a combination of these two factors—suspension of the genital tract by the ligaments and fasciae and closure of the pelvic floor by the levator ani—that holds the vagina over the levator ani muscles and forms a flap-valve closure. This flap-valve mechanism is instrumental in keeping the posterior cul-de-sac closed and preventing the development of an enterocele.

Epidemiology of Surgically Managed Pelvic Organ Prolapse and Urinary Incontinence

Prevalence

Olsen and colleagues reported the prevalence of surgery for pelvic organ prolapse and urinary incontinence within a defined population. They studied 149,554 women over 25 years of age who were members of the Kaiser Permanente Northwest Health Maintenance Organization. During 1995, they identified 384 women who had surgical treatment for either pelvic organ prolapse or urinary incontinence, or both of these problems. A woman's lifetime risk for needing a single operation by age 80 years was 11.1%. Among this group of women, there was great variety in types and sizes of prolapse (Table 45.1), and the overall incidence of surgery increased with age (Fig. 45.3). The higher incidence was primarily due to the increase in surgery among older women for prolapse rather than for incontinence. Repeated operation was remarkably common, with 29.2% of patients requiring a second surgery. There is increasing risk of pelvic organ prolapse with subsequent parity (Fig. 45.4), and the study of the obstetric factors that cause pelvic floor injury has been neglected.

TABLE 45.1. *Preoperative prolapse severity according to operative site*

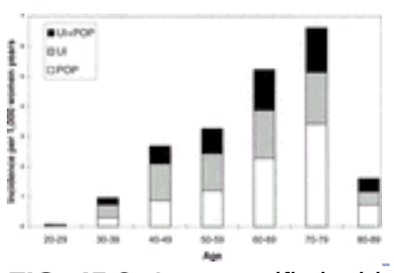

FIG. 45.3. Age-specific incidence of surgery for pelvic organ prolapse or urinary incontinence. (From Olsen AL, Smith VJ, Bergstrom JO, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501, with permission.) UI, urinary incontinence; POP, pelvic organ prolapse.

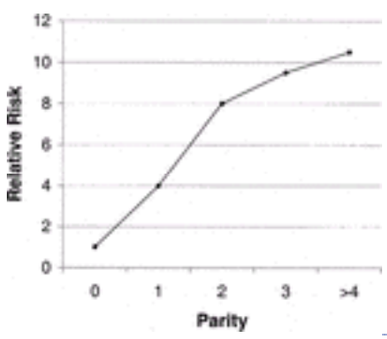

FIG. 45.4. Increase in risk of needing surgery for prolapse with increasing parity. (From Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association study. Br J Obstet Gynaecol 1997;104:579–585, with permission.)

These data show the remarkable frequency with which women require surgery for incontinence and prolapse but certainly underestimate the prevalence of these problems within the population. One would expect that many women who have prolapse and incontinence choose not to have surgery, so these data represent only those women operated on. Therefore, serious consideration needs to be given these conditions.

Vaginal Delivery and Pelvic Organ Prolapse

It is commonly accepted that vaginal delivery increases the likelihood that pelvic organ prolapse will develop. Mant, using the Oxford family planning cohort, found that the likelihood of a woman developing prolapse increased approximately eight-fold after two vaginal births and about 12-fold with four or more vaginal deliveries. Timonen and co-workers compared information concerning parity in 1,422 patients operated on for prolapse in their hospital between 1955 and 1965 with national parity data in Finland; these data are displayed in Figure 45.5. Only 4% of women with prolapse are nulliparous, while among the Finnish population 13.3% of women are nulliparous. In addition, they evaluated the size of the largest infant delivered by women in whom prolapse subsequently developed (Fig. 45.6) and compared that with birthweight information for Finland (N = 52,955) during the same period (1957–1958). These data lend some sense of the degree to which vaginal birth influences pelvic organ prolapse.

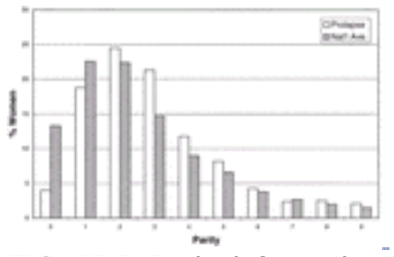

FIG. 45.5. Parity information for women operated on for pelvic organ prolapse compared with national average. (From Timonen S, Nuoranne E, Meyer B. Genital prolapse: etiological factors. Ann Chir Gynaecol Fenn 1968;57:363, with permission.)

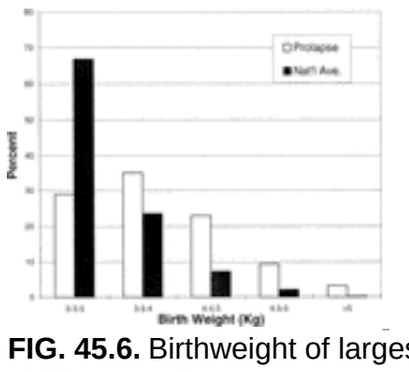

FIG. 45.6. Birthweight of largest infant delivered vaginally to women with pelvic organ prolapse and normative birthweight data for Finland. (From Timonen S, Nuoranne E, Meyer B. Genital prolapse: etiological factors. Ann Chir Gynaecol Fenn 1968;57:363, with permission.)

BASIC ANATOMY AND PATHOPHYSIOLOGY OF THE PELVIC FLOOR

Viscerofascial Layer

The topmost layer of the pelvic floor is a combination of the pelvic viscera and their connections to the pelvic walls and will be referred to as the viscerofascial layer. Although it is common to speak of the fasciae and ligaments as separate from the pelvic organs, unless these fibrous structures have something to attach to (e.g., the pelvic organs) they have no structural integrity.

The uterus and vagina are attached to the pelvic walls by the fibrous tissue referred to as the *endopelvic fascia.* It forms a sheetlike mesentery that is continuous from the uterine artery to the point at which the vagina fuses with the levator ani muscles as it passes through the urogenital hiatus. The tissues that connect the uterus are called the *parametria*, and those that attach to the vagina are the paracolpium. Although they are given regional names, they are actually one continuous entity. The parametria comprise the cardinal and uterosacral ligaments. These are two different elements of the same tissue (Fig. 45.7). The uterosacral ligaments are the visible and palpable medial margin of the cardinal–uterosacral ligament complex. As is true of the remainder of the parametria, they contain smooth muscle, nerves, and blood vessels and are not the same type of tissue seen in the fascia of the rectus abdominus muscle, which is dense regular connective tissue.

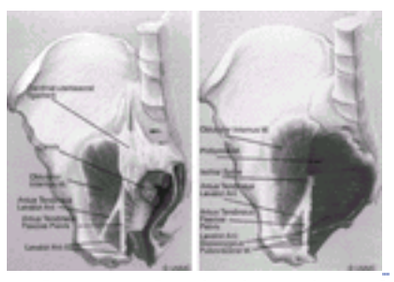

FIG. 45.7. Sagittal section of the pelvis shows the support structures of the genital tract. **A:** The bladder, urethra, and uterine corpus (above the cervix) have been removed. **B:** All of the pelvic organs have been removed to show the levator ani muscles.

Opposite the external cervical os, the sheet of tissue that attaches the genital tract to the pelvic wall arbitrarily changes name from the parametrium to the paracolpium. The paracolpium has two portions (Fig. 45.8). The upper portion (i.e., level I) consists of a relatively long sheet of tissue that suspends the vagina by attaching it to the pelvic wall in an area similar to that of the cardinal–uterosacral ligament complex. It is this portion that prevents the upper vagina from prolapsing after the uterus has been removed.

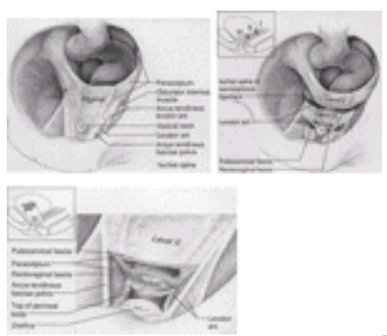

FIG. 45.8. Support structures of the vagina after hysterectomy. The bladder has been removed to expose the vagina. **A:** The paracolpium. **B:** The different levels of support structures. **C:** The details of the pubocervical and rectovaginal fasciae after a wedge of vagina and urethra has been removed **(inset).** (From DeLancey JOL. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992;166:1717, with permission.)

In the midportion of the vagina, the paracolpium attaches the vagina laterally and more directly to the pelvic walls (i.e., level II). This stretches the vagina transversely between these two lateral attachments (see Fig. 45.8B). This arrangement has functional significance. The structural layer that supports the bladder (i.e., pubocervical fascia) is composed of the anterior vaginal wall and its attachment through the endopelvic fascia to the pelvic wall. The term *fascia* is used commonly, but this is not a layer separate from the vagina. A term has been proposed for this layer, the *fibromuscular layer* of the vagina, that contains both smooth muscle and connective tissue. We use these terms interchangeably in the remainder of the text, because the surgeon generally refers to this layer as *fascia.* Similarly, the posterior vaginal fibromuscular layer and its connection to the pelvic walls forms the restraining layer that prevents the rectum from protruding forward. In the distal vagina (i.e., level III), the vaginal wall is attached directly to surrounding structures without any intervening paracolpium.

The support that lies under the urethra has special importance for urinary incontinence. The endopelvic fascia in this region is better developed and is tougher than the tissues of the upper vagina, in the area under the bladder. This provides better support for the vesical neck than for the bladder. This layer of suburethral endopelvic fascia attaches laterally to the arcus tendineus fasciae pelvis and also to the medial border of the levator ani muscles. Loss of this normal support of the urethra at the vesical neck is responsible for stress incontinence of urine.

Levator Ani Muscles

Below the uterus, vagina, bladder, and rectum lie the levator ani muscles (see Fig. 45.7B). The medial portion of the levator ani muscles frequently has been called the *pubococcygeus*, but the *puboviscera*l *muscle* is a better term because it extends from the pubic bone and attaches to the vagina and rectum, with only a few

insignificant fibers ending in the coccyx (Lawson, 1971). This strong, robust, fatigue-resistant striated muscle starts on the inner surface of the pubic bone near the midline and passes behind the rectum, to return to the pubic bone on the other side. The lateral walls of the vagina are attached to this muscle, which then inserts into the anus in the intersphincteric groove between the internal and external anal sphincter, as well as passing around its dorsal surface in a slinglike loop. The normal resting tone of this muscle squeezes the rectum, vagina, and urethra closed by compressing them against the pubic bone. The pubo-rectalis muscle originates lateral to the pubovisceral muscle and forms a sling behind the rectum at the anorectal angle. Arising from the lateral pelvic walls (at the tendineus arch of the levator ani muscles) is the iliococcygeal muscle that forms a horizontal shelf on which the upper pelvic organs rest.

Interaction Between the Muscles and Fasciae

The interaction between the pelvic floor muscles and ligaments is critical to proper function. As long as the pelvic floor musculature functions normally, the pelvic floor is closed, and the ligaments and fasciae are under no tension. They simply act to stabilize the organs in their position above the levator ani muscles. When the pelvic floor muscles relax or are damaged, the pelvic floor opens. The vagina lies between the high intraabdominal pressure and low atmospheric pressure, where it must be held in place by the ligaments. Although the ligaments can sustain these loads for short periods, if the pelvic floor muscles do not close the pelvic floor, then it is more likely that the connective tissue will become damaged and eventually fail to hold the vagina in place.

ISSUES RELATING TO INCONTINENCE

The mechanisms of urinary and fecal incontinence are more difficult to explain than the mechanical basis of genital tract support, and they are not understood entirely. As is true for genital prolapse, urinary continence depends on both support of the urethra and its ability to remain closed as a result of its innate constriction. Normal support of the urethra allows it to be compressed closed by increases in abdominal pressure (i.e., pressure transmission). Although both support of the urethra and pressure transmission are important for stress urinary continence, they are not the only factors involved. Stress incontinence may occur in women with normal urethral support of the vesical neck and urethra but with inadequate constriction by the muscles within the urethral walls. If the a-adrenergically innervated smooth muscle of the vesical neck does not function normally and the vesical neck is open, this is referred to as type III incontinence. This type of incontinence is differentiated from types I and II incontinence, which involve different degrees of support loss. When the proximal urethra is patent at rest, urine already lies below the area where pressure transmission has its effect and, therefore, bypasses this mechanism of continence.

The support of the urethra is not due exclusively to fascial structures; active muscle contraction plays an important role in urethral support. In addition, the musculature of the urethra contracts during a cough and increases urethral closure. Therefore, neuromuscular mechanisms play an important role in the pathophysiology of stress incontinence and must be considered in understanding this group of diseases.

By the same token, anal continence can be explained only partially by the mechanical structures that support the anorectum and by preservation of the anorectal angle through contraction of the puborectalis. Anal incontinence can occur with normal support of the anorectum and preserved anorectal angle. There are other important factors in maintaining anal continence, including normal integrity of the muscles of the anal sphincter complex and their innervation.

CAUSES OF PELVIC FLOOR DAMAGE

Several factors influence the development of genital prolapse and urinary incontinence (Table 45.2). The inherent strength of the muscles and connective tissue of an individual, damage to these structures that occurs with birth, the rate at which they deteriorate with age, and the loads that they are subjected to during life all play a role in the development of genital prolapse and incontinence. Understanding the interplay among these various factors is critical to appreciating the pathophysiology of genital prolapse.

Inborn strength of connective tissue and muscle
Loss of connective tissue strength
Damage at childbirth
Deterioration with age
Poor collagen repair
Loss of levator function
Neuromuscular damage during childbirth
Metabolic diseases that affect muscle function
Increased loads on the supportive system
Prolonged lifting
Chronic coughing from chronic pulmonary disease
Disturbance of the balance of the structural parts
Alteration of vaginal axis by urethral suspension
Failure to reattach the uterosacral—cardinal ligament complex at hysterectomy

TABLE 45.2. *Factors involved in pelvic organ prolapse*

Although it is obvious that the native strength of the levator ani muscles and endopelvic fascia plays an important role in prolapse, the changes that vaginal birth causes in the pelvic floor deserve specific examination. Distension of the vagina during vaginal birth usually is blamed for prolapse, yet the cervix undergoes a much greater degree of dilation during parturition but recovers sufficiently so that forceful dilation is needed if dilation and curettage is done later in life. Damage to the levator ani muscles and their innervation is common during vaginal birth, and loss of the muscle's ability to support the pelvic organs and unload the ligaments may be partially responsible for the breakage and elongation of the ligaments later in life.

Certainly, some damage to the connective tissue of the parametria and paracolpium occurs during childbirth and can contribute to subsequent prolapse. Although usually thought of as stretching, prolapse also includes instances in which the connective tissue supports rupture. This acute injury mechanism is much more likely than stretching, because usually it is rupture that occurs with overload of other ligaments in the body (e.g., knee). Chronic injury through attenuation of the endopelvic fascia with age contributes and explains why prolapse occurs many years after childbirth. Failure of connective tissue to heal the many minor injuries that occur from day to day may also play a role. Age and chronic disease may cause weakening of the tissues, and heavy lifting or chronic coughing may cause progressive damage. This wear and tear on the connective tissues depends on the magnitude of the stresses placed on them, as well as how well damage is repaired by the body.

DIAGNOSIS AND CLASSIFICATION

Determining the type and severity of prolapse in any given patient is a skill that should be acquired through practice and careful observation. Characterizing the degree of support loss as normal or abnormal depends on comparisons with the findings in normal multiparous women in the examiner's experience. It is, therefore, helpful to perform the same examination on a sufficient number of asymptomatic patients without prolapse to become familiar with the range of normal support. In performing an examination to determine the type and severity of prolapse, the practitioner has two important points to consider:

- Examination must be made with the patient straining forcefully enough that the prolapse is at its greatest.
- The examiner must examine each element of support independently.

If a patient is not able to strain sufficiently in the lithotomy position so that the prolapse is at its largest, examination in the standing position may be necessary. This is a critical point, because it is only when the prolapse can be seen in its fullest extent that all of its various elements can be assessed. If the entire extent of the prolapse is not observed, some element may be overlooked. For example, a large cystocele may be seen initially when the patient strains. It may be only with continued effort by the patient that an enterocele and prolapse of the vaginal apex can be demonstrated. To make sure all aspects of the prolapse can be evaluated, the patient should be asked how large her prolapse is at its largest, and the physician should persist in the examination until that size is achieved. Once the prolapse is visible, the elements of the vagina and pelvic organs that have prolapsed can be evaluated. The examination should then focus on what specific defects in support are present and how severe the prolapse is, and there should be some evaluation of the cause of the prolapse. Once the prolapse is maximally developed, the physician should begin by identifying how much the anterior wall, cervix, and posterior wall have prolapsed. The anterior and posterior walls should be examined separately by retracting the opposite wall with the posterior half of a vaginal speculum. A stepwise, site-specific examination is important because a large cystocele, for example, may hold a potential rectocele in place and, therefore, hide it. If a rectocele is not recognized preoperatively, its repair may be overlooked and the defect can become symptomatic postoperatively. These observations have been confirmed on dynamic colpoproctography imaging studies of the pelvic floor, with contrast placed in the bladder and rectum while the patient strains in the standing position. If the patient has a full bladder when imaging is performed, a rectocele can be obstructed and will not be evident until the patient empties her bladder. Care must also be taken to assess how much of the loss of support is from a defect of the apical (level 1) support. It is not uncommon to correct the apical defects and find that much of what was considered a cystocele and rectocele have been corrected. Examination while under anesthesia is used to evaluate pelvic masses, but it is not the optimal time to identify defects caused by prolapse because of the patient's inability to perform the Valsalva maneuver and because of loss of normal levator tone.

EVALUATING INDIVIDUAL ELEMENTS OF SUPPORT

Anterior Vaginal Wall

Examination of the anterior vaginal wall should establish the status of urethral support, as well as bladder support. The urethra is fused with the lower 3 to 4 cm of the vaginal wall, and abnormal support in this region is properly referred to as a *urethrocele* (Fig. 45.9). Defective support of the upper portion of the vagina is called a *cystocele*, because the bladder lies adjacent to this portion of the vaginal wall (Fig. 45.10). The urethrovesical crease, normally visible on examination, forms the line of demarcation between these two areas of support (Fig. 45.11). When support of the entire anterior wall is defective, the term *cystourethrocele* is used.

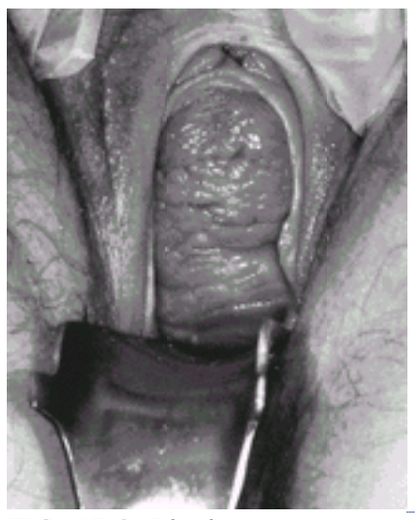

FIG. 45.9. Displacement cystourethrocele with intact rugal folds caused by lateral detachment of the pubocervical fascia. (Copyright © DeLancey, 1993.)

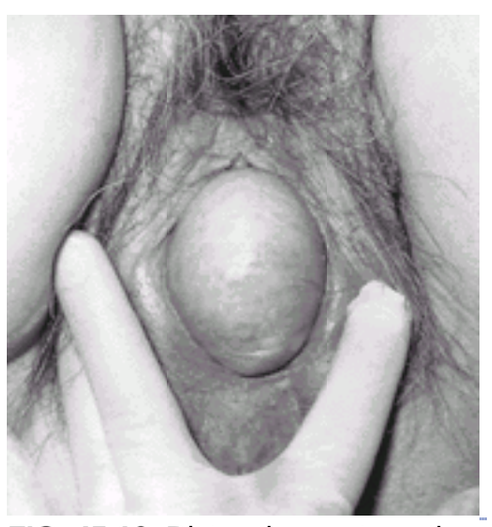

FIG. 45.10. Distension cystourethrocele caused by midline failure of the pubocervical fascia. (Copyright © DeLancey, 1993.)

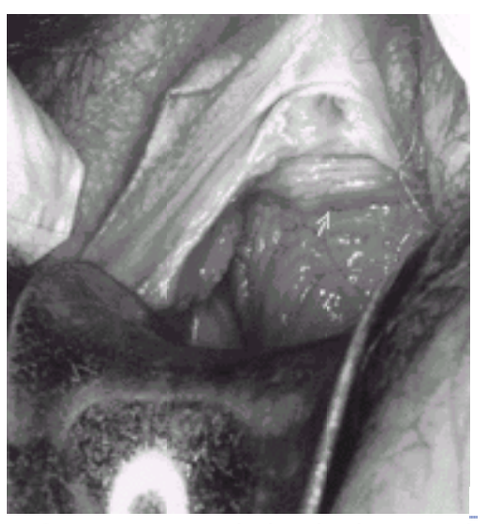

FIG. 45.11. Angulation in the anterior vaginal wall, called the urethrovesical crease *(arrow)*, indicates the location of the urethrovesical junction. (Copyright © DeLancey, 1993.)

The anterior vaginal wall should be above the hymenal ring during straining. Descent of the lower anterior vaginal wall to the level of the hymenal ring during straining is characteristic of a urethrocele and is seen often in patients with stress urinary incontinence. This is due to loss of urethral support and corresponds to the loss of the posterior urethrovesical angle on radiographic studies of patients with stress incontinence. The lower anterior vaginal wall is mobile in all women and may move significantly in continent multiparas. Therefore, motion of this region does not establish stress incontinence but rather indicates the degree to which the support of the urethra has failed. Descent below the hymenal ring is definitely abnormal and indicates a cystourethrocele whether or not stress incontinence is present.

The anterior vaginal wall above the urethrovesical crease usually lies in a flat plane at about a 45-degree angle from the horizontal (see Fig. 45.11). Descent below the level of the hymenal ring is significant. This descent can be caused by one of three entities:

- Separation of the paravaginal attachment of the pubocervical fascia from the white line due to detachment from the ischial spine
- Loss of the vagina's attachment to the cervix
- Tearing in the pubocervical fascia that results in herniation of the bladder through this layer

Uterus and Vaginal Apex

The vagina and cervix are fused with one another, and prolapse of the uterine cervix is associated invariably with prolapse of the upper vagina, as well. When the uterus descends below its normal level, the term *uterovaginal prolapse* is appropriate, although *uterine prolapse* commonly is used. In patients in whom the uterus has been removed, descent of the vaginal apex below its normal position in the pelvis is referred to as *prolapse of the vaginal apex*, and when the vagina turns entirely inside out, the term *vaginal eversion* is used.

The location of the cervix customarily is used to gauge the severity of uterine prolapse (Fig. 45.12). Its position relative to the hymenal ring should be noted while the prolapse is at its greatest. If the cervix is not visible because of a cystocele or rectocele, then its location may be palpated while having the patient strain. When the cervix descends to within 1 cm of the hymenal ring, there is a significant loss of support. In instances in which the uterus is not necessarily going to be removed, uterine support should be tested before it is assumed that the uterus is well supported. This can be done by grasping the cervix with a tenaculum or ring forceps and applying

traction until it stops descending. Occult prolapse, in which the cervix comes below the hymenal ring, can be detected in this way.

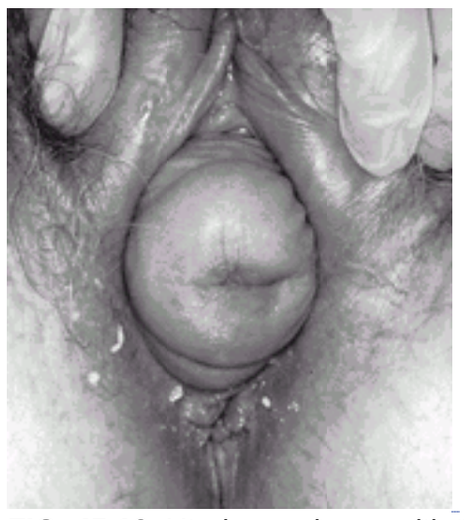

FIG. 45.12. Uterine prolapse with the cervix extending 3 cm below the hymen. (Copyright © DeLancey, 1993.)

In addition to determining how far the cervix descends, its length should be measured. Cervical elongation is frequent in individuals with prolapse, and the uterine corpus often may lie in its normal location. Awareness of cervical elongation preoperatively will allow the surgeon to proceed expeditiously with the hysterectomy, rather than hoping with every pedicle that the uterine arteries will soon appear.

Posterior Vaginal Wall

The posterior vaginal wall is the site of both rectoceles and enteroceles. Evaluation and correction of these two problems challenge even the most experienced gynecologic surgeon, and they are probably the most difficult to understand of all pelvic support defects. Because dyspareunia can follow repair, correction of asymptomatic posterior wall defects is not without risk. On the other hand, having a rectocele or enterocele develop after vaginal hysterectomy and anterior colporrhaphy is an undesirable outcome, and careful consideration of the support of the posterior vaginal wall is important.

Three questions should be asked by the physician when examining the posterior wall.

- Is it supported normally?
- If not, is it a true rectocele or a pseudorectocele?
- Is an enterocele present?

A rectocele is present when the anterior rectal wall and overlying vagina protrude below the hymenal ring. An enterocele exists when the cul-de-sac becomes distended with the intestine and bulges the posterior vaginal wall outward. There are also occasions in which the posterior wall appears to bulge into the vagina, not because of poor support of the rectal wall but because of a deficiency in the perineal body. This has been referred to by Nichols and Randall as a pseudorectocele and can be differentiated easily from a true rectocele because the anterior rectal wall contour is normal on rectal examination. Another type of pseudorectocele may be suspected when there is apical descent of the upper vagina or cervix and apparent loss of posterior support. However, often when the normal apical support is restored (by temporarily supporting it with ring forceps in the office or after surgical repair of the apical descent), a suspected rectocele is not evident. This is important to determine preoperatively, because loss of tone of the levator ani muscle and anal sphincter muscle with muscle paralyzing agents during anesthesia make it harder to establish the existence of a true rectocele.

Enterocele

There is always a cul-de-sac between the upper vagina and the rectum. This allows a culdocentesis to be performed and a colpotomy to be made through the posterior vaginal wall at the beginning of a vaginal hysterectomy. The peritoneal pouch normally extends 3 to 4 cm beyond the junction of the vagina and cervix. Therefore, the absence of an enterocele in normal women must be explained by factors that keep the cul-de-sac closed rather than by the absence of a peritoneal space between the upper vagina and rectum. It is the suspension of the upper vagina near the sacrum in a position where it may rest over the rectum and intact levator plate that keeps this space closed.

There are two types of enteroceles: pulsion enterocele and traction enterocele. A pulsion enterocele exists when the cul-de-sac is distended and appears as a bulging mass that is inflated by increases in abdominal pressure. This may occur with either the vaginal apex or uterus well suspended, in which case the cervix or vaginal apex is at a normal level and the enterocele dissects between the vagina and the rectum. When an enterocele is associated with prolapse of the uterus or vaginal apex, then the prolapse and enterocele occur together.

A traction enterocele represents a situation in which prolapse of the uterus pulls the cul-de-sac peritoneum down with it, but there is no bulging or distension of the cul-de-sac when abdominal pressure rises. This condition usually is found at the time of vaginal hysterectomy when the cervix has prolapsed. It represents a potential enterocele rather than an actual enterocele, because there is no bulging mass separate from the uterus.

Unlike uterine prolapse, which is obvious because of the protrusion of the easily recognized uterine cervix, enteroceles and rectoceles rarely are evident on examination. Therefore, the key to detecting an enterocele lies in actively looking for it whenever a patient who has prolapse is examined. Detection of an enterocele is performed best in the awake, straining patient by noting a mass of small intestine between the rectum and vagina; it may not be suspected in a supine individual at rest.

Anatomically, an enterocele extends from the apex of the vagina downward, whereas a rectocele typically begins in the lower portion of the vagina. An enterocele sometimes is evident as a bulge that overrides the more caudal rectocele (Fig. 45.13). Careful inspection of the posterior vaginal wall with a speculum retracting the anterior wall sometimes can suggest that an enterocele is present. The key to detecting a pulsion enterocele lies in palpating the small bowel between the vagina and rectum during rectovaginal examination, with the patient straining so that the prolapse is protruding. To do this, an index finger is placed in the rectum and a thumb is placed in the vagina. Then, with the patient straining, the rectovaginal space may be palpated to detect the bulge of the enterocele and the presence of small bowel, omentum, or large bowel.

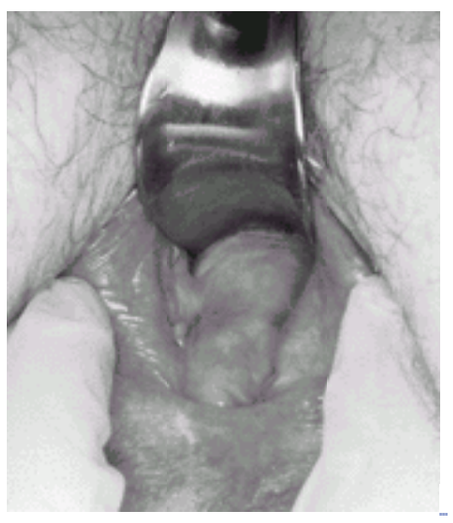

FIG. 45.13. “Double hump” sign of an enterocele overriding a rectocele. (Copyright © DeLancey, 1993.)

Rectocele

The hallmark of a typical rectocele is the formation of a pocket that allows the anterior rectal wall to balloon downward through the introitus. When a rectal examination is performed with the prolapse fully developed, a rectocele exists if there is an extension of the rectal lumen below the axis of the anus (Fig. 45.14). This not only provides the diagnosis but also illustrates the mechanism by which rectoceles create their symptoms. As long as the anterior rectal wall has a smooth contour and no sacculation, even though it may be more mobile than normal, stool will pass through the anus. However, when a pocket develops as the patient strains, stool becomes trapped in it, and difficulty with evacuation can occur.

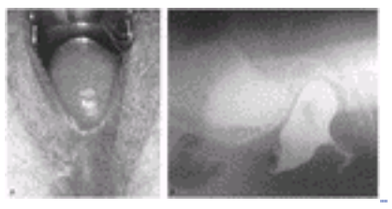

FIG. 45.14. A: Pelvic examination shows a rectocele. **B:** Lateral bead chain cystourethrogram with the patient supine and with contrast in the vagina and rectum shows a protruding rectocele. (Copyright © DeLancey, 1993.)

Prolapse Subsequent to Hysterectomy

Special consideration should be given to patients who have prolapse after hysterectomy to assess whether or not prolapse of the vaginal apex is present. When the uterus is in situ, the cervix calls attention to the poor support of the cervix and upper vagina. In instances of posthysterectomy vaginal prolapse, descent of the vaginal apex is more easily missed. If it is overlooked and an anteroposterior colporrhaphy is not accompanied by suspension of the vaginal apex, the colporrhaphy will fail to cure the apical prolapse, and the problem is not corrected. Overlooking apical support loss also can lead to overly aggressive excision of vaginal tissues during anteroposterior colporrhaphy and a shortened vagina. Examination of patients who have previously had a hysterectomy should include a specific effort to determine the location of the vaginal apex when the prolapse is at its largest. The apex is identified by the vaginal scar at the hysterectomy site (Fig. 45.15). Vaginal prolapse is present when the hysterectomy scar lies below the level of the hymenal ring. If the apex descends to within the lower one third of the vagina with straining, a significant deficit in support of the apex is present, and the vagina should be resuspended during repair.

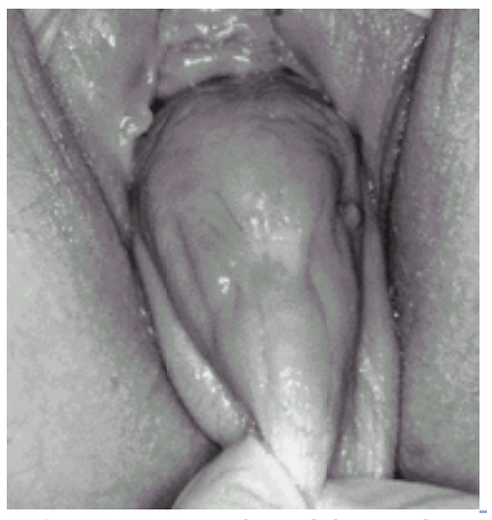

FIG. 45.15. Eversion of the vagina after hysterectomy. Note that the vaginal apex, indicated by the puckered scar where the cervix had been removed, lies below the hymenal ring. (Copyright © DeLancey, 1993.)

PELVIC ORGAN PROLAPSE CLASSIFICATION

Several classification systems have been used to describe the sizes and types of pelvic organ prolapse in an individual woman. Because many of these systems use similar words to indicate different degrees of prolapse, confusion has arisen concerning the size of prolapse. For example, grade 2 uterine prolapse in some systems indicates that the cervix descends halfway between its normal position and the introitus. In other classifications, grade 2 can mean that one half of the uterus is outside the introitus. A system that standardizes terminology has been adopted by several groups, including the International Continence Society, the American Urogynecologic Society, and the Society of Gynecologic Surgeons. This standardized terminology (Pelvic Organ Prolapse Quantification, or POP-Q) provides a system that can describe the type of prolapse, as well as quantify the degree of prolapse in each area. Although this standardized system seems somewhat cumbersome when described in writing, in actual practice it is quite simple. The following section first considers the measurements that describe the type and size of prolapse and then discusses the measurements concerned with the changes in the urogenital hiatus in the levator ani muscles through which the prolapse descends.

Measurements Describing Prolapse Type and Size

To describe the nature of a woman's prolapse, it is necessary to do the following: (a) document what part or parts of the genital tract have prolapsed and (b) indicate how far down each part of the vaginal wall or cervix has descended.

Prolapse description must include a consideration of anterior vaginal wall descent, posterior wall descent, and uterine descent (or prolapse of the vaginal apex after hysterectomy). Furthermore, because different parts of the anterior wall might suffer support damage, the system provides for determining the status of each level of vaginal support. For example, the distal anterior vaginal wall adjacent to the urethra may be well supported, while the portion of the vagina under the bladder may prolapse. This system addresses the need to make individual assessments of different parts of the vaginal wall.

The three levels of vaginal support (see Fig. 45.8) must be assessed, corresponding to the different anatomic regions of vaginal support.

- Level I: support of the vaginal apex and uterus
- Level II: support of the bladder and rectum
- Level III: support of the urethra and perineal body

In levels II and III, the anterior and posterior vaginal wall are considered separately, while in level I the cervix (or vaginal apex) and posterior fornix must be assessed.

To understand the POP-Q classification system, refer to Figure 45.16. The size and type of prolapse are measured by determining the location of a series of points on the anterior and posterior vaginal walls relative to the hymenal ring. Points at each of the three levels are measured. Positive numbers reflect measurements of the vaginal points that have prolapsed below the level of the hymen and negative numbers reflect measurements above the hymen. It should be noted that this descriptive scheme does not distinguish between rectocele and enterocele but simply provides a way to quantify the amount of vaginal wall descent in each specific area. Additional examination and written comments concerning these important differences should be made.

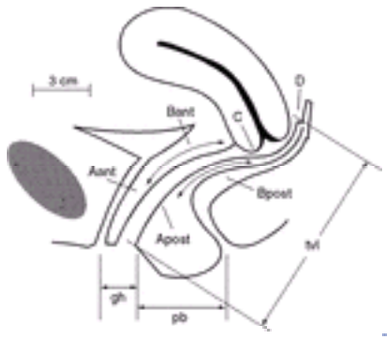

FIG. 45.16. Six sites (points *A* $_{ant}$, *B* $_{ant}$, *C, D, B* $_{post}$, and *A* $_{post}$), genital hiatus *(gh)*, perineal body *(pb)*, and total vaginal length *(tvl)* used for pelvic organ support quantitation.

A summary of the measurements obtained during the POP-Q examination is noted in Table 45.3.

Stage 0	No prolapse is demonstrated. Points A_{ant}, A_{post}, B_{ant}, and B_{post} are all at −3 cm and either point C or D is between − total vaginal length (tvl) cm and − (tvl–2) cm (i.e., the quantitation value for point C or D is ≤ − [tvl–2] cm)
Stage I	The criteria for stage 0 are not met, but the most distal portion of the prolapse is >1 cm above the level of the hymen (i.e., its quantitation value is >−1 cm)
Stage II	The most distal portion of the prolapse is between 1 cm above and 1 cm below the plane of the hymenal ring (i.e., its quantitation value is ≥−1 cm but ≤+1 cm)
Stage III	The most distal portion of the prolapse is >1 cm below the plane of the hymen but protrudes no farther than 2 cm less than the tvl in centimeters (i.e., quantitation value is >+1 cm but <+ [tvl–2] cm)
Stage IV	Essentially, complete eversion of the total length of the lower genital tract is demonstrated. The distal portion of the prolapse protrudes to at least (tvl–2) cm (i.e., its quantitation value is <−1 cm)

TABLE 45.3. *Stages of pelvic organ prolapse based on measurement of specific sites*

I. Vaginal points (vaginal profile): patient straining maximally
   A. Level I: apex and cervix: points C and D (D is omitted if patient has had a hysterectomy)
   B. Level II: midvaginal points
      1. Anterior wall: B $_{a}$ or B $_{ant}$
      2. Posterior wall: B $_{p}$ or B $_{post}$
   C. Level III: distal vagina (perineum and urethrovesical neck)
      1. Anterior wall: A $_{a}$or A $_{ant}$
      2. Posterior wall: A $_{p}$ or A $_{post}$
      3. External measurements: obtained with patient at rest and again straining
   A. Genital hiatus: length gh
   B. Perineal body: length: pb
II. Internal digital measurements: obtained with patient at rest with vaginal apex restored to normal position
   A. Total vaginal length: tvl

To measure the lower third of vaginal support (level III), the location of a pair of points that normally lies 3 cm above the hymenal ring is assessed. Points measured at level III are called *points A.* One can imagine marking these vaginal points 3 cm above the hymen with a marker and then recording the position of these points in relation to the hymen with the subject straining maximally. Anteriorly, this corresponds to the approximate location of the urethrovesical junction, and this measurement assesses urethral descent (A $_{a}$ or A $_{ant}$). Posteriorly, this region is normally occupied by the tissues of the perineal body (A $_{p}$ or A $_{post}$). By definition, the highest possible position of either point A $_{ant}$ or A $_{post}$ is 3 cm above the hymen (-3), and the lowest position is 3 cm below the hymen (+3).

To assess midvaginal support (level II), the most dependent part of the vaginal wall above point A $_{ant}$ is used. This point is called B $_{a}$, or B $_{ant}$, on the anterior wall and B $_{p}$, or B $_{post}$, on the posterior wall. This is, therefore, not a fixed point along the surface of the vagina, but rather it is marked at whatever location is the most caudal (distal) portion of that vaginal segment at maximal prolapse protrusion. In a normally supported vagina, this will be the same as point A $_{ant}$, whereas in a woman with procidentia it will be the same as point C. The same is true for the posterior vaginal wall at point B $_{post}$. Point C corresponds to the most distal portion of the uterine cervix or of the hysterectomy scar in the vagina in those patients who have had the uterus removed. Point D denotes the posterior fornix (that point at which the posterior vaginal wall changes direction). In addition to the positions of these points, the total length of the vagina is noted. Once these data have been gathered, a simple line diagram can be constructed by plotting these points relative to the hymen to provide a graphic representation of the prolapse (Fig. 45.17).

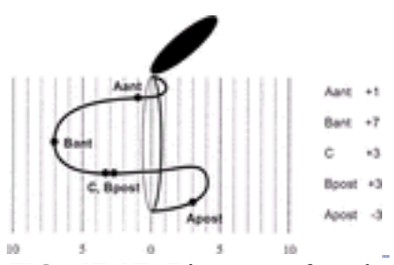

FIG. 45.17. Diagram of prolapse sites. (From Viereck V, Peschers U, Singer M, et al. Metrische Quantifizierung des weiblichen Genitalprolapses: eine sinnvolle Neuerung in der Prolapsdiagnostik? *Geburtshilfe Frauenheilk* 1997;57:177, with permission.)

So far, each element of the prolapse has been considered separately. It is also possible to give an overall description to the size of the prolapse by looking at the most dependent part of the protruding vagina or uterus. In this way, different stages—stage 0 through stage IV-can be defined; a description of these is shown in Table 45.3. A briefer version of the original description of the POP-Q staging system has been summarized, also.

The choice of the term *stage* here is somewhat unfortunate, because most women with stage I and II support are anatomically normal. The implication that they have a stage of prolapse is incorrect. Hopefully this problem with terminology will be corrected in the future.

Pelvic Floor Measurements

In normal women, the levator ani muscles close the pelvic floor. In women with pelvic organ prolapse, the urogenital hiatus within the levator ani muscles is the opening through which the vagina prolapses. This hiatus is enlarged in women with pelvic organ prolapse. The size of the urogenital hiatus and thickness of the perineal body can easily be measured to describe the changes that have occurred in the pelvic floor. The anteroposterior diameter of the genital hiatus extends from the arch of the pubic bone to the front of the perineal body, while the thickness of the perineal body is measured from the anterior margin of the perineal body to the center of the anal verge. The urogenital hiatus is held closed by the constant activity of the levator ani muscles, and the diameter of this opening enlarges in many women with prolapse.

This classification system is detailed and specific. It requires careful examination and assessment. Although at first it seems quite detailed, it is simply the quantitative documentation of the individual defects that experienced surgeons always have found necessary to assess. Some clinicians will not find it expedient to measure each of these sites, but intelligent, detailed analysis of each site of support is important to plan properly any repair for pelvic organ prolapse.

SYMPTOMS

All types of prolapse have several symptoms in common. Once the vagina prolapses below the introitus, it becomes the structural layer between the high pressures in the abdominal space and the relatively low atmospheric pressure. The downward force that this pressure differential creates puts tension on the fasciae and ligaments that support the vagina and uterus. This results in a dragging sensation where the tissues connect to the pelvic wall, usually identified by patients as occurring in the groin, and in sacral backache caused by traction on the uterosacral ligaments. This type of discomfort resolves when the patient lies down and the downward pressure is reduced. In addition, exposure of the moist vaginal walls leads to a sensation of perineal wetness that may be confused with urinary incontinence, and it also can give rise to ulceration of the vaginal wall. Most patients have an underlying sense of insecurity that is difficult for them to describe and is often expressed as a feeling that “something is just not right.” Sometimes patients who feel the cervix or vagina protruding have fears that they have a cancer and may be relieved to find that the condition is related to prolapse. Although patients may find it difficult to put their symptoms into words, the symptoms can cause significant distress and should not be ignored.

Symptoms of Anterior Wall Prolapse

The symptoms of cystourethrocele are varied, and the two primary ones are paradoxical. On the one hand, loss of support of the urethra and the lower vaginal wall is associated with stress urinary incontinence, whereas loss of support of the upper anterior vaginal wall and bladder base can cause difficulty in emptying the bladder. This inability to empty the bladder completely is probably related to voiding by the Valsalva maneuver. If there is a detrusor contraction, there should be no reason for a woman with a cystocele not to empty her bladder, and many women with a significant cystocele have normal postvoid residual urine volumes. When a woman strains to void, however, the cystocele simply gets bigger, and no impulse is provided for urine to flow through the urethra.

In addition to these functional symptoms, many patients with a cystourethrocele complain of urinary urgency and frequency. This probably arises from stretching of the bladder base that accompanies its prolapse through the vaginal introitus; it is often less pronounced at night when patients are supine.

Patients have a varying amount of support loss under the urethra or bladder, and symptoms vary along the spectrum from incontinence to urinary retention. As is true for other forms of prolapse, it is important to correlate a patient's symptoms with the physical findings so these problems can be addressed.

Symptoms Associated With Prolapse of the Uterus, Prolapse of the Vaginal Apex, or Enterocele

Few specific symptoms are related to prolapse of the uterus, prolapse of the vaginal apex, or enterocele. Patients with these conditions usually complain of the generalized symptoms of prolapse mentioned above. Some have urgency and frequency, probably related to pressure of the prolapse on the bladder base, but this is variable. In addition, patients with large, thin enteroceles occasionally have a sense of impending rupture. Although this is an uncommon problem, it should not be overlooked.

Symptoms of Rectocele

The cardinal symptom of a rectocele is difficulty in emptying the rectum. As a woman bears down to evacuate the rectum, stool is pushed into the rectocele, and the harder she strains, the bigger the rectocele becomes. Because constipation is common in older women, it is important to differentiate between infrequent bowel movements due to poor colonic motility or inadequate dietary fiber and difficulty due to a rectocele. Many women have found that if they press between the vagina and rectum to elevate the rectocele, this maneuver helps with defecation. This finding supports the fact that the rectocele is the source of the problem.

WHO SHOULD BE TREATED SURGICALLY

A decision about when an operation for prolapse should be performed is based on the individual woman's situation. It depends on the size of the prolapse, the presence or absence of symptoms, and whether or not physiologic complications have arisen because a prolapse is present. Conservative treatment with a pessary may be considered. There is little data on continuance rates with long-term pessary use. Contrary to prior recommendations that pessaries should be offered only to those women who are not operative candidates or to those awaiting surgery, a survey of urogynecologists found that 77% would offer a pessary for symptomatic patients as first-line treatment.

When the prolapse lies at or above the level of the hymenal ring, surgery should be performed only if definite symptoms are present and can be attributed reliably to the prolapse. Examples of this include:

- A patient with a cystourethrocele at the level of the hymen who has significant stress incontinence
- A woman with the cervix in the lower one third of the vagina, who has the characteristic dragging discomfort of a prolapse that resolves when she lies down or puts a supportive pessary in place
- A patient with a small rectocele in whom a definite pocket can be detected on rectal examination and elevation of the perineum relieves problems with defecation

It is unusual for women in whom the uterus has not yet descended to the level of the hymenal ring to have symptoms caused by descent of the uterus. Symptoms of pressure, back pain, or feelings that something is coming out should be studied to confirm that they are related to the prolapse, and not to other factors, before a decision to operate is made. If the symptoms go away when a pessary is placed or a patient notices prompt relief when she lies down, this helps to confirm that the prolapse is the source of the symptoms. A woman with low back pain whose discomfort persists after she is supine is more likely to have arthritic or musculoskeletal pain than pain caused by uterine prolapse, and the results of surgery are likely to disappoint her.

Among patients whose prolapse descends several centimeters below the hymenal ring, symptoms are usually present, and surgery will relieve this distress. Some women with a large prolapse will deny any symptoms, because they do not wish to undergo surgery or because they simply are not troubled by the prolapse. Their wishes should be respected. On the other hand, potential complications from the prolapse should be considered and discussed frankly.

A prolapse should be repaired, despite a lack of symptoms, if a patient has recurrent urinary tract infections associated with an increased postvoid residual urine volume. Ureteral dilation caused by the prolapse, which leads to an impairment of renal function, occurs in some patients with large prolapses and should be considered an indication for repair. An intravenous pyelogram and renal function testing can detect these abnormalities and indicate the need for treatment. The intravenous pyelogram should include films made with the patient standing and the prolapse present, because the supine position may mask significant dilation.

SURGICAL PROCEDURES

Vaginal Hysterectomy and Anteroposterior Colporrhaphy

Vaginal hysterectomy with appropriate anteroposterior colporrhaphy is the operation most often performed for the treatment of uterovaginal prolapse. Because simple removal of the uterus does nothing to correct the prolapse of the vaginal walls that accompanies descent of the cervix, it is necessary to consider how an operation works to cure these conditions properly.

Basic Principles Underlying the Surgical Repair of Prolapse

Removal of the uterus does not improve support of the genital tract. Successful repair depends on the way in which a surgeon resuspends the vagina and repairs other defects in pelvic organ support when performing a vaginal hysterectomy and anteroposterior repair. Once the uterus has been removed, the vaginal apex should be attached to a point that is higher in the pelvis than the vagina to elevate it to a normal position. During the vaginal hysterectomy, the cardinal and uterosacral ligaments can be shortened and used to resuspend the vagina. In addition, techniques such as McCall culdoplasty anchor a suture to a point on the uterosacral ligaments higher than the preoperative position of the vagina and use this suture to pull the vaginal apex to a point higher in the pelvis. It is the elevation of the vagina rather than removal of the uterus that is critical.

Preoperative Considerations

In addition to the usual thorough history, physical examination, and other medical measures necessary prior to any major operation, preoperative preparation for vaginal hysterectomy should include a pelvic examination, Pap smear, and urinalysis. Special care should be taken, as previously described, to determine the exact type and degree of prolapse and to detect any potential ovarian malignancy. A saline enema (e.g., Fleet enema) the night before surgery empties the rectum in the

event that a rectal examination is required during surgery and provides more room posteriorly, improving exposure. Patients should receive a prophylactic antibiotic to minimize the risk of postoperative infections (cefazolin sodium 1 g intramuscularly or intravenously, just before going to the operating room, is appropriate). Cervical cytologic examination results should be documented prior to hysterectomy, and if abnormal uterine bleeding is present, the endometrium should be sampled and tested preoperatively. Finally, special consideration should be given to assessing whether or not concomitant cystocele, stress incontinence, enterocele, or rectocele is present.

Before the hysterectomy is begun, a sterile preparation of the vulva and vagina is performed. An indwelling urinary catheter usually is not placed at this point, to allow the bladder to accumulate enough urine so that an inadvertent cystotomy may be recognized easily. Care should be taken in positioning and draping the patient to avoid compression of the femoral or peroneal nerve, but there should be adequate access to the operative site. An examination should be performed under anesthesia to, once again, assess whether or not any abnormalities exist that would make vaginal hysterectomy impossible and would indicate a switch to an abdominal approach.

Technique of Vaginal Hysterectomy

The elements of vaginal hysterectomy in the United States are derived from the operation described by Heaney (Fig. 45.18). A circumscribing incision is made through the vaginal wall at the cervicovaginal junction (see Fig. 45.18A). Anteriorly, the incision is placed at the lower edge of the bladder to allow entry into the vesicocervical space. The lower edge of the bladder can be palpated against the cervix to determine where this incision should be made. In addition, the junction of the vaginal rugae and the smooth surface of the cervix can be used as landmarks to identify the proper site of incision. Some operators inject saline into the tissues around the cervix to facilitate dissection. This injection should not contain epinephrine, because its use increases the incidence of postoperative pelvic infection. Several studies have documented decreased blood loss after infiltration of a dilute vasopressin solution at the cervical portio, without concomitant increased infection rates. The incision should be made through the full thickness of the vaginal wall. This can be determined by placing a retractor anteriorly while pulling forcefully on the cervix so that the vaginal wall is placed under tension. Once the vagina has been transected it separates, exposing the underlying cleavage plane. On the posterior aspect of the cervix, this exposes the area of the cul-de-sac. Blunt dissection here frees the peritoneum, which can then be grasped and entered (see Fig. 45.18B). Care should be taken not to dissect the peritoneum off the uterus, because that makes entry more difficult. Once the cul-de-sac incision has been extended laterally as far as the medial margins of the uterosacral ligaments, it can be sutured to the posterior vaginal cuff to minimize bleeding. At this point, it is appropriate to palpate the adnexal structures through the colpotomy to detect unsuspected tumors and to make a final decision concerning the feasibility of the vaginal approach, if any doubt existed. This is an easy time to acquire this valuable information, and if unsuspected disease is found, an abdominal approach can be taken.

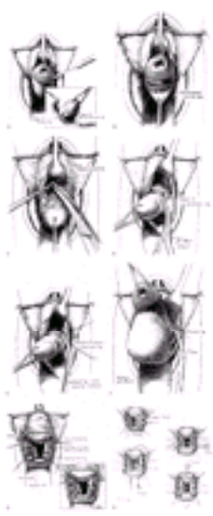

FIG. 45.18. A: Vaginal hysterectomy is initiated by circumscribing the cervix at the cervicovaginal junction. **B:** The posterior cul-de-sac is opened. **C:** The peritoneum of the anterior cul-de-sac is incised. **D:** The base of the uterosacral and cardinal ligament usually is clamped in two bites. **E:** The upper cardinal ligament is clamped prior to its transection. **F:** The uterine fundus is delivered, and the connections between the adnexal structures and uterine corpus are clamped. **G:** Ligaments and vaginal cuff as they appear after hysterectomy. The posterior cuff is whip-stitched **(inset). H:** Technique for resuspension of the vaginal cuff and obliteration of the cul-de-sac: *1*, placement of suture through exteriorized ligaments and vaginal wall; *2*, reefing sutures placed in peritoneum; *3*, modified internal McCall suture; *4*, high purse-string suture to close the cul-de-sac. (From Mattingly RF, Thompson JD, eds. *Te Linde's operative gynecology*, sixth ed. Philadelphia: JB Lippincott Co, 1985:554, with permission.)

Next, the long blade of an Auvrard retractor is placed in the cul-de-sac, and attention is turned to entering the anterior cul-de-sac. Dissection along the vesicocervical plane is best performed by lifting the fascia anteriorly while cutting with Mayo scissors placed tip-down on the cervix. This avoids the problems that sometimes occur when a knife is used, because the scissors held in this orientation will not cut into the dense fibrous tissue of the cervix. Once the cleavage plane of the vesicocervical space is reached, gentle dissection with a gloved finger is all that is needed to elevate the bladder off of the cervix. If the bladder pillars are prominent, they can be clamped next to the cervix, transected, and ligated to provide better lateral exposure. The location of the peritoneum may be detected by moving a finger from side to side and feeling the way in which the two slippery mesothelial surfaces slide on one anther. The peritoneum can then be lifted, transilluminated, and incised (see Fig. 45.18C). After the incision is extended laterally, a suture is placed in its vesical edge and held with a hemostat to facilitate its identification at the time of reperitonealization.

Once the cul-de-sacs have been entered, the ureter should be palpated to determine its position prior to shortening and transecting the cardinal ligaments. This is a critical step, because only if the ligaments are shortened will the vagina be held at a level higher than that of the prolapsed cervix. A retractor is placed in the lateral fornix of the vagina and a finger in the anterior cul-de-sac. Because the ureter must pass under the uterine artery and end in the bladder anterior to the examining finger, it can be palpated against the retractor blade. The characteristic snap of the ureter permits its identification, and it can be followed for some distance by moving the retractor and examining finger anteriorly and posteriorly.

After the ureter is identified the uterosacral and cardinal ligaments are shortened by clamping them at a safe distance from the ureter, somewhat lateral to the cervix (see Fig. 45.18D, Fig. 45.18E). After the ligaments are cut and suture-ligated, the sutures are left long and marked for use in resuspending the vagina at the end of the procedure. The uterine arteries are similarly clamped, transected, and suture-ligated, but they are not tagged, to avoid dislodging the suture from this vascular pedicle.

At this point, the corpus of the uterus usually is brought through the posterior colpotomy by pulling on it with a tenaculum, to expose the connections between the adnexal structures and the uterus (see Fig. 45.18F). When this is not possible because of a small vagina or large uterus, the uterus can be divided along its sagittal plane, and one half can be pushed up into the peritoneal cavity. A long tenaculum is left attached to the elevated half of the uterus to allow its later retrieval, while the contralateral adnexal pedicles are dealt with. Clamps are placed across the adnexal structures, with care taken not to include bowel or adjacent structures, and the pedicles are transected.

Next, consideration should be given to removal of the ovaries. If the ovaries are to be removed, the mesovarium or infundibulopelvic ligament is clamped, the ovary is removed with or without the fallopian tube, and the remaining pedicle is suture-ligated.

Management of the Cul-de-sac and Suspension of the Vaginal Apex

Once the uterus has been removed and the ligaments have been prepared by shortening them, the reconstructive phase of the operation begins. These steps use the ligaments that were tagged during the hysterectomy (see Fig. 45.18G). The goals are to close the peritoneum and suspend the vaginal apex, while also correcting any existing enlargement of the cul-de-sac. The cul-de-sac peritoneum is attached to the uterus. Whenever the uterus prolapses, it pulls the cul-de-sac peritoneum with it. If this extension is not distended with bowel, it is referred to as a *traction enterocele*, and when the cul-de-sac is not only elongated but also distended with bowel, it is referred to as a *pulsion enterocele*, a true enterocele.

When little prolapse has been present (i.e., the cervix does not extend below the hymenal ring), simple closure of the cul-de-sac and attachment of the ligaments to the vaginal cuff suffice. An indwelling catheter usually is placed at this time to drain the bladder. This brings the anterior peritoneum closer to the surgeon and, thereby, facilitates its closure.

Closure of the vaginal cuff should accomplish two things: resuspension of the vaginal apex and closure of the cul-de-sac (see Fig. 45.18H). A suture is placed through the vaginal cuff and through the ends of the suspensory ligaments to reattach them to the vagina. Next, the cul-de-sac may be reefed and a suture placed through the uterosacral ligaments to bring them to the midline. Finally, the peritoneum is closed with a purse-string suture of 0 silk placed at the highest level possible, beginning on

the vesical peritoneum. A finger is placed in the peritoneum while this suture is tied, to avoid trapping intraabdominal contents in the suture, and is removed as the suture is snugged down.

Anterior Colporrhaphy

After the uterus has been removed and before the ligaments are reattached to the vaginal cuff, an anterior colporrhaphy is performed for patients with cystoceles (Fig. 45.19). Scissors are used to undermine and incise the mucosa of the anterior vaginal wall as far as the midurethra (see Fig. 45.19A). The vaginal fascia is then mobilized widely from the vaginal epithelium, with use of a combination of sharp and blunt dissection, until the superior lateral sulcus of the vagina is reached (see Fig. 45.19B). Care should be taken to remain superficial in this dissection to avoid transecting the fascia that is to be plicated in the midline. Special attention should be given to adequately developing the fascia that lies under the urethrovesical junction, because this is critical to improving urethral support. Once mobilization has been accomplished, a series of plication sutures are taken in the fascia, just medial to the junction of the anterior and lateral vaginal walls (see Fig. 45.19C).

FIG. 45.19. A: The vaginal epithelium is undermined when commencing anterior colporrhaphy. **B:** The fascia is separated from the mucosa. **C:** The ascia is sutured together in the midline. Special care should be taken to ensure adequate support at the urethrovesical junction. **D:** Excess epithelium is trimmed. **E:** The epithelium is closed. A bite of the underlying fascia is included to minimize dead space. (From Mattingly RF, Thompson JD, eds. *Te Linde's operative gynecology*, sixth ed. Philadelphia: JB Lippincott Co, 1985:612, with permission.)

Plication of the suburethral fascia deserves special attention. Once the first suburethral suture has been placed and tied, it pulls some of the more lateral fascia into view, and this offers an opportunity to place a second suture in this same region and improve the elevation that was possible with the first suture. Once the remainder of the fascia has been closed, the cranial edge of the fascia at the vaginal apex should be tagged so that it may be included in the sutures that reattach it to the cardinal and uterosacral ligaments. This step will help elevate the upper margin of the fascia and pull it higher in the pelvis. An appropriate amount of vaginal epithelium is then trimmed (see Fig. 45.19D), and the epithelium is closed with running or interrupted sutures (see Fig. 45.19E).

Posterior Colpoperineorrhaphy

Next, a rectocele, if present, must be corrected. Although often undertaken at the end of a tiring operation, this repair requires the most skill and judgment of all phases of surgery for prolapse. Overcorrection of the posterior wall may leave the patient unable to have satisfying intercourse, yet a failure to reinforce the supportive position of the posterior vaginal wall may increase the likelihood that prolapse will recur. The goal of this portion of the operation is to reinforce the rectovaginal septum and to return the size of the introitus to normal.

The posterior colporrhaphy is begun by establishing the size that the introitus should be at the end of the procedure. This is accomplished by estimating the amount of vaginal and perineal skin that must be removed to return the introitus to a normal diameter. Allis forceps are placed to grasp a solid bite of tissue at the hymenal ring bilaterally at the margins of the mucosa that is to be excised. These forceps are then approximated in the midline to bring the soon-to-be-united parts of the introitus together. This allows a preview of the degree to which the introitus will be narrowed. Adjustments may then be made in the placement of the forceps to obtain an optimal result before an irrevocable incision is made into the perineum. A patient with a normal introitus who has a rectocele above this level need not have any tissue excised, and a vertical incision can be made in the introitus.

After the skin of the introitus is incised, the mucosa is undermined (Fig. 45.20A). The vagina and perineal body are fused, so dissection in the 3 cm inside the hymenal ring must be done sharply. If the rectovaginal septum is thin, placing a finger in the rectum to guide dissection will minimize the likelihood of proctotomy.

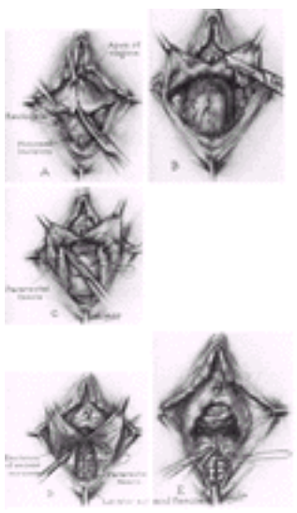

FIG. 45.20. A: To begin posterior colporrhaphy, a transverse incision is made in the perineal body, and a vertical incision is extended toward the vaginal apex. **B:** The perirectal fascia is mobilized from the mucosa. **C:** The perirectal fascia is sutured, beginning above the site of the rectocele. **D:** The inner surface of the levator ani muscles are approximated in the perineal body, and redundant mucosa is excised. **E:** The mucosa and perineal skin are closed. (From Mattingly RF, Thompson JD, eds. *Te Linde's operative gynecology*, sixth ed. Philadelphia: JB Lippincott Co, 1985:578, with permission.)

The rectovaginal space begins at the top of the perineal body and lies between the rectovaginal fascia and the rectum. It is a loose areolar plane and dissects easily. Once it is entered, it should be developed laterally (see Fig. 45.20B) until the inferior lateral sulcus of the vagina has been reached and the inner surfaces of the levator ani muscles can be felt. The upper limit of the dissection depends on the location of the rectocele and should extend, at least, to a point several centimeters above the upper limit of the bulge. When a posterior repair is used in a patient who previously had a hysterectomy, the upper vaginal dissection should include a search for an enterocele.

Once the rectovaginal space has been developed adequately, the repair may begin. With a finger depressing the rectum, the connective tissue lateral to the rectum is grasped with a needle and elevated, and the needle is retrieved (see Fig. 45.20C). A similar bite of the endopelvic fascia on the contralateral side is then taken. Successive sutures are then placed from that point to the introitus. After this is complete, it is prudent to make sure that no ridge has formed. If it has, the offending suture should be removed and replaced to avoid distortion. After this first layer has been placed, the space between the levator ani muscles may be narrowed by suturing their fascial covering, and the perineal body can be reconstructed (see Fig. 45.20D). This requires a second layer of sutures in the distal 3 cm of the vagina. After these sutures are placed, one final stitch usually is placed at the level of the hymenal ring to establish the triangular nature of the perineal body when seen in sagittal section. Finally, an appropriate amount of vaginal mucosa is trimmed, and the vaginal edges are reapproximated with interrupted or running absorbable sutures

(see Fig. 45.20E).

When the operation is finished, the adequacy of the vagina for intercourse should be assessed. Despite precautions to avoid vaginal stenosis, it sometimes is noted after the repair is complete. If so, relaxing incisions may be made in the vaginal wall to relieve the stricture, or part of the repair may be taken down and resutured. Time rarely improves a bad initial repair, and correction in the operating room is far superior to taking the patient back to the operating room later for revision.

Le Fort Partial Colpocleisis

In elderly patients who will no longer be engaging in intercourse, a colpocleisis may be used to cure the prolapse. This operation carries less operative and postoperative morbidity and may be performed under local anesthesia in the rare patient whose medical condition puts her at too great a risk to have a regional anesthetic. It consists of denuding a rectangle of anterior and posterior vagina and sewing them together (Fig. 45.21). This prevents the uterus and vagina from prolapsing. An adjunctive high perineorrhaphy at the time of the colpocleisis forms a shelf for the repair to rest on, so as to lessen the likelihood of prolapse recurring. Channels are left below the cervix and lateral to the closure to provide egress of cervical secretions and blood, should postmenopausal bleeding occur. Because the uterus is not removed and access to the cervix is blocked, care should be exercised in the preoperative evaluation to make sure that endometrial carcinoma is not present or likely to develop. Intraoperative dilation and curettage should be considered, as well, to exclude carcinoma.

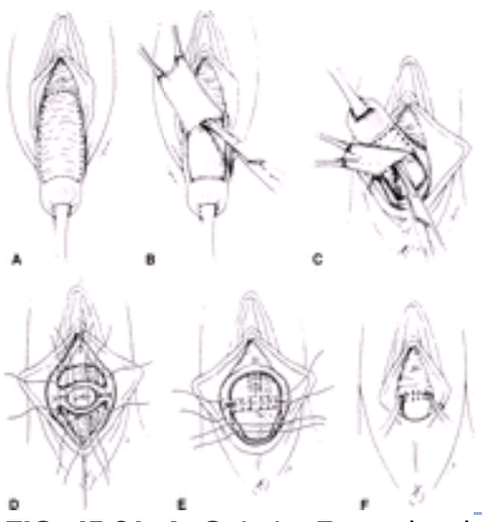

FIG. 45.21. A–C: In Le Fort colpocleisis, rectangles of vaginal mucosa are removed from the anterior and posterior vaginal walls. **D,E:** The denuded areas are then sutured together, leaving **(F)** channels on each side open. (From Mattingly RF, Thompson JD, eds. *Te Linde's operative gynecology*, sixth ed. Philadelphia: JB Lippincott Co, 1985:562, with permission.)

Stress incontinence may follow colpocleisis if there is poor urethral support associated with the prolapse. In this instance, steps should be taken during the operation to improve the situation. Preoperatively, occult stress incontinence may be detected by examining the patient with a full bladder and having her cough with the prolapse reduced. If stress incontinence is elicited, steps must be taken to improve urethral support by plicating the endopelvic fascia under the urethra or considering an incontinence procedure such as a postoperative collagen instillation, a pubovaginal sling, or a tension-free vaginal tape procedure.

Vaginal Repair of the Posthysterectomy Enterocele

The description earlier in this chapter concerning care of an enterocele and the cul-de-sac involves management of an enterocele encountered with the uterus in situ during vaginal hysterectomy. Because enterocele after hysterectomy is a significant problem in its own right, it will be considered separately here. Certain features of enterocele, such as its occurrence after high retropubic urethral suspension, warrant special consideration. Repair of an enterocele should not only obliterate the cul-de-sac but also should pull the vagina over the rectum by shortening the ligamentous suspension of the vagina, so that the normal closure of this space may be maintained. In addition, if the vaginal wall has been stretched because of its protrusion below the pelvic floor, the excess vaginal wall must be excised. Although transabdominal enterocele repairs (e.g., Moschcowitz, Halban) are useful as prophylaxis at the time of abdominal repair, an enterocele that appears after hysterectomy can almost always be repaired vaginally. This is the preferred method, because it avoids the morbidity of an abdominal incision and is much easier to perform.

The vaginal wall is opened over the enterocele sac. If a concomitant rectocele is present, this may be done by extending the incision made for the posterior repair up to the apex of the vagina. If a pure enterocele is present, the incision is made directly over the enterocele. In instances where the prolapsed vaginal wall has become stretched, a diamond-shaped incision may be made to excise the excess vaginal skin (Fig. 45.22A). Once identified, the peritoneum is separated from the vaginal wall (see Fig. 45.22B), and the excess peritoneum is excised. Next, the remnants of the uterosacral ligaments are brought together under the peritoneum and attached to the vaginal apex to improve its support (see Fig. 45.22C). At that point, any excess vaginal wall is trimmed, a posterior repair performed if needed, and the vaginal incision closed. Most enterocele repairs should be accompanied by a posterior colpoperineorrhaphy.

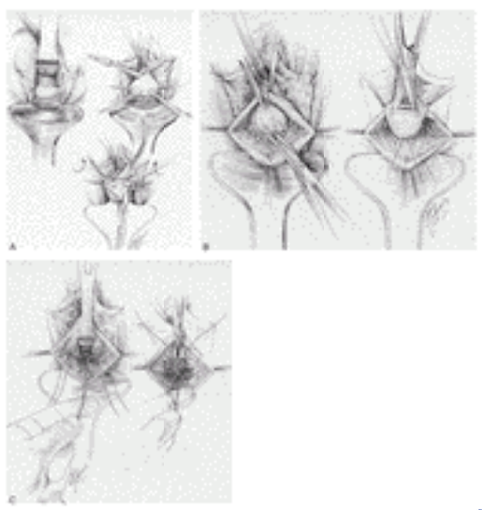

FIG. 45.22. A: The enterocele is exposed, and a diamond-shaped piece of vaginal wall is excised to reduce the size of the stretched upper vagina. **B:** The peritoneum is dissected from the surrounding structures, and it is closed with a purse-string suture. **C:** The uterosacral ligaments are defined by creating opposing traction with a retractor and suture to complete repair, after which the vaginal wall is closed. (From Segala CJ. New technique for the repair of vaginal vault prolapse following hysterectomy. *Int Surg* 1969;51:36, with permission.)

Posthysterectomy Prolapse

Prolapse subsequent to hysterectomy deserves special consideration. One third to one half of women will have had a hysterectomy by the age of 65, so prolapse in older women often will occur in the absence of a uterus. Although it might appear that these individuals would have only a cystocele or rectocele, because there could be no uterine prolapse, prolapse of the vaginal apex is often present. Apical prolapse must be recognized; otherwise, repair of a cystocele or a rectocele associated with prolapse of the vaginal apex is doomed to failure. Additionally, without recognition of the apical prolapse, the surgeon is likely to excise too much vaginal tissue with anterior and posterior colporrhaphy, leaving the patient with a very shortened, narrow vagina.

When the apex of the vagina, marked by the scar at the former location of the cervix, prolapses below the hymenal ring, vaginal prolapse is present. This usually is accompanied by an enterocele and often is seen in combination with a cystocele or a rectocele. To cure these patients, the apex of the vagina must be returned to and held in its normal position in the pelvis, and the cystocele or rectocele must be repaired. This may be accomplished by suturing the vaginal apex to the sacrospinous

ligament (Fig. 45.23A) or to the sacrum, using an interposing graft in an operation known as *abdominal sacral colpopexy* (Fig. 45.23B), or by performing a high uterosacral suspension. Each of these operations is accompanied by repair of the enterocele and whatever other prolapse must be addressed. In women who are no longer interested in preserving coital function, a complete colpocleisis obliterates the vagina and prevents prolapse from occurring, and this provides an easy, safe, and effective technique to relieve the symptoms.

FIG. 45.23. A: The vagina is fixed to the sacrospinous ligament. (From Morely GW, DeLancey JOL. Sacrospinous ligament fixation for eversion of the vagina. *Am J Obstet Gynecol* 1988;158:872, with permission.) **B:** The vaginal apex is attached to the sacrum with an intervening graft. (From Addison WA, Timmons MC, Wall LL, et al. Failed abdominal sacral colpopexy: observations and recommendations. Obstet Gynecol 1989;74:480, with permission.)

Paravaginal Repair

When a cystourethrocele persists or returns soon after anterior colporrhaphy, this often means that the loss of anterior vaginal wall support is due to a paravaginal separation of the pubocervical fascia from its normal lateral attachment to the arcus tendineus rather than to a midline defect in the fascia. In this instance, repeating the anterior colporrhaphy will not be effective, and repair of the separation will be required. Although the paravaginal repair usually is described as an operation to treat stress incontinence associated with cystourethrocele, it also is helpful in treating cystourethrocele in the absence of stress urinary incontinence, especially when an anterior colporrhaphy has failed. This retropubic operation reattaches the lateral margin of the pubocervical fascia to the pelvic sidewall along a line from the undersurface of the pubic symphysis to the ischial spine, along the line of the arcus tendineus. This reestablishes the normal lateral attachments of the pubocervical fascia and, therefore, prevents downward displacement of the bladder. It has not yet been established as a necessary procedure in the primary treatment of cystourethrocele without stress incontinence but, in instances of recurrent cystocele after anterior repair, simply repeating an operation that has not helped the patient is not desirable.

Conservative Measures

Vaginal pessaries are perhaps the oldest effective treatment for prolapse. Named after an oval stone (i.e., a *pessos*) used in certain Greek games, innumerable natural and man-made materials have been used to make pessaries. These objects are placed in the vagina. Because they are larger than the introitus, they are retained in the vagina above the pelvic floor musculature and thereby prevent the somewhat smaller uterine cervix from passing through the opening. When the pelvic muscles are relatively normal, these devices work well. When the pelvic floor opening is enlarged because of damage to the levator ani, a pessary may not be retained.

There are countless varieties of pessaries. The ones most commonly used for prolapse are the doughnut-shaped pessaries, either permanently inflated or inflatable. The largest pessary that the vagina will accommodate without undue pressure on the vaginal walls is inserted. Often, patients can be taught how to place and remove them. Having the patient remove the pessary at night minimizes the discharge inevitably associated with its use. Adjunctive treatment with topical or systemic estrogen helps the vaginal mucosa tolerate the foreign body. Because pessaries may cause erosion and ulceration, they should be checked periodically. If an ulcer is developing, pessary use should be discontinued or a smaller one fitted, and the ulcer should be monitored until it heals.

SUMMARY

Pelvic organ prolapse affects between 5% and 10% of women. It arises due to damage to the levator ani muscles and endopelvic fascia that occurs at the time of vaginal birth and the deterioration that occurs in these tissues with advancing age. Women who have these conditions express distress from the constant, unrelenting feelings of pressure and incontinence and from fear that this protrusion may lead to other problems.

The term *pelvic organ prolapse* encompasses a variety of related conditions that arise when the muscles and connective tissues of the pelvic floor can no longer hold the pelvic organs in their normal positions. The location and nature of the muscle injury and fascial ruptures determine which pelvic organ falls downward. The symptoms experienced by a woman come from this mechanical misalignment, along with the functional derangements of the pelvic viscera determined by neurologic injury and these prolapses. Identifying both the location of the abnormality and the symptoms experienced by the individual woman are critical to successful treatment.

Surgical treatment is aimed at resuspending the prolapsed pelvic organs and rearranging the damaged muscles to place them in the most favorable locations for function. This field is characterized by a great diversity of operative procedures used to correct individual elements of defective pelvic organ support. The particular operation that is chosen depends on the anatomic and functional abnormalities that a woman experiences, as well as the training of the surgeon. Individual surgeons become familiar with a subset of these techniques that allows them to address the problems they face. No two surgeons treat these problems in exactly the same way, and a good surgeon rarely will do two operations that are exactly alike.

SUMMARY POINTS

- Pelvic organ prolapse is a remarkably common and distressing condition.
- Vaginal delivery and advancing age are the most common factors causing pelvic organ prolapse.
- Pelvic organ prolapse arises due to a combination of neuromuscular and connective tissue injury and has variable symptoms associated with its development.
- Evaluating the status of each element of pelvic organ support is critical prior to instituting treatment.
- Surgical treatment of pelvic organ prolapse must be tailored to each woman's condition, so that all areas of pelvic support loss are corrected.

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Chapter 46

Joseph S. Sanfilippo and Lisa M. Roberts

Laparoscopic Surgery

LAPAROSCOPY
Patient Positioning
Equipment
Physiologic Effects of the Pneumoperitoneum
Anatomy of the Anterior Abdominal Wall
Obtaining Intraabdominal Access
Laparoscopic Procedures
Complications
SUMMARY POINTS

SUGGESTED READINGS

Introduction
Laparoscopy
Complications

In one sense, the historical perspective of endoscopic surgery begins in 1847, with Sir James Y. Simpson of Edinburgh, Scotland, introducing chloroform narcosis. This advance was followed by the first endoscopic evaluation of the abdominal cavity, using a dog model in 1901, by Kelling. Ten years later, Jacobaeus reported the first laparoscopic procedure in the human. Cold illumination fiberoptics followed, by Semm in 1963, and then the surgical area rapidly evolved. The first laparoscopic appendectomy was performed in 1980 and the first cholecystectomy in 1985.

This relatively new aspect of endoscopic surgery has far-reaching and ever increasing innovative aspects. Hysteroscopy has altered the approach to the myomatous uterus. Laparoscopy has blossomed to include radical hysterectomies and node sampling. This chapter provides the technical advances in a segment of gynecologic surgery that appears to be in a continuous state of evolution and ever more far-reaching new instrumentation.

LAPAROSCOPY

Patient Positioning

Proper patient positioning is paramount. The surgeon should position the patient so as to prevent any excessive pressure on the lower extremities. Nerve injuries can result from improper placement of the lower extremities in stirrups. Lithotomy position with access to steep Trendelenburg is appropriate. The physician should discuss with anesthesia personnel decisions regarding whether the arms should be extended or “tucked” along the sides of the patient. The latter requires particular attention to prevent any trauma to the hands and fingers when the table is maneuvered.

With the patient in the low lithotomy position and the legs supported in stirrups, the buttocks should protrude slightly from the lower edge of the table. The lateral aspect of the knee should be protected with padding in the stirrup to prevent peroneal nerve injury. The knees should be kept in slight flexion to minimize stretching of the sciatic nerves and to provide increased stability in the Trendelenburg position. With respect to positioning of the arms, care should be taken not to stretch or traumatize the brachial plexus.

It has been advocated that an angle of 145 degrees between the abdomen and the lower extremity (thigh) is ideal, providing the surgeon with adequate space for instrumentation. The typical patient positioning for endoscopic surgery is noted in Figure 46.1.

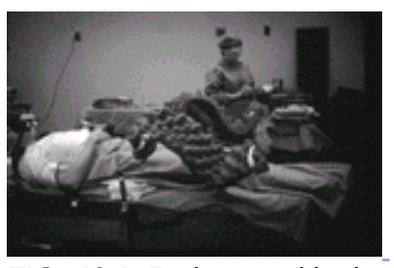

FIG. 46.1. Patient positioning for laparoscopic surgery.

Equipment

An array of instruments designed to facilitate operative laparoscopic procedures continues to evolve. This section describes a number of instruments.

Viewing System The video equipment should include a three-chip camera, a processor, a 300-watt xenon light source with fiberoptic cable, a high-resolution monitor, and a video recorder. The three-chip camera provides a sharper, brighter image with higher resolution than the older single-chip cameras (Fig. 46.2). Three-chip cameras can deliver over 600 lines of resolution; therefore, the video monitor's horizontal resolution should be greater to maximize image quality. Fiber light cables should be inspected for broken fibers, because damaged fibers will result in suboptimal light delivery.

FIG. 46.2. Autoclavable Goldtip videolaparoscope with camera processor and xenon light source (Olympus, Melville, NY).

Table An operating room table that allows 30 degrees of flexion (Trendelenburg position) is ideal for visualization of the deep pelvis. Shoulder braces (Stierlen-Maquet Shoulder Braces, Siemens Medical Systems, Englewood, CO) placed at the acromioclavicular joints and the arms placed at the patient's sides will minimize nerve injuries.
Insufflator For most procedures, the pneumoperitoneum may be maintained with an insufflator that flows at a rate of 2 to 7 L/min. High-flow insufflators that achieve up to 30 L/min are available and will maintain the pneumoperitoneum during procedures that allow escape of large amounts of CO_2, such as during tissue morcellation.
Carbon Dioxide Warmer There is evidence that warmed CO_2 is less irritating to the peritoneal surface and, therefore, may cause less adhesion formation. CO_2 warmers are commercially available.
Laparoscopes Laparoscopes are telescopes that vary in size from 2 to 10 mm. Zero-degree, 30-degree, 45-degree, and 70-degree viewing angles are available. Diagnostic laparoscopes do not contain an operating channel. Operative laparoscopes contain a channel through which instruments or laser may be passed, but they have a smaller number of optic fibers (Fig. 46.3 and Fig. 6.4).

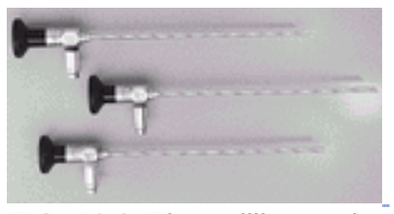

FIG. 46.3. Five-millimeter laparoscopes (Karl Storz Endoscopy-America, Culver City, CA).

FIG. 46.4. Ten-millimeter laparoscope (Karl Storz Endoscopy-America, Culver City, CA).

Trocars Trocars come in a variety of sizes, materials, and designs. Sizes range from 3 to 15 mm. Reusable metal trocars have the advantage of cost efficiency, but they may actually be more dangerous if the tips are not kept sharp (Fig. 46.5, Fig. 46.6 and Fig. 46.7). Disposable trocars are more expensive but are always sharp, which may decrease the risk of injury during insertion (Fig. 46.8). Some trocars are designed to stretch the fascia so that fascial closure is not necessary. Others have been designed to allow visualization of tissue layer separation with the laparoscope during insertion. Advocates assert that this type of trocar decreases bowel and vascular injuries. There are no objective data supportive of a reduction in risk for any trocar. The trocar chosen should be based on the surgeon's preference. Hasson-type trocars have a blunt end for placement in open laparoscopy (Fig. 46.9 and Fig. 46.10).

FIG. 46.5. Five- and ten-millimeter trocars (Karl Storz Endoscopy-America, Culver City, CA).

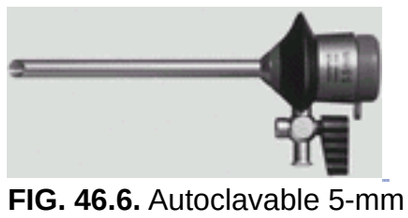

FIG. 46.6. Autoclavable 5-mm slim trocar with duckbill (Olympus, Melville NY).

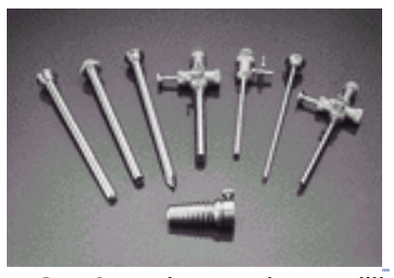

FIG. 46.7. Five- and ten-millimeter reusable trocars.

FIG. 46.8. Ten-millimeter disposable trocar (Olympus, Melville, NY).

FIG. 46.9. Ten-millimeter blunt trocar for open laparoscopy (Marlow Surgical Technologies, Inc., Willoughby, OH).

FIG. 46.10. Ten-millimeter blunt trocar for open laparoscopy (Apple Medical, Bolton, MA).

Operating Instruments A standard laparoscopy set should include the following: Trocars
Bipolar forceps (Fig. 46.11 and Fig. 46.12)

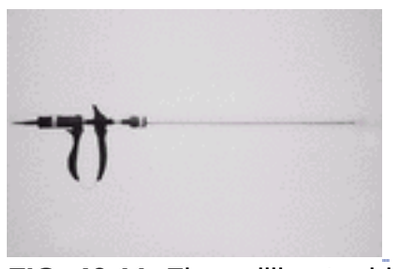

FIG. 46.11. Five-millimeter bipolar forceps (Olympus, Melville, NY).

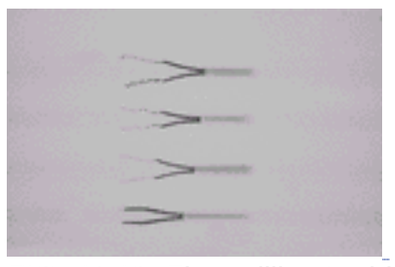

FIG. 46.12. Five-millimeter bipolar forceps (Olympus, Melville, NY).

Atraumatic grasping forceps (Fig. 46.13, Fig. 46.14 and Fig. 46.15)

FIG. 46.13. Atraumatic tissue grasper (Applied Medical, Rancho Santa Margarita, CA).

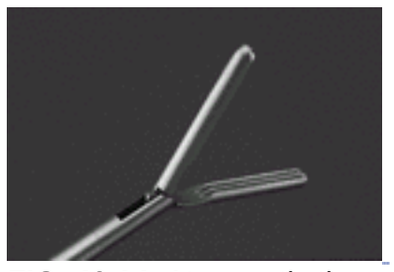

FIG. 46.14. Atraumatic tissue grasper.

FIG. 46.15. Atraumatic tissue grasper.

Biopsy forceps (Fig. 46.16)

FIG. 46.16. Biopsy forceps.

Blunt probe
Blunt sawtooth scissors (Fig. 46.17)

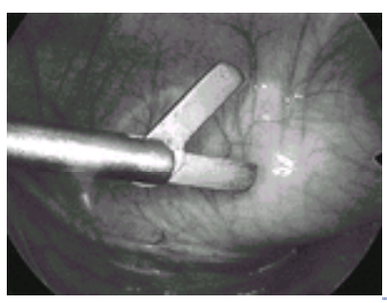

FIG. 46.17. Blunt sawtooth scissors (Richard Wolf Medical Instruments, Vernon Hills, IL).

Pointed Metzenbaum scissors (Fig. 46.18)

FIG. 46.18. Metzenbaum scissors (Richard Wolf Medical Instruments, Vernon Hills, IL).

Cyst aspiration needle (Fig. 46.19)

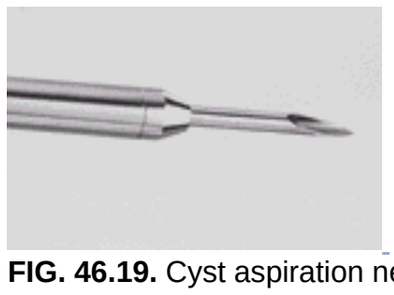

FIG. 46.19. Cyst aspiration needle.

Suction and irrigator
Uterine manipulator (Fig. 46.20 and Fig. 46.21)

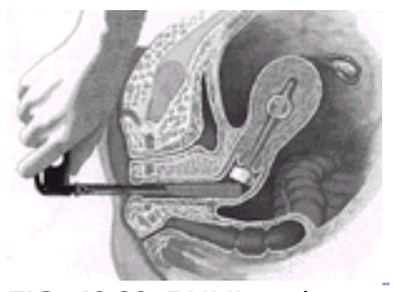

FIG. 46.20. RUMI uterine manipulator (Cooper Surgical, Shelton, CT).

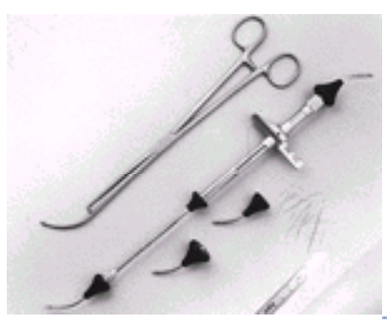

FIG. 46.21. Hulka uterine manipulator tenaculum (Richard Wolf Medical Instruments, Vernon Hills, IL) and Cohen Uterine Cannula (Karl Storz Endoscopy-America, Culver City, CA).

An advanced laparoscopy set may also include: Needle holders (Fig. 46.22, Fig. 46.23 and Fig. 46.24)

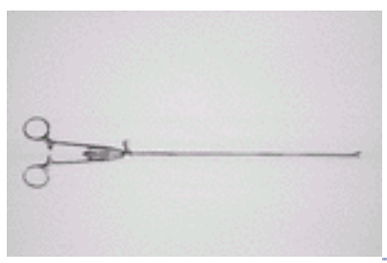

FIG. 46.22. Five-millimeter needle holder (Olympus, Melville, NY).

FIG. 46.23. Five-millimeter needle holder (Olympus, Melville, NY).

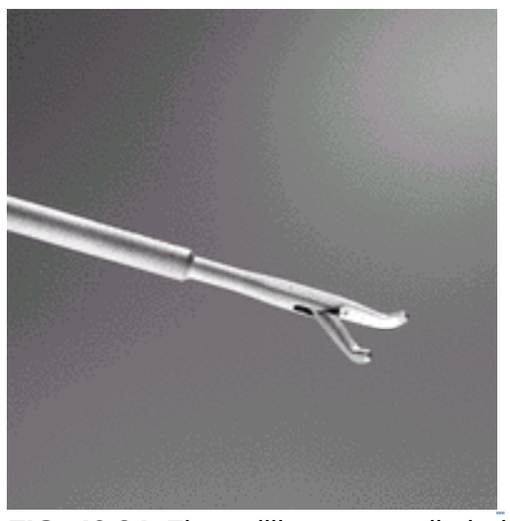

FIG. 46.24. Five-millimeter needle holder (Karl Storz Endoscopy-America, Culver City, CA).

Knot pusher (Fig. 46.25)

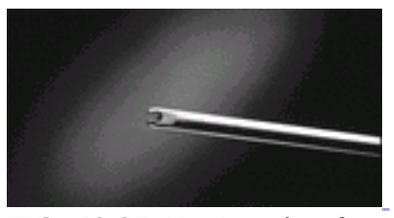

FIG. 46.25. Knot pusher for extracorporeal suturing (Marlow Surgical, Roebling, NJ).

Vaginal delineator (Fig. 46.26)

FIG. 46.26. Koh Cup Vaginal Fornices Delineator (Cooper Surgical, Shelton, CT).

Babcock clamp (Fig. 46.27)

FIG. 46.27. Babcock atraumatic grasper.

lAlis clamp
Adson forceps (Fig. 46.28)

FIG. 46.28. Adson forceps.

Corkscrew
Single-tooth tenaculum
Atraumatic bowel grasper
Monopolar spatula (Fig. 46.29)

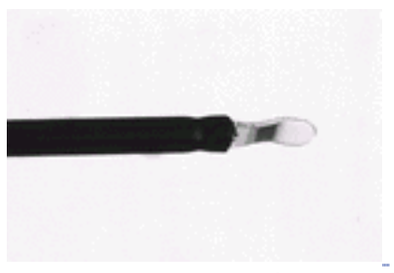

FIG. 46.29. Monopolar spatula for cutting and coagulation.

Endoscopic specimen retrieval bags (Fig. 46.30 and Fig. 46.31)

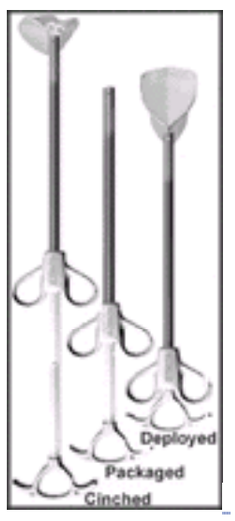

FIG. 46.30. Endo Catch instrument with a specimen bag (U.S. Surgical, Norwalk, CT).

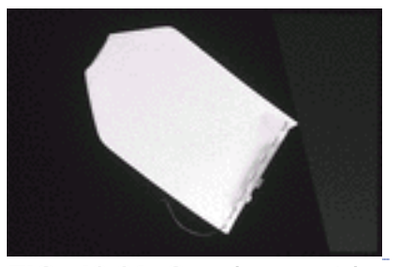

FIG. 46.31. Specimen retrieval bag (Cook Ob/Gyn, Spencer, IN).

Endoscopic suture ligatures (Fig. 46.32)

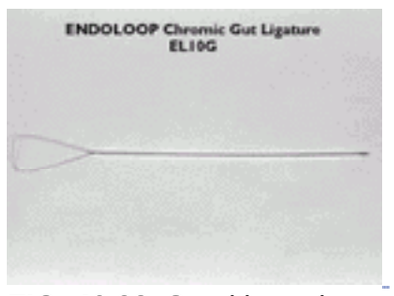

FIG. 46.32. Surgitie endoscopic suture ligature (U.S. Surgical, Norwalk, CT).

Microbipolar forceps
Morcellator
Rectal probe
Staplers Endoscopic staplers that simultaneously ligate and divide tissue are available. In gynecologic procedures, they are used most commonly on the infundibulopelvic ligament, round ligament, fallopian tubes, and uteroovarian ligaments in laparoscopically assisted vaginal hysterectomies. They also may be used when excising endometriosis from the bowel (Fig. 46.33).

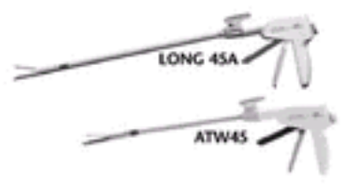

FIG. 46.33. Stapling device (U.S. Surgical, Norwalk, CT).

Harmonic Scalpel The active blade of the Harmonic Scalpel (Ethicon Endosurgery, Cincinnati, OH) vibrates at a rate of 55,000 cycles per second, resulting in coagulation and tissue separation. The scalpel is available as a 5- or 10-mm “hook,” “ball” dissector, spatula, or opposing jaws. Although electrical energy is not used, the tissue still becomes heated and a 2-mm lateral energy spread, which can cause thermal injury, may be seen.
Electrosurgery Unipolar electrosurgical instruments are used to cut and coagulate tissue. Cutting occurs when there is sufficient voltage (at least 200 volts) between the electrode and the tissue to produce an electric arc. This arc concentrates the current to points along the tissue, resulting in a cutting effect. In contrast to cutting current, coagulation is produced through instrument contact with the tissue. Contact allows heating of the tissue followed by irreversible cellular damage, evaporation of intracellular water, and contraction of blood vessels and surrounding tissue. Electrosurgical burns may occur due to insulation failure, direct coupling (activated electrode makes unintended contact with another metal object in the area of the surgical field), or capacitive coupling (induction of stray current to a surrounding conductor through the intact insulation of an active electrode). Bipolar electrosurgical instruments contain the electrical current between an active and return electrode, usually the two blades of forceps. The flow of alternating current is passed between the two electrodes rather than passing through the patient to a grounding pad. This eliminates the risk of capacitive coupling and stray current.
Laser Lasers offer an alternative method of cutting and vaporizing tissue. The CO_2 laser with a depth of penetration of 1 mm allows the surgeon some security when working around bowel, ureters, and large blood vessels. In addition, a CO_2 laser will not traverse through water, thus irrigation fluid may be used as a backstop. The Coherent 5000L (Coherent Laser, Palo Alto, CA) laser offers high-power density over a short period of time, minimizing thermal damage to surrounding tissue. This laser uses a ^{13}C isotope of CO_2 with an 11.1-mm–wavelength beam. The wavelength of the CO_2 purge gas in the operating channel of the laparoscope is 10.6 mm. Because the wavelengths are different, there is no absorption of the laser beam by the purge gas, keeping the power density 10 times more than at similar settings with other standard laser beams with 10.6-mm wavelengths. The 1.5-mm spot size is maintained at all power settings, offering precision, minimal surrounding tissue damage, and less charring. Fiber lasers (potassium-titanyl-phosphate [KTP], argon, and Nd:YAG [YAG]) are introduced through small channels of the operating laparoscope or through ancillary trocars. The KTP and argon lasers may be used for cutting and coagulating. As the tip of the fiber approaches the tissue, the power density increases and the laser is used for cutting. As the tip is moved away from the tissue, the spot size increases and power density decreases rapidly. The clinical applications for the YAG laser are more limited. The YAG laser coagulates well, but it doesn't cut well unless a sapphire tip is used to increase the power density.
Handoscopy Hand-assisted laparoscopy, or “handoscopy,” has become popular, mainly in the field of solid organ and bowel surgery. To date, the only gynecologic procedure where this device has been used is rectal resection for deep fibrotic endometriosis. The main advantage of handoscopy is that it allows the surgeon to regain the tactile feel of tissues lost in standard laparoscopies.

Physiologic Effects of the Pneumoperitoneum

The respiratory, hemodynamic, and renal consequences of the pneumoperitoneum are substantial but usually are well tolerated by the healthy patient. These changes may be severely problematic in the patient whose cardiopulmonary or renal system is compromised.

Respiratory Changes Ventilation during laparoscopic surgery is altered by the increased intraabdominal pressure (IAP) of the pneumoperitoneum. The airway pressure required for adequate ventilation consequently is increased. Thoracic compliance, diaphragmatic excursion, and functional residual capacity are all decreased. Studies have shown that the increase in IAP alone reduces compliance by 30%; this may be decreased by another 20% when the patient is placed in a Trendelenburg position. In addition to mechanical changes, the CO_2 pneumoperitoneum produces changes in acid–base balance. Because carbon dioxide is absorbed rapidly from the peritoneal cavity, the minute volume must be increased as indicated by the end-tidal CO_2 to prevent respiratory acidosis (Table 46.1).

1. Hypercapnia with subsequent acidosis
2. Increased airway pressure
3. Decreased functional residual capacity
4. Decreased thoracic compliance
5. Decreased diaphragmatic excursion

TABLE 46.1. *Ventilatory effects of carbon dioxide pneumoperitoneum*

Hemodynamic Changes Circulatory changes seen during laparoscopic surgery are the result of the mechanical compressive effects of the increased IAP and its associated hormonal changes (Table 46.2). Catecholamines, angiotensin, and vasopressin are all increased, resulting in increased systemic vascular resistance. An increase in systemic vascular resistance results in an increase in mean arterial pressure and a decrease in cardiac index. The increased IAP also causes increased intrathoracic pressure, with resultant increases in central venous pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance.

1. Increased systemic vascular resistance
2. Increased mean arterial pressure
3. Decreased cardiac index
4. Increased central venous pressure
5. Increased pulmonary vascular resistance
6. Increased pulmonary capillary wedge pressure

TABLE 46.2. *Hemodynamic effects of carbon dioxide pneumoperitoneum*

Renal Blood Flow Changes Animal studies have shown an increase in renal vascular resistance and a decrease in renal perfusion and glomerular filtration rate secondary to increased IAP. A subsequent decrease in urine output may be observed and may continue to remain low 1 hour after release of the pneumoperitoneum (Table 46.3).

1. Increased renal vascular resistance
2. Decreased renal blood flow
3. Decreased glomerular filtration rate
4. Decreased urine output

TABLE 46.3. *Renal effects of carbon dioxide pneumoperitoneum*

Compromised Patient The multiple cardiopulmonary and renal changes observed during CO_2 laparoscopy are well tolerated by the healthy patient. Extreme caution must be taken when performing gaseous laparoscopy in patients with compromised respiratory function, ischemic heart disease, congestive heart failure, and renal dysfunction. These compromised states may even be considered relative contraindications to gaseous laparoscopy. The lowest IAP that allows adequate visualization should be used to minimize increases in intrathoracic pressure. An alternative consideration would be to use an abdominal wall lift method (elevating the ventral abdominal wall by an inflatable balloon or fan retractor), eliminating the consequences of CO_2 in the peritoneum. The use of alternative gases such as argon, nitrous oxide, and helium for pneumoperitoneum has been considered. Carbon dioxide's advantages over these gases include higher solubility and, therefore, possibly fewer deleterious effects in event of gas embolism, ability to use cautery in its presence, and it is inexpensive. It is the surgeon's responsibility to take a careful history and perform appropriate preoperative diagnostic testing when determining a patient's candidacy for laparoscopic surgery. All of the advantages of laparoscopic surgery are inconsequential if the procedure is performed on an inappropriate patient.

Anatomy of the Anterior Abdominal Wall

Knowledge of the anterior abdominal wall vascular anatomy will reduce vascular complications associated with trocar placement. Of particular concern are the superior and inferior epigastric vessels. The superior epigastric artery, one of the terminal branches of the internal thoracic artery, enters first the rectus sheath and then the rectus muscle coursing near its lateral border. This artery and its adjacent vein often can be visualized by transillumination of the abdominal wall with the laparoscope.

Visualization of the ventral abdominal wall laparoscopically often will locate the deep inferior epigastric vessels. The artery, a branch of the external iliac, and its accompanying vein course along the abdominal wall peritoneum just lateral to the rectus muscle until midway between the symphysis pubis and umbilicus, where it blends into the body of the rectus muscle. These vessels may be seen medial to the insertion of the round ligament at the deep inguinal ring. Therefore, placement of the trocar lateral to the deep inguinal ring and lateral border of the rectus muscle will avoid injury to these vessels.

If placement of the trocar is too far laterally, branches of the superficial circumflex iliac vessels may be injured. Again, transillumination of the anterior abdominal wall using the laparoscope will assist in avoiding these vessels.

As a general guideline, the superficial and inferior epigastric vessels are located approximately 5.5 cm from the midline. The superficial circumflex iliac vessels are approximately 7 cm from the midline. Theoretically, a “safe area” would be 8 cm above the symphysis pubis and 8 cm from the midline. If transillumination is not effective due to a thick abdominal wall, the surgeon may consider insertion of a spinal needle through the abdominal wall at the selected trocar insertion site. If no bleeding is observed after removal of the needle, the location is likely safe for trocar placement.

Obtaining Intraabdominal Access

For most laparoscopic surgeons, obtaining access to the peritoneal cavity is the most anxiety-provoking step of the entire endoscopic procedure. There are a number of ways to obtain intraabdominal access for trocar placement and establishment of a pneumoperitoneum. None of the available methods precludes the possibility of complications from trocar or needle insertion. In general, these methods of entry can be classified as either open or closed.

An open entry uses the technique first described by Harry Hasson. An incision into the peritoneal cavity through all anterior abdominal wall layers at the umbilicus is made carefully. A blunt-tipped trocar is placed through the incision into the abdominal cavity. Insufflation is conducted through this trocar sleeve. This technique may reduce vascular injuries due to sharp trocar or needle placement, but the possibility of bowel injury still exits if there are abdominal wall adhesions.

The closed entry may be performed with or without the use of a Veress needle to insufflate CO_2. Placement of the sharp trocar through the umbilicus without prior insufflation has lost favor due to the higher risk of bowel and vascular injuries.

Insufflation of CO_2 through a Veress needle is the most common method of entry, although some would argue the open technique should become the method of choice. One technique of access using a Veress needle is performed in the following manner:

1. A vertical incision through the skin corresponding to the size of the trocar is made at the base of the umbilicus. Note that this incision ideally is made at the *base* of the umbilicus and not infraumbilically as is classically taught. This is because the distance between skin and peritoneum on the anterior abdominal wall is shortest at the base of the umbilicus. In addition, the peritoneum is firmly attached, which will prevent tracking through the subcutaneous tissue and subsequent retroperitoneal insufflation.
2. The Veress needle is inspected for sharpness and a functioning spring mechanism to extend the protective sheath in the absence of pressure.
3. The anterior abdominal wall inferior to the umbilicus is grasped with the nondominant hand and the umbilicus is moved in the caudad direction, further displacing it below the bifurcation of the aorta. Alternatively, the incision may be elevated by grasping the edges of the umbilical incision with two Alice clamps and lifting.
4. The tip of the Veress needle is held in the dominant hand between the thumb and forefinger while the ulnar palm rests on the patient's abdomen. The needle is inserted carefully at a 90-degree angle, through the base of the umbilicus, millimeter by millimeter, until a click is heard and resistance is no longer felt, identifying intraabdominal placement.
5. A saline-filled 10-cc syringe is attached to the Veress needle and aspirated, inspecting for blood or bowel contents. If only bubbles are visible, saline is injected and observed to fall from the trough on the needle into the peritoneal cavity.
6. The syringe is removed, the insufflation tubing (with CO_2 turned on low flow) is attached, and the initial IAP is observed. If the pressure is greater than 10 mm Hg, the needle should be removed quickly to avoid retroperitoneal insufflation, which further displaces the peritoneum from its attachment to the anterior abdominal wall. A second needle placement attempt is then made.
7. Once intraperitoneal placement is confirmed, a CO_2 pneumoperitoneum is obtained. Insufflation up to an IAP of 20 to 25 mm Hg, as initially described by Reich and others, remains one accepted method. This temporary increase in IAP increases the distance between abdominal viscera and the anterior abdominal wall (in the absence of adhesions) during primary sharp trocar placement through the umbilicus. It is also extremely beneficial for surgeons with small hands, who may find it difficult to grasp and further elevate the abdominal wall if the initial pressure is less than 20 mm Hg.
8. The end of the sharp trocar is held in the palm of the dominant hand, with the forefinger extended along the shaft as close to the sharp tip as possible. The tip is inserted through the umbilical incision until the fascia at the base of the umbilicus is felt. Insertion is carried through at a near-90-degree angle until the tip is felt to pass through the peritoneum. The trocar is then directed toward the pelvis to minimize risk of vascular or bowel injury.
9. After placement of the primary trocar, the intraabdominal placement is confirmed visually and the IAP is reduced to 12 to 15 mm Hg.

Alternative methods for obtaining pneumoperitoneum have been described and are useful in cases in which adhesions at or near the umbilicus are suspected. The most common method is insertion of the Veress needle in the left upper quadrant, followed by placement of a 5-mm trocar and laparoscope. Others have performed insufflation after inserting a Veress needle transfundally or through the posterior cul-de-sac into the intraabdominal cavity.

There are no prospective randomized studies comparing the safety and efficacy of open-entry with closed-entry techniques. The incidence of injuries is so low that a very large study population would be required to show any statistical difference. Randomized studies comparing the Veress needle with the direct trocar insertion technique favor the Veress needle. The vast majority of surgeons agree that the method used should be that with which the surgeon has the most experience and is, therefore, most comfortable.

Laparoscopic Procedures

Ectopic Pregnancy Through earlier diagnosis, ultrasonography has reduced significantly the morbidity and mortality associated with ectopic pregnancies. In 98% of cases after the fifth week of pregnancy (when HCG levels are greater than 1,000), transvaginal ultrasonography can reliably visualize a normal gestational sac. The absence of an intrauterine sac above this level should alert the physician of a high likelihood of ectopic pregnancy. With the advent of methotrexate use, the total number of ectopic pregnancies treated surgically has decreased. Laparoscopy remains a standard for surgical management in the stable patient. While obtaining

informed consent, the surgeon must discuss management alternatives. Should the pregnancy alone be removed leaving the fallopian tube in place, or should a salpingectomy be performed? Assuming the pregnancy can be aborted without significant bleeding from the fallopian tube, this decision should be based on the status of the contralateral ovary and tube. If the contralateral tube and ovary are normal in appearance, without adhesions, then a salpingectomy or salpingostomy may be performed with a subsequent intrauterine pregnancy rate of 85% and a repeat ectopic rate of 90%. If the contralateral tube is impaired, then the subsequent intrauterine pregnancy rate is 46% and repeat ectopic rate 52%. In this situation, the affected fallopian tube should be removed.

Technique for Salpingostomy or Salpingectomy Laparoscopic access is obtained as previously described. In addition to the umbilical port, two 5-mm lower abdominal ports are indicated, left and right. A suction-irrigator is used to aspirate the hemoperitoneum, if present. The pregnancy is identified within the fallopian tube, usually within the ampullary portion. The tube is stabilized with a Babcock or atraumatic grasper. There is considerable debate regarding the use of dilute vasopressin prior to making the incision on the antimesenteric side of the tube overlying the pregnancy. Clinicians must understand the use of vasopressin has the potential for delayed bleeding postoperatively. An incision parallel to the axis of the tube is now made on the antimesenteric side. This may be performed using a spoon, knife, or hook monopolar electrocautery, set at 50 to 80 watts to minimize bleeding. The suction-irrigator is used to “aquadissect” the attachments between the pregnancy and tube, thus aborting the pregnancy into the pelvis. Alternatively, the pregnancy may be grasped using atraumatic graspers and pulled from its attachment. It is then removed from the abdomen through the operating channel of a right-angle laparoscope or a 10-mm or larger port. If significant bleeding is encountered or the pregnancy does not dissect freely, a salpingectomy may need to be performed. Again, the fallopian tube is grasped with an atraumatic grasper and lifted. The tube is transected approximately 1 cm from its cornual end. Transection is performed after complete desiccation using bipolar cautery via Kleppinger forceps or may be performed after suture ligation (a window is created within the mesosalpinx inferior to the ligation site). The mesosalpinx, immediately inferior to the fallopian tube, is then desiccated using bipolar cautery and transected, freeing the tube and pregnancy from its anatomic attachments.

Adnexal Mass Laparoscopic management of adnexal masses is gaining acceptance but still conjures considerable debate. The patient's age, transvaginal sonographic findings, and CA-125 level (if indicated based on patient's age) will determine if a laparoscopic approach rather than laparotomy is acceptable. Ultrasonographic criteria for benign and malignant tumors are presented in Table 46.4 and Table 46.5. CA-125 levels are most useful in postmenopausal women. A level of 35 units in postmenopausal women carries a sensitivity of 81% and specificity of 91% for malignancy. If the level is greater than 50, then the sensitivity remains essentially the same and the specificity increases to 97%. In premenopausal women, sensitivity remains 60% as the level increases, but specificity increases from 73% at a level of 35 to 95% at a level of 100.

Size greater than 5 cm
High (solid) echogenicity
Internal septations
Irregular border
Papillary intracystic formations
Ascites

TABLE 46.4. *Ultrasonographic criteria for malignant ovarian tumors*

Size less than 10 cm
Unilateral border
Smooth border
Absence of excrescences
Absence of solid parts
Absence of fluid in the cul-de-sac

TABLE 46.5. *Ultrasonographic criteria for benign ovarian tumors*

A primary concern for those advocating laparotomy over laparoscopy for management of suspicious adnexal masses is the potential increased risk of rupture during laparoscopic surgery. Preoperative or intraoperative rupture changes a stage Ia ovarian carcinoma to a stage Ic. Studies have shown that intraoperative iatrogenic rupture of the tumor capsule does not adversely affect survival, but survival is negatively influenced by spontaneous or preoperative rupture. The American College of Obstetricians and Gynecologists guidelines for intraoperative management of adnexal masses are presented in Table 46.6. As a general rule, if malignancy is highly suspected, then a laparotomy and complete surgical staging procedure should be performed. If a laparoscopy is performed initially and malignancy subsequently is identified histologically, the staging procedure should be completed within 1 week.

Obtain peritoneal washings
Explore the upper abdomen
Obtain biopsy specimens from any abnormal areas
Look for external excrescences
Perform laparotomy for any question of malignancy or if mass is removed inadequately
Use frozen sections for cytologic analysis; perform laparotomy if malignant

ACOG, American College of Obstetricians and Gynecologists.

TABLE 46.6. *ACOG guidelines for laparoscopic intraoperative management of adnexal masses*

Technique for Ovarian Cystectomy After obtaining intraperitoneal access and placement of trocars, the uteroovarian ligament is grasped to stabilize the ovary. The ovarian cortex overlying the cyst is incised very superficially so as not to rupture the cyst. This may be performed using a CO_2 laser set at 5 to 10 watts, a monopolar electrode (knife, hook, spoon) set at 30 to 50 watts of cutting current, or scissors. The edge of the cut ovarian cortex is grasped with a biopsy forceps and elevated. The suction-irrigator is placed gently at the opening between cortex and cyst wall. Aquadissection is performed using Ringer's lactate. A blunt grasper is introduced within the space and the cyst is shelled out from its attachment to the cortex. The incision is made longer as necessary. The cyst is placed within an impermeable sac introduced through the umbilical port or through a culdotomy incision. For larger cysts, a zip-lock type sandwich bag may be gas sterilized and placed through the 10- to 12-mm umbilical port. The sac is then removed either through the umbilicus or transvaginally. A spinal needle may be used to aspirate the contents of the cyst within the sac prior to removal to decrease its volume.

Technique for Oophorectomy The first step in an oophorectomy procedure is always identification of the adjacent ureter. The ureter is most easily located at the pelvic brim near the bifurcation of the common iliac. Its retroperitoneal course may then be followed and location relative to the infundibulopelvic ligament noted. Once certain of the ureteral location, the infundibulopelvic ligament is grasped gently, elevated, and brought medially using a Babcock or other atraumatic grasper. The ligament is then desiccated at its attachment to the ovary using bipolar cautery. It is then transected. Alternatively, an opening through the peritoneum inferior to the ligament may be created using scissors. Suture ligatures may then be placed and tied. After transection of the infundibulopelvic ligament, the uteroovarian ligament is desiccated and transected. Desiccation of the mesovarium is followed by transection, completely freeing the ovary. The ovary is then placed in an impermeable sac and removed as described previously.

Tubal Sterilization Surgical occlusion of the fallopian tubes is the most common method of contraception in developing countries. The techniques have evolved from a laparotomy to minilaparotomy to a laparoscopic approach including excision, electrosurgical desiccation using bipolar cautery, and application of clips or rings. A Pomeroy tubal ligation is easily performed laparoscopically by grasping the fallopian tube at its isthmic portion and placing a chromic endoloop suture around a segment of tube. The knuckle of tube may then be excised. Two clips are approved by the U.S. Food and Drug Administration for tubal occlusion, the Hulka-Clemens clip and the Filshie clip. Both clips are placed properly at the proximal isthmus after the tube has been placed on stretch. The clip should be applied at 90 degrees to the long axis of the tube and advanced until the hinge reaches the tube, incorporating the mesosalpinx at its tip. The falope ring is placed on the ampullary portion of the fallopian tube by grasping the tube with the applicator and drawing the tube inside the applicator. A 1- to 2-cm segment of tube is drawn into the ring. Although sterilization failure rates are lowest with unipolar cautery, most are performed using bipolar cautery. Bipolar desiccation is performed correctly with an in-line ammeter (indicating complete desiccation), current set at 25 watts, and desiccation of three contiguous areas of the isthmus incorporating the blood supply from the mesosalpinx. The results of the U.S. Collaborative Review of Sterilization study found that all methods of tubal occlusion are very effective, although failure rates were higher than expected. The Hulka-Clemens clip and bipolar methods carry the highest failure rates, likely due to improper application technique.

Myomectomy Women with symptomatic leiomyomas who wish to retain their reproductive potential or who wish to retain their uteri are candidates for myomectomy. Most of these procedures are still performed abdominally, because laparoscopic myomectomy is one of the more difficult laparoscopic procedures. There is controversy as to whether a laparoscopic closure of the myometrium is comparable to a closure achieved in an open procedure. In general, a laparoscopic approach should not be selected if leiomyomas are larger than 5 to 8 cm, multiple, or embedded deep within the myometrium. If a laparoscopic approach is chosen, the patient should be informed of the potential increased risk of spontaneous uterine rupture prior to labor and of recurrence (33% after 27 months). Most myomectomies can be performed with three trocar sites. One 10-mm trocar is placed umbilically and 5-mm ones in the lower left and right abdomen. A vertical incision is made in the myometrium overlying the myoma using a spoon electrode (or other electrosurgical instrument) set at 80 watts of cutting current to minimize bleeding. The incision is continued through the myometrium to the surface of the myoma, identifying the plane between the pseudocapsule and fibroid. The myoma is grasped with a 5-mm single-toothed tenaculum or corkscrew, and traction is applied. The plane between the fibroid and pseudocapsule is entered and adhesions released with a combination of blunt and sharp dissection. The suction-irrigator works well here for blunt dissection. The adhesive attachments are desiccated using bipolar forceps prior to their transection to minimize bleeding. These adhesions may also be vaporized using the CO_2 laser. The process is continued until the base of the myoma is reached, where the remaining attachments are desiccated using bipolar cautery. The myoma is freed and placed in the posterior cul-de-sac for later retrieval. Hemostasis of the myometrium is achieved. A multilayer closure is now performed using single interrupted sutures placed and tied laparoscopically. Alternatively, if the operator is not skilled in laparoscopic suturing, or if there is a concern regarding obtaining a maximally tight closure, a small laparotomy incision may be made and the suturing performed abdominally. A uterine manipulator placed within the uterus can help to elevate the uterine incision to the laparotomy incision and make suturing through a smaller incision easier. The myoma is now removed from the abdomen. If a small laparotomy incision has been made, the myoma may be removed through this incision. Morcellation using a scalpel or scissors may be necessary if the myoma is larger than the incision. If the entire procedure has been performed laparoscopically, the myoma may be removed using a morcellator introduced through the umbilical incision and visualized with a 5-mm laparoscope placed in one of the lower trocar sleeves. Alternatively, a culdotomy incision can be made and the myoma removed vaginally. The culdotomy incision may then be closed vaginally or

laparoscopically.

Hysterectomy The advanced surgical skills required to perform a laparoscopic hysterectomy and the economic factors involved have limited the acceptance of this procedure in gynecologic practice. The laparoscopic hysterectomy or laparoscopically assisted vaginal hysterectomy was never intended to replace the vaginal hysterectomy. The primary role of this procedure is to reduce the number of abdominal hysterectomies performed. Seventy percent of hysterectomies in the United States are performed abdominally. A review of the data from the Health Insurance Commission Medicare in Australia showed a decrease in the incidence of abdominal hysterectomy from 70% in 1991-1992 to 57% in 1994-1995 after the introduction of laparoscopically assisted hysterectomies in private hospitals. The American College of Obstetricians and Gynecologists has agreed on the indications listed in Table 46.7 for laparoscopically assisted vaginal hysterectomy (there has been no comment on total laparoscopic hysterectomies, but the same indications inherently would apply).

Prior pelvic surgery requiring lysis of adhesions
Endometriosis requiring treatment or lysis of adhesions or both
Pelvic inflammatory disease requiring lysis of adhesions
Ligation of infundibulopelvic ligaments for ovarian removal allowing completion by vaginal hysterectomy
Pelvic mass
Limited uterine mobility
Narrow pubic arch
Constricted vagina with no prolapse

TABLE 46.7. *Indications for laparoscopically assisted vaginal hysterectomy*

Several randomized controlled trials comparing laparoscopically assisted vaginal hysterectomies with abdominal hysterectomies reported that the former are associated with significantly less postoperative pain, shorter hospital stays, faster return to work and normal activities, but possibly longer operative times.

Technique for Total Laparoscopic Hysterectomy A uterine manipulator (e.g., RUMI system), a vaginal extender (e.g., Koh Cup Vaginal Fornices Delineator), and a pneumooccluder (Colpo-Pneumo Occluder; all products from Cooper Surgical, Shelton, CT) or similar instruments are put in place at the beginning of the procedure. A 10-mm reusable trocar is introduced through the umbilicus after pneumoperitoneum is obtained as described previously. Five-millimeter trocars are introduced into the lower left and right abdomen under direct visualization. The course of the ureters is identified retroperitoneally. If the ovaries are to be removed, the infundibulopelvic ligament is isolated, desiccated, and transected as described previously for oophorectomy. If ovaries are to remain, then the round ligament, fallopian tube, and uteroovarian ligaments are desiccated using bipolar forceps and transected approximately 1 cm from their uterine attachments. The anterior leaves of the broad ligament are incised bilaterally to meet in the midline, releasing the bladder peritoneal attachment to the lower uterine segment. The harmonic scalpel with the hook attachment works well to minimize oozing. The bladder is gently pushed inferiorly over the vaginal metal colpodelineator. The posterior broad ligaments are incised downward using scissors to the insertion of the uterosacral ligaments, allowing lateral retraction of the ureters. The uterine arteries are identified within the broad ligament, and the surrounding loose, areolar tissue is skeletonized in a blunt fashion. The uterine arteries are then desiccated completely, as indicated by the ammeter, by placing the bipolar forceps at right angles to the lower uterine segment on either side, above the level of the vaginal metal colpodelineator. The uterus should take on a bluish hue if complete desiccation has been achieved. The desiccated arteries are transected, freeing the cardinal ligament attachment. The vaginal pneumooccluder balloon is then insufflated prior to the colpotomy incision. The vaginal metal colpodelineator is emphasized by pushing the uterus cranially. The harmonic scalpel with hook electrode is used to make a circumferential incision over the metal ring, releasing the cervicovaginal attachment. The occluder balloon is deflated, and the uterus is brought into the vagina and now serves as the pneumooccluder. Hemostasis of the vaginal cuff is achieved. The cuff is sutured and closed laparoscopically, incorporating the uterosacral ligaments for pelvic support. The uterus is then removed from the vagina.

Endometriosis Surgical treatment of endometriosis usually is performed for pain or infertility. There are no randomized controlled trials comparing excision, vaporization, fulguration, and desiccation of endometriotic lesions. Although each method of destruction has its proponents, the authors prefer excision of deep fibrotic endometriosis and vaporization of superficial implants. The only definitive cure for endometriosis is surgical resection or complete destruction of the endometriotic lesion. Surgical management does not include bilateral salpingo-oophorectomy. Removal of the ovaries will not necessarily ensure relief of symptoms. Estrogen, in addition to that produced by the ovaries, also is produced by peripheral conversion of androgens in the presence of aromatase. Aberrant aromatase expression has been identified in some endometriotic implants, causing local production of estradiol within them. This may explain the reason for failures or “recurrences” after bilateral salpingo-oophorectomy or only superficial destruction of the implant. Ovarian endometriomas should be treated by cystectomy rather than drainage and coagulation, as evidenced by the results of a randomized clinical trial. Often, these ovaries are adherent to the pelvic sidewall, adjacent bowel, or the opposing ovary. During adhesiolysis, the endometrioma often is ruptured, spilling its thick, chocolate-like fluid into the cul-de-sac. The thick fluid should be aspirated and opening to the endometrioma identified. If necessary, the opening is enlarged until the thick endometrioma cyst wall is identified. Using a biopsy forceps (single-toothed grasper), the cyst wall is grasped and peeled from its attachment to the ovarian cortex. Once hemostasis is achieved, the cortex usually does not require suture closure.

Complications

Information regarding entry access injuries is provided in a review reflecting the Physician Insurers Association of America (PIAA). They noted that entry access injuries occurred in between 5 per 10,000 and 3 per 1,000 patients undergoing laparoscopic surgery. Bowel, rectal, and retroperitoneal vascular injuries accounted for 76% of all injuries incurred in the process of establishing a primary port. The PIAA reported that approximately 50% of bowel injuries were unrecognized for 24 hours or longer following the laparoscopic surgical procedure. A delay in recognition, age over 59 years, and major vascular injuries were independent factors associated with death.

In a Canadian Task Force study, the overall complication rate for all laparoscopic procedures was 0.65%; for operative laparoscopy it was 0.80%. The American Association of Gynecologic Laparoscopists has noted similar results (1.45 complications per 1,000 procedures).

In a review of 32,205 gynecologic laparoscopic procedures in a Finnish study, 130 major complications were noted. The total complication rate was reported as 4 per 1,000 and, more specifically, 0.6 per 1,000 diagnostic laparoscopies, 0.5 per 1,000 sterilizations, and 12.6 per 1,000 operative laparoscopies. Intestinal injuries were reported in 0.7 per 1,000 procedures, incisional hernias in 0.3, urinary tract injuries in 2.5, major vascular injuries in 0.1. Overall, laparoscopically assisted vaginal hysterectomy was associated with the highest complication rate at 2.3%, with ureteral injuries occurring in 1% of women undergoing the procedure.

Gas and air emboli have been reported with both laparoscopic and hysteroscopic procedures. Oxygen saturation monitoring, as well as end-tidal carbon dioxide and, more recently, capnography and mass spectrometry, are designed to provide early diagnosis. If an embolus occurs, it frequently is accompanied by cardiac arrhythmia and cardiac arrest. It is beyond the scope of this chapter to provide detailed information regarding cardiopulmonary resuscitation.

Ureteral injury, as noted above, has been reported in association with minimally invasive surgery. Often times it is not recognized at the time of the initial procedure. The diagnosis should be considered when a patient exhibits postoperative fever, hematuria, flank pain, or evidence of peritonitis. Initial treatment with ureteral stenting on occasion is inadequate, resulting in subsequent ureteroneocystostomy. With respect to bladder injury, if one suspects such, distension of the bladder with methylene blue can identify a defect. If there is suspicion of ureteral injury, intravenous administration of indigo carmine frequently proves helpful in identifying the defect.

Other minimally invasive surgery–associated complications have included spleen laceration. The injury was reported in four patients, and predisposition included splenomegaly, with injury occurring primarily during trocar insertion. This was associated with a laparoscopic salpingoplasty. However, this complication is extremely rare.

Death, although extremely rare following minimally invasive surgical procedures, has been reported. It is more commonly associated with unrecognized trauma to the intestinal tract with ensuing sequelae. It also has been reported in association with major vascular trauma.

SUMMARY POINTS

- Endoscopic surgery has replaced open surgery for many commonly performed gynecologic procedures such as tubal sterilization, excision of unruptured tubal pregnancies, ablation of peritoneal endometriosis, and simple ovarian cystectomy.
- Endoscopically assisted vaginal hysterectomy with removal of the adnexal structures demonstrates the potential for this technology.
- Endoscopic procedures have several advantages. They can be performed on an ambulatory basis, require shorter recovery times, cause less postoperative pain, and improve the cosmetic impact of incisions.
- Endoscopic procedures require specialized equipment and a high degree of technical skill.

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Chapter 47

R. Stanford Williams

Hysteroscopic Surgery

INTRODUCTION
INSTRUMENTATION
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INTRODUCTION

Although hysteroscopy has been described since the early 1800s, widespread use by practicing gynecologists did not occur until the 1980s. With improvements in optics, video systems, and distension media, there has been an increased acceptance of hysteroscopy as the gold standard in the evaluation of the uterine cavity and treatment of intracavitary pathology.

Hysteroscopy is used most commonly for evaluation of abnormal uterine bleeding, but it also is used frequently for evaluation of the endometrial cavity in patients with recurrent pregnancy loss and infertility. Many studies have shown that blind dilation and curettage may miss up to 60% of endometrial pathology, such as endometrial polyps and submucous leiomyoma, although with increasing expertise in ultrasonographic techniques such as the saline sonohysterogram, endometrial pathology often can be suspected prior to performing definitive operative hysteroscopy. Alternatively, many practitioners perform office hysteroscopy with small-diameter hysteroscopes, which do not require significant dilation of the cervix, can provide direct visualization of the endometrial cavity, and facilitate a directed biopsy of suspected endometrial lesions.

Operative hysteroscopy requires larger diameter instrumentation and is best performed under anesthesia in the outpatient operating room because of the need for significant cervical dilation and more extensive instrumentation. Hysteroscopic surgery allows a variety of intrauterine surgical procedures such as myomectomy, polypectomy, resection of a uterine septum, endometrial ablation, correction of intrauterine synechiae, and cannulation of proximal tubal occlusion.

INSTRUMENTATION

Hysteroscopy can be used both as a primary diagnostic tool and as a more definitive operative technique. Diagnostic hysteroscopy can be performed either in an office setting or in the outpatient operating room and requires only small 3.6-mm to 5-mm hysteroscopes. These hysteroscopes may be either flexible or rigid. A small channel often is provided for a small biopsy instrument, but these are rather delicate, and significant surgical procedures will require larger hysteroscopes.

The flexible hysteroscope is used often for office hysteroscopy because it can be inserted through a narrow cervical os and can negotiate the cervical canal, using a deflecting lever to guide the instrument. The flexible hysteroscope is available in two diameters, 3.6 mm and 4.9 mm, both with a zero-degree optical view. The larger diameter endoscope also provides a 2.2-mm diameter instrument channel, which allows for directed biopsies of endometrial pathology. The larger instrument provides better optics than the smaller flexible hysteroscope but is still somewhat inferior optically to a 4-mm rigid scope.

Most small diagnostic hysteroscopes have only a single channel for installation of a distending medium. In an office setting, many physicians employ CO_2 as the distension medium, necessitating the use of a hysteroscopic insufflator to control intrauterine pressure. If blood or mucus is present within the endometrial cavity, a liquid medium will be required. If a low-viscosity liquid distension medium is used, then a continuous flow sheath, which allows for the continuous simultaneous inflow and outflow of the medium, thus flushing any blood or mucus from the cavity, will give the optimal view.

Rigid hysteroscopes are available with 0-, 12-, 15-, 30- and 70-degree optical view telescopes. Thirty-degree scopes are used primarily for diagnostic procedures in order to see easily the entire endometrial cavity by rotating the telescope 360 degrees. Operative procedures most commonly require the 12- or 15-degree telescopes, so that the operational component of the instrumentation can be visualized fully.

The operative hysteroscope uses a 4-mm rigid telescope within a 7- to 8-mm operative sheath, which can be configured to either provide a port for the insertion of accessory instruments (scissors, biopsy forceps, catheters) or use a resectoscope with a working element for resectoscope electrodes. Older models of operative hysteroscopes included only a single channel for installation of distension medium. Adequate egress of fluid usually is not possible with these hysteroscopes, because the only available exits are the fallopian tubes or around the hysteroscope through a patulous or over-dilated cervix. Use of these single-channel hysteroscopes should be limited to high-viscosity distension media. Most commonly, operative hysteroscopy is performed with a continuous flow sheath allowing for input of the distension medium through a middle channel and egress of the medium through an outer evacuation channel. This provides for constant washing of the uterine cavity, removing blood and debris and allowing the use of a low-viscosity distension medium.

Infusion of low-viscosity fluids can be accomplished either by the force of gravity or with infusion pumps. Suction tubing attached to the outflow port can be directed to wall suction or allowed to drain by gravity. Low-viscosity–fluid pumps have been designed to operate in pressure ranges of 0 to 80 mm Hg. They can deliver fluid at a rate necessary to maintain a preset pressure with a maximum flow rate of 300 mL/minute, although the upper limit of flow through the outflow ports for most hysteroscopes is 250 mL/minute. Outflow usually is adjusted to be significantly lower than the maximum to allow adequate visualization free from blood and debris, maintain adequate uterine distension, and minimize the amount of fluid needed to complete the procedure.

Alternatively, inflow of the distension medium can be controlled by gravity. The height of the bag of infusion medium above the patient controls the maximum intrauterine pressure. Every 1 foot of height above the patient that the bag of distension medium is placed will deliver approximately 25 mm Hg of pressure to the endometrial cavity. This system is then regulated by the amount of outflow, to maximize visualization while maintaining adequate uterine pressure. Because pressure of inflow is constant, changes in intrauterine pressure, and thus distension, are affected by alterations of the rate of the outflow. Use of standard suction containers to collect the outflow will make fluid measurement and calculation of any fluid deficit straightforward.

Modern operative hysteroscopy requires a video camera and video monitor for adequate operative visualization. A halogen or xenon light source providing 150 to 300 watts of incandescent light is used and attached to the hysteroscope by a fiber optic light cable. The light cable should be inspected frequently to ensure that a significant number of the internal fibers have not broken and that the light cable is capable of delivering an adequate amount of light through the hysteroscope. Most chip cameras have the capability to adjust gain and can be integrated with the light source for automatic light balance.

For documentation of findings and recording of procedures, video capture units may be used. Most commonly, VCRs are used to videotape pertinent portions of the procedure. Also available are video capture units for taking still pictures or storing digital images on a computer hard disk or CD.

Energy for operative hysteroscopy can be delivered either with the Nd:YAG laser or with electrosurgical generators delivering either unipolar or bipolar energy. Other

lasers, such as the CO_2 laser, are not used in hysteroscopy because of their failure to penetrate fluid and because of the generation of smoke if CO_2 is used as the distension medium. The Nd:YAG laser can be delivered through a flexible quartz fiber passed through the instrument channel of the operating hysteroscope, and its wavelength penetrates through the liquid distension medium used in hysteroscopy. The extent of tissue necrosis can be up to a depth of 4 to 5 mm. Varying the distance of the fiber tip and incident angle can regulate the extent of thermal damage. It is rendered ineffective at distances greater than 2 cm or as the incident angle deviates more than 90 degrees. This laser is used often to perform endometrial ablation, using power outputs of 50 watts by dragging the fiber over endometrial surfaces.

Electrosurgery through a standard resectoscope usually utilizes a monopolar technique, with the electrical probe serving as the source electrode and the return plate on the patient as the return electrode. The resectoscope can be used with either cut or coagulation output settings on the electrosurgical generator, or a blend of the two. When used in the cutting mode a high-frequency sine wave is delivered, which creates extremely high current density, instantly superheating cellular water to vaporization, causing cellular architecture to explode, resulting in tissue cutting. In the coagulation mode, delivery of high-frequency energy is interrupted by periods of modulation. This alternation of frequency and interruption results in wider zones of lateral tissue coagulation and damage, resulting in coagulation and sealing of blood vessels. A variety of electrode tips are available including a cutting loop for excision of tissue, a roller ball or bar for coagulation and ablation, and a knife electrode for incision.

A new family of bipolar electrical generators (Versapoint, Gynecare of Ethicon, Somerville, New Jersey) has been developed. Electrodes have been designed in several configurations producing variable tissue effects. A ball tip can be used for vaporization with limited tissue desiccation, a spring tip for vaporizing larger amounts of tissue, and a twizzle tip for resecting and morcellating tissue. These tips have both active and return electrodes and require an electrolyte-containing medium such as saline. In contrast, if one is using a monopolar resectoscope, a nonelectrolyte distension medium such as glycine must be used.

Distension Media

Four basic types of distension media are used for hysteroscopy. The first type, CO_2, is used primarily for diagnostic hysteroscopy in an office setting. Secondly, a high-viscosity medium such as Hyskon is used primarily with inflow only–type hysteroscopes. The third and fourth types are both low-viscosity solutions that are used with continuous flow hysteroscopes, electrolyte solutions and nonelectrolyte solutions. The choice between an electrolyte and nonelectrolyte solution will depend on the use of monopolar versus bipolar electrocautery.

For diagnostic procedures in the office, many physicians choose CO_2 as the distension medium. CO_2 use requires a hysteroflator that delivers the gas at preset intrauterine pressures and has regulated flow rates. CO_2 may be used with either a small diagnostic rigid hysteroscope or a flexible hysteroscope and does not require a return channel for continuous flow, because the CO_2 gas will escape from the cervix or through patent fallopian tubes into the peritoneal cavity where it is absorbed. Starting pressures for CO_2 are usually between 50 and 75 mm Hg. If adequate distension is not achieved, it may be necessary to increase the intrauterine pressure to a maximum of 100 mg Hg or a maximal flow of 100 mL/minute. Higher pressures or flow rates may produce a gas embolus and fatalities have been reported. CO_2 will give an ideal view of a uterus that is not bleeding, because light reflection is identical to that of room air. However, any blood or mucus within the endometrial cavity will require changing to a liquid medium.

Thirty-two percent high-molecular-weight Dextran-70, Hyskon, was used commonly as a liquid distension medium for operative hysteroscopy for many years prior to the evolution of hysteroscopes that accommodate continuous flow. Its nonmiscibility with blood allowed its use when either blood or mucus was present in the endometrial cavity or bleeding is anticipated. Hyskon is compatible with either the Nd:YAG laser or electric cautery devices. When using Hyskon as the distension medium, its delivery requires significant constant pressure to overcome the resistance of a high-viscosity fluid flowing through a standard diagnostic sheath. The major disadvantage of Hyskon is the difficulty in cleaning the solution from the instruments and stopcocks. If the instrumentation is not thoroughly cleaned, the dextran crystallizes and results in clouding of the hysteroscope lens and freezing of stopcocks. Rarely, patients may have an anaphylactic reaction to the dextran. Intravascular absorption of Hyskon will also result in a ten-fold increase of intravascular volume, with accompanying cardiovascular overload and pulmonary edema. Careful monitoring of the amount of Hyskon intravasated during the procedure is mandatory, and absorption of 100 to 200 mL of Hyskon should warrant terminating the procedure. Because the molecular weight of Hyskon exceeds that which can pass into the circulation from the peritoneal cavity, spill through the fallopian tubes is inconsequential.

Operative hysteroscopy most commonly now uses low-viscosity solutions, which can be either electrolyte solutions or nonelectrolyte solutions. If monopolar resectoscopes are used, this equipment requires nonelectrolyte solutions, so that the flow of energy will be directed from the electrode tip into the tissue and not allowed to “short circuit” through an electrolyte-containing medium throughout the entire uterus. Nonelectrolyte solutions that have been used commonly for operative hysteroscopy include 1.5% glycine, sorbitol, 5% mannitol, and dextrose in water. Significant intravasation of distension medium may occur with resectoscope use. As tissue is resected, venous channels within the endometrium and myometrium are opened, and the pressure of the distension medium will result in the absorption of these solutions. The primary complications associated with nonelectrolyte low-viscosity solutions include fluid overload and hyponatremia. Fluid overload may result in pulmonary edema, and severe hyponatremia may result in neurologic sequela such as confusion, seizures, and even death. Intraoperative monitoring of inflow and outflow must be performed every 5 to 10 minutes throughout the procedure, and a discrepancy between 500 and 1,000 mL with nonelectrolyte solutions should warrant termination of the procedure. Glycine use has also been reported to cause hyperammonemia because of its conversion from glycine to ammonia by the liver.

Electrolyte solutions, such as normal saline or lactated Ringer solution, are used with bipolar electrical devices or for continuous flow diagnostic hysteroscopy. Because bipolar devices contain both the active and return electrodes at the electrode tip, electrolytes are needed to complete the electrical circuit. The primary complication associated with electrolyte solutions is fluid overload, and a discrepancy of 1,500 to 2,000 mL during the procedure warrants termination of the procedure.

During operative hysteroscopy with significant operating time and use of large amounts of distension medium, the anesthesiologist should keep intravascular fluid replacement to a minimum to avoid fluid overload. Anesthesia personnel should also monitor the patient carefully for electrolyte abnormalities when using nonelectrolyte solutions and anaphylactic shock when using Hyskon.

General Technique

Hysteroscopy can be difficult to perform during the luteal phase because of the abundance of endometrial tissue. Performing hysteroscopy during the early to middle follicular phase should ensure adequate visualization of the uterine cavity. Alternatively, the endometrium can be suppressed with 2 to 4 weeks of progestin therapy, or hysteroscopy may be performed at any time in a patient taking oral contraceptives because of the dominant atrophy effect of progestin. Gonadotropin-releasing hormone (GnRH) analogs have most commonly been used to prepare the endometrium for endometrial ablation. At least 4 weeks of preoperative treatment are required for GnRH analogs such as leuprolide acetate (Depo-Lupron), because these medications are initially agonists and will actually increase estrogen output for the first 7 to 10 days before subsequent down-regulation of the pituitary ovarian axis and subsequent endometrial atrophy.

The cervix should be dilated no larger than the outer diameter of the hysteroscope that will be used. With many larger operative hysteroscopes, this will require dilation of the cervix to at least the diameter of a 20-French Hank dilator or a 9/10-French Hegar dilator. Care should be taken to avoid cervical lacerations and uterine perforation during cervical dilation.

With insertion of the hysteroscope, the cervical canal can be visualized and the hysteroscope guided into the endometrial cavity under direct vision. If over-dilation of the cervix has occurred and the distension medium cannot be kept within the endometrial cavity, an additional tenaculum may be placed on the posterior lip of the cervix, or a special four-pronged tenaculum can be used to compress the cervix around the hysteroscope. The cervical canal and internal os will appear off-center within the field of view when using offset-angle lenses. When the angle of the lens is oriented to look downward, the internal os will appear at the 12 o'clock position. If the telescope is inverted and the lens pointed upward, the os will appear in the 6 o'clock position. The latter position is useful for viewing a retroverted uterus. The surgeon always should maintain the camera position in a straight-up-and-down configuration so that the view on the screen corresponds anatomically to the patient's position. As the hysteroscope is rotated to visualize the entire endometrial cavity, one hand should be kept on the camera to prevent its rotation, or the view on the monitor will be oriented improperly.

With insertion of the hysteroscope, the cervical canal should be visualized and the endometrial cavity entered carefully through the internal os. If adequate visualization is prevented by blood and mucus, continuous flow of the distension medium should be maintained for 30 to 60 seconds to wash out blood and debris. If the field of view still appears red, the hysteroscope should be pulled back 1 to 2 centimeters, because it is a common mistake to insert the hysteroscope too far and the lens may be abutting the uterine fundus. Visualization can also be compromised by inadequate distension of the uterine cavity because of insufficient intrauterine pressure. The fluid delivery devices should be checked to ensure adequate pressure, or if a gravity system is being used, the height of the bag above the patient should be extended. Careful adjustment of the outflow should be made to clear any ongoing bleeding and debris without decreasing intrauterine pressure or using extremely large volumes of distension medium.

The entire endometrial cavity should be inspected carefully, including the identification of both tubal ostia, the fundus, and the anterior and posterior portions of the

uterine wall. Video documentation of the intraoperative findings is useful. If operative techniques are to be used during the hysteroscopy, inflow and outflow should be measured carefully and reported to the surgeon every 5 to 10 minutes. If significant bleeding or a long operative time is anticipated, vascular constriction through the paracervical injection of a dilute pitressin solution may be used. Care should be taken that pitressin is not injected intravascularly, because reports of fatalities with inadvertent intravenous administration have been reported.

ENDOMETRIAL ABLATION

Approximately 35% of gynecologic complaints concern menorrhagia, and it is estimated that 60% of these women ultimately will be treated with hysterectomy. Endometrial ablation originally was developed as an alternative treatment for patients who are medically too unstable for the surgical stress of hysterectomy. Since its original development in the 1980s, however, patient selection criteria have now expanded and hysteroscopic endometrial ablation is viewed by many as an alternative to hysterectomy, even in healthy patients. Prior to consideration of hysteroscopic endometrial ablation, endometrial pathology needs to be excluded with either a combination of endometrial biopsy to rule out hyperplasia or carcinoma and transvaginal ultrasonography with saline infusion to rule out polyps or submucous myomas or, alternatively, office diagnostic hysteroscopy could be performed with directed biopsies.

Because the goal of an endometrial ablation is the artificial creation of intrauterine synechiae, many experts feel that preoperative preparation of the endometrium with an GnRH agonist or continuous progestin will maximize the chance of adequate scar formation within the endometrial cavity postoperatively. Alternatively, some authors perform a mechanical preparation of the endometrium using a sharp curette or suction curettage immediately prior to endometrial ablation. This technique has the advantage of being able to immediately perform the procedure without a lengthy preoperative medical suppression of the endometrium. The disadvantage of a mechanical preparation, however, is the possibility of inadequate visualization during the procedure because of bleeding and the possibility of a compromised outcome secondary to inadequate destruction of the endometrial basalis.

Endometrial ablation can be done either with the Nd:YAG laser or the hysteroscopic resectoscope, using either a wire lube or roller ball technique. The Nd:YAG laser system uses a 600-μ bare fiber with power settings of 55 to 70 watts. The Nd:YAG laser penetrates 4 to 5 mm into the endometrium, destroying not only the superficial endometrial layers but also the endometrial basalis and superficial myometrium. A touching technique was described originally, dragging the fiber against the endometrium, thus destroying the endometrium and superficial myometrium by vaporization and necrosis. Alternatively, a nontouch technique with the higher power setting has been described in which the fiber is held perpendicular to the endometrium without touching the surface, achieving a deep coagulation effect. Many practitioners use a combination of the two techniques, and results of the two techniques appear comparable.

Due to the expense of laser ablation, electrosurgical ablation is performed more commonly. Most resectoscopes use monopolar electrodes, necessitating a nonelectrolyte low-viscosity medium. Hysteroscopic resection of the endometrium has been described using a loop electrode to excise strips of endometrium, although the incidence of uterine perforation is reportedly higher with this technique when compared with a roller ball or laser ablation. Most commonly, a roller ball technique is used. With a roller electrode, a blend 1 setting with 70 to 140 watts of power is used, depending on the width and thickness of the electrode. This current will allow consistent penetration and destruction of the uterine tissue. Care must be taken to ensure adequate ablation of the uterine cornu and to avoid destruction of the endocervical canal to prevent cervical stenosis.

Extensive studies of the outcome following endometrial ablation have been published. Approximately 80% to 90% of women will have a significant reduction of their menorrhagia and will be satisfied with the outcome, including approximately 25% to 40% of women experiencing amenorrhea postoperatively.

Complications of endometrial ablation include a 10% hysterectomy rate because of dissatisfaction with the outcome of surgery. In addition to the immediate postoperative complications previously discussed, there also have been reports of isolated endometrial carcinoma in areas of the uterus not adequately ablated and symptomatic hematometra developing in loculated areas of inadequate ablation. Although most women are sterile after this procedure, intrauterine pregnancies can occur and patients should be counseled to use adequate contraception.

HYSTEROSCOPIC SEPTUM RESECTION

The septate uterus is the most common congenital uterine malformation associated with recurrent reproductive failure and obstetric complications. The appearances of a septate uterus and bicornuate uterus are extremely similar on hysterosalpingogram, and the distinction must be made by demonstrating a normal external fundal contour with a uterine septum, as opposed to the presence of two uterine horns in a bicornuate uterus. The uterine septum may be thin or broad and may be of varying length, from an exaggerated arcuate appearance to total division of the uterine corpus, possibly including the cervix (Fig. 47.1). Indications for hysteroscopic resection of a uterine septum include repeated first- or second-trimester losses, a history of premature labor and delivery and, possibly, concurrent infertility.

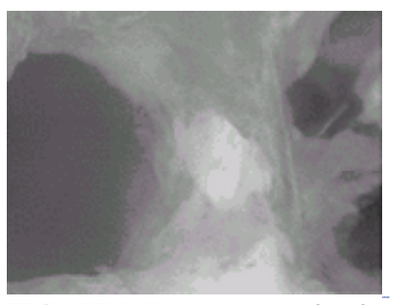

FIG. 47.1. Hysteroscopic view of a uterine septum extending down to the lower uterine segment before division.

The hysteroscopic approach to the division of the uterine septum is performed almost exclusively today rather than the classic transabdominal resection or incision of the septum performed prior to the 1970s. The hysteroscopic approach allows for ambulatory treatment of this disorder and, because the uterine wall has not been invaded, cesarean delivery is not indicated postoperatively.

After adequate documentation of the diagnosis of a septate uterus and the exclusion of concurrent causes of pregnancy wastage, the surgery should be scheduled during the early follicular phase to allow adequate visualization of the septum. The use of GnRH analogs or other drugs to induce endometrial suppression may result in the iatrogenic formation of postoperative intrauterine scar formation unless postoperative estrogen replacement is given. Semi-rigid scissors are most commonly used to divide uterine septa (Fig. 47.2). The uterine septum is usually avascular and cautery is typically unnecessary. Under direct visualization, the septum is incised at its midpoint. As the incision is carried toward the fundus, the septal tissue normally retracts anteriorly and posteriorly into the myometrial wall, and resection of tissue usually is not needed. When the uterine cavity is symmetric, or when normal myometrial tissue is observed because of bleeding, the dissection should stop (Fig. 47.3). It is also useful to perform concurrent laparoscopy to both visualize the normal fundal contour before dividing the septum, as well as to guide the direction and extent of the dissection hysteroscopically.

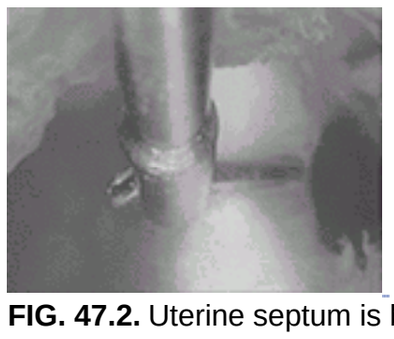

FIG. 47.2. Uterine septum is being divided by hysteroscopic rigid scissors.

FIG. 47.3. The uterine septum has been resected completely and a contour of the fundus is normal, with normal myometrial tissue visible.

The septum also can be divided with either fiberoptic lasers or cutting loop resectoscopes. The disadvantages of these techniques include additional instrumentation and further complications should uterine perforation occur. When perforation occurs with hysteroscopic scissors, bleeding is unlikely and damage to surrounding structures is rare. When uterine perforation has occurred using an electrical cutting loop or laser fiber, damage to the surrounding bowel is possible. There is also concern that these modalities may damage surrounding normal myometrial and endometrial tissue.

Although some surgeons routinely administer high-dose estrogen therapy for 30 days postoperatively, randomized studies have shown no benefit when used in normally cycling women. Similarly, an intrauterine splinting device such as a pediatric Foley catheter has been advocated by some authors but usually is not needed because of the rapid reepithelialization of the endometrial cavity postoperatively.

Normal reproductive outcome following the division of a uterine septum is reported to be between 70% and 85% term delivery rate in patients with prior recurrent spontaneous abortions. Pregnancy outcome is equal with all three methods of septum division.

HYSTEROSCOPIC MYOMECTOMY

Uterine leiomyomas are the most common benign tumors of the uterus, and submucous myomas are common causes of menorrhagia and abnormal uterine bleeding. Submucous myomas also are associated with recurrent pregnancy loss and infertility. The evaluation of abnormal uterine bleeding and menorrhagia should include either a diagnostic hysteroscopy or a saline infusion sonohysterography to diagnose submucous myomas. Blind procedures, such as endometrial biopsy and dilation and curettage, will commonly miss these tumors. Most submucous myomas do not have a pedicle but project into the endometrial cavity with a broad base. Myomas that have greater than 50% of their volume projecting into the cavity and are less than 3 to 4 cm in size can be approached adequately for resection hysteroscopically. It is often useful to pretreat patients with a GnRH analog prior to a hysteroscopic myomectomy to shrink the myoma, as well as thin the endometrium. If the patient is anemic from menorrhagia, GnRH-agonist pretreatment also will allow her a period of amenorrhea and permit her hemoglobin level to normalize.

The resectoscope with a loop electrode is used commonly to shave the myoma until it is flush with the endometrial cavity. Power settings of 100 to 120 watts are used. With unipolar devices, a nonelectrolyte solution must to be used as the distension medium. The loop should be advanced past the myoma, and resection of strips of tissue is accomplished by pulling the loop toward the operator (Fig. 47.4). This technique will minimize the risk of uterine perforation. It is frequently necessary to remove the chips of tissue when they become so numerous as to obscure the surgical view. After removal of the resectoscope, a uterine polyp forceps can be used to blindly remove the chips. Even if all the tissue fragments are not removed, they will be expelled from the uterus with the next menstrual period.

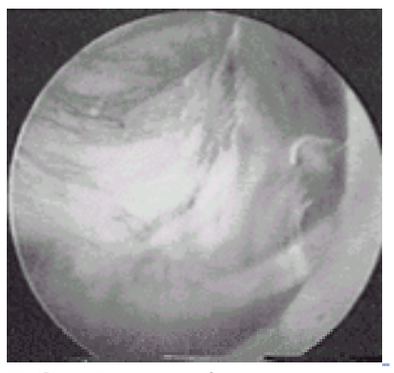

FIG. 47.4. A submucous myoma is being resected with a resectoscope loop electrode.

It may be useful to reduce intraoperative bleeding and reduce intravasation of distension medium by injecting a dilute solution of pitressin, 20 units per 100 cc injectable saline, paracervically prior to the endometrial resection to achieve vascular constriction. Care should be taken not to inject this solution intravascularly, because deaths have been reported. A total of 5 to 10 cc is usually sufficient. Intraoperatively, small bleeding vessels may be coagulated with the loop electrode using 40 watts of coagulation current.

Bipolar systems have been developed (Versapoint, Gynecare, a division of Ethicon), which cause vaporization of tissue. Because these devices use a bipolar electrode, an electrolyte solution is needed as the distension medium. This system requires its own generator and will not work with other electrical generators such as Valley Lab's product. The advantage of these systems is the prevention of multiple tissue fragment generation as the technique vaporizes tissue. If pathologic diagnosis is desired, the tips can be used to isolate and remove a portion of tissue to be sent to the pathology department.

When performed for menorrhagia, success rates of hysteroscopic myomectomy have been reported in approximately 80% of patients. Conception rates have been reported between 43% and 63% following hysteroscopic myomectomy in previously infertile women.

HYSTEROSCOPIC POLYPECTOMY

Endometrial polyps are diagnosed in approximately 20% of women with abnormal uterine bleeding. This diagnosis usually requires either direct visualization of the polyp with a diagnostic hysteroscope or the visualization of a polyp using saline infusion sonohysterography. Hysteroscopically, endometrial polyps generally are more often pedunculated than submucous myomas and have a softer, fleshier appearance (Fig. 47.5).

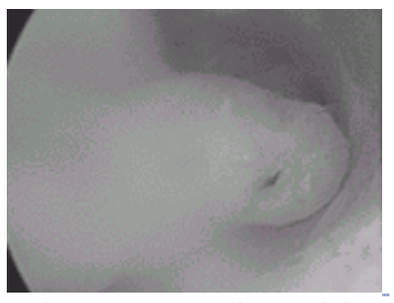

FIG. 47.5. An endometrial polyp is seen hysteroscopically as a soft fleshy growth.

Depending on the size of the endometrial polyp, it may be removed by one of several techniques. With a small pedunculated polyp, grasping the polyp stalk with a hysteroscopic grasper and rotating of the grasper to remove the polyp can be performed easily (Fig. 47.6). With larger polyps or polyps with a larger base, a cutting loop resectoscope should be used. By resecting the base of the polyp with the loop electrode, the polyp subsequently can be removed intact with grasping forceps. If a small portion of the base remains, it can be destroyed with the loop electrode. Care should be taken not to destroy adjacent normal endometrial tissue to prevent postoperative adhesion formation.

FIG. 47.6. A rigid grasper is placed through the hysteroscope to grasp the base of an endometrial polyp for removal.

ASHERMAN SYNDROME

Intrauterine adhesions or synechiae, Asherman syndrome, may develop when opposing endometrial surfaces are damaged and heal as a coalescing adhesion. This typically occurs when inflammation or infection persists after spontaneous first-trimester abortion and when estrogen production is low. Patients who have had late postpartum curettages for retained placental fragments are at high risk for the development of Asherman syndrome (Fig. 47.7). Postpartum, estrogens of placental origin are metabolized rapidly and ovarian suppression continues for several weeks. With the absence of estrogen, the endometrium will fail to proliferate and reepithelialize damaged areas of endometrium following a curettage. Any concurrent inflammation or infection will increase the risk of intrauterine synechiae. Patients who have had elective abortions or postabortal curettages for any reason are also at risk for the development of intrauterine adhesions. The patient with Asherman syndrome may have amenorrhea if the extent of the adhesions is severe, but more commonly it manifests with normal menses or mild hypomenorrhea with recurrent spontaneous abortion or with infertility. The diagnosis of Asherman syndrome can be made by hysterosalpingogram, saline infusion sonohysterography, or direct visualization with diagnostic hysteroscopy.

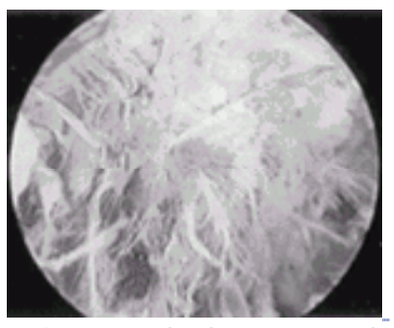

FIG. 47.7. The hysteroscopic appearance of a retained placental fragment 1 month postpartum.

Intrauterine adhesions should be lysed with hysteroscopic scissors under direct visualization. This procedure is straightforward with mild to moderate cases of Asherman syndrome but can be very complicated in severe cases with complete obliteration of the endometrial cavity. In difficult cases, concurrent laparoscopy can be useful to guide the hysteroscope. Pockets of normal endometrium are used as guides to the lysis of thick adhesion bands. Both cornu of the uterus ultimately should be visualized, and the uterine contour should be relatively normal at the end of the procedure.

Postoperatively, most practitioners will place patients with Asherman syndrome on high-dose estrogen replacement, Premarin (conjugated estrogens) 2.5 mg twice daily, or its equivalent, for 30 days to help induce proliferation of any remaining endometrium to reepithelialize the previous site of adhesions. Stenting of the uterus with a pediatric Foley catheter balloon filled with approximately 3 cc of saline for 1 week postoperatively also will prevent the damaged endometrial surfaces from coming immediately into contact with one another. With this foreign body in place, antibiotics should be used to prevent infection.

PROXIMAL TUBAL CANNULATION

Approximately 20% of tubal occlusion occurs in the intramural portion of the fallopian tube at the uterotubal junction. Pathologically, proximal occlusion may be caused by debris plugs or fibrosis from inflammation, intraluminal endometriosis, or salpingitis isthmica nodosa. The diagnosis of proximal tubal occlusion often is made by hysterosalpingography. However, a definitive diagnosis cannot be made with this technique, because uterine muscle spasm falsely suggesting proximal tubal occlusion may be a consequence of the procedure itself. If pathologic proximal tubal occlusion is suspected, selective injection of contrast medium into the fallopian tubes may be performed either fluoroscopically or via hysteroscopy with concurrent laparoscopy. The latter technique has the advantage of simultaneously inspecting the distal portion of fallopian tube for damage. If the patient has both a proximal and a distal occlusion, the tubes are not candidates for surgical correction, and in vitro fertilization should be recommended. If selective injection of one or both of the fallopian tubes does demonstrate proximal tubal occlusion, then hysteroscopic cannulation of the fallopian tube can be performed immediately.

Hysteroscopically, a flexible guidewire, 0.3 to 0.8 mm in outer diameter, is guided into the uterine cornu. The softness of this guidewire usually allows it to penetrate the occlusion while staying within the tubal lumen. When the guidewire is seen in the proximal portion of the fallopian tube laparoscopically, a soft Teflon catheter of 1.3-mm outer diameter is pressed over the guidewire until this is also within the proximal portion of fallopian tube. The guidewire can then be removed and methylene blue injected through the Teflon catheter to confirm tubal patency.

Approximately 80% of proximal tubal occlusions can be cannulated successfully. Complications include perforation of the guidewire through the proximal portion of fallopian tube, but this rarely results in troublesome bleeding or infection. Intrauterine pregnancy rates have been reported as approximately 30% to 40% following proximal tubal cannulation.

SUMMARY POINTS

- The development of good hysteroscopy skills is important to gynecologists so that they may use the diagnostic and operative advantages these techniques offer.
- Careful attention to the surgical technique and particularly the distension medium employed is important in order to perform hysteroscopy safely.
- Diagnostic hysteroscopy is the gold standard for evaluation of the endometrial cavity.
- Operative hysteroscopy offers an outpatient surgical approach to many uterine problems including submucous and intracavitary leiomyomata, endometrial polyps, intrauterine synechiae, uterine septa, and proximal tubal occlusion.
- Endometrial ablation offers women an alternative to hysterectomy for the management of abnormal uterine bleeding or menorrhagia.

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Chapter 48

Dee E. Fenner

Incontinence

DEFINITIONS OF TERMS AND DIFFERENTIAL DIAGNOSIS OF URINARY INCONTINENCE
EPIDEMIOLOGY
Prevalence and Social Impact
Risk Factors
Gender and Age
Race
Childbirth
Smoking, Exercise, and Obesity
EVALUATION OF URINARY INCONTINENCE
History
Physical Examination
Urinary Diary or Bladder Record
Urinalysis and Postvoid Residual Volume
Stress Test
Pad Test
Specialized Tests
TREATMENT OPTIONS
Behavioral Techniques
Electrical Stimulation Therapy
Pharmacotherapy
Surgical Management
SELECTING THE APPROPRIATE SURGICAL PROCEDURE FOR STRESS INCONTINENCE
SUMMARY
SUMMARY POINTS

SUGGESTED READINGS
Definition of Terms
Epidemiology
Evaluation of Urinary Incontinence
Nonsurgical Management of Urinary Incontinence
Surgical Management of Urinary Incontinence

Urinary incontinence is a medical condition affecting 15% to 50% of adult women depending on the age and risk factors of the population studied. As we live longer and enjoy more active lives, increasing numbers of women will be affected. Costing approximately $12.4 billion dollars to treat women alone in 1995, urinary incontinence ranks in the top ten in expenditures for treatment of illnesses.

While once considered a “natural” consequence of aging, further investigations have shown that urinary incontinence is seen in women of all ages, with varying degrees of severity and different etiologies. Unfortunately, incontinence often goes undetected and only half of the women suffering from this condition seek treatment. This is unfortunate because there are many types of effective therapies available including bladder retraining, pelvic floor exercises, and surgery.

As health care providers for women, we are obligated to ask the question “Do you have difficulty controlling your bladder?” Once the condition is identified, specific questions targeted at identifying the type of incontinence, the frequency of loss, and the social impact for the woman can be addressed. Many times with the use of voiding diaries, detailed physical examinations, and simple bladder testing, the cause of incontinence can be determined and treated.

DEFINITIONS OF TERMS AND DIFFERENTIAL DIAGNOSIS OF URINARY INCONTINENCE

Maintenance of urinary incontinence requires that many anatomic, neurologic, and psychological functions and relationships be intact. Therefore, it is not surprising that many conditions may affect urinary continence (Table 48.1, Table 48.2).

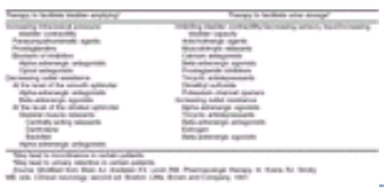

TABLE 48.1. *Drug effects on lower urinary tract function*

Reversible conditions	Treatable conditions
Medications	Detrusor overactivity
Urinary tract infection	Stress incontinence
Stool impaction	Mixed urinary incontinence
Hypercalcinuria	Fistula
Hyperglycemia	
Volume overload	
Delirium	
Decreased mobility	
Psychological	

TABLE 48.2. *Causes of urinary incontinence*

In order to communicate with the patient and other practitioners that evaluate, diagnose, and treat the various causes of urinary incontinence, a standardization of terms and description of conditions is required. A committee on terminology as part of the International Continence Society (ICS) has provided standardized terms and definitions for the classifications of functions of the lower urinary tract. The ICS definitions of terms and conditions of urinary incontinence are listed in Table 48.2 and Table 48.3.

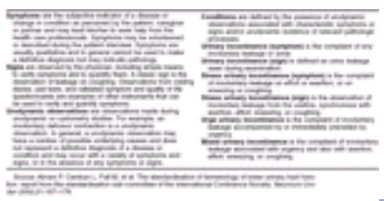

TABLE 48.3. *International Continence Society terms and definitions*

Patients with symptoms of urinary incontinence are generally not concerned about the strict definition of their condition but are rightly focused on the cause and

foremost the treatment of their incontinence. As clinicians, we may or may not agree with the patient on the severity of her symptoms. Generally, when the symptoms are mild, the patient and practitioner are nearer in agreement than when the patient perceives her symptoms as severe. Therefore, it is useful to use standardized criteria or a validated quality-of-life measure to determine the impact of the incontinence condition on the patient's ability to perform her daily activities. Several such questionnaires exist and can be beneficial in the initial assessment as well as determining the benefit of therapy. An example of such a validated questionnaire is seen in Table 48.4.

TABLE 48.4. *Urogenital distress inventory (UDI-6)*

A patient complaining of stress symptoms may actually have cough-induced detrusor overactivity or mixed incontinence. Therefore the clinician must not only listen to the symptoms of the patient, but also document some sign of urinary incontinence. Signs of urinary incontinence are objective measures of urine loss evaluated in conjunction with the bladder state (empty or full) and conditions of leakage. Signs include urine loss documented by a voiding diary noting physical activity or bladder urgency linked to incontinence, a pad test, a cough stress test, or urine leakage at the time of urodynamic testing.

EPIDEMIOLOGY

Prevalence and Social Impact

Urinary incontinence is a common problem among women. The estimated prevalence ranges from 3% to 40% depending on the population studied and how the condition is defined. Approximately 10% to 30% of community-dwelling women between the ages of 15 and 64 years of age and 25% of women older than 65 years experience urinary incontinence. Approximately 50% of nursing home patients have urinary incontinence. One in five women with urinary incontinence will also suffer from fecal incontinence or “dual incontinence.” Urinary incontinence is two to three times more likely in women than in men. This is especially true for women under the age of 60, when stress incontinence is more likely the dominant type. As men and women age, the likelihood of urge incontinence or voiding dysfunction increases in both sexes.

How urinary incontinence is defined determines the prevalence of the condition in the population or the incidence of the condition at any given time. Clinicians generally use the ICS definition of urinary incontinence that is “the involuntary loss of urine sufficient to be a social or hygienic problem for the patient.” For some women this may mean leaking urine once a day, while for others urinary incontinence occurring only periodically with exercise may be unacceptable. Survey studies of community-dwelling women using “daily,” “weekly,” or “most of the time” criteria for diagnosing urinary incontinence report prevalence ranges of 3% to 14%. This amount of leakage corresponds with the frequency of leakage found in women seeking treatment. Higher estimates of incontinence are based on broader definitions, such as “any incontinence in the prior year” or “leakage more than twice a month.”

Many etiologies and factors contribute to urinary incontinence and many of the factors are variable over time and affect the presence and severity of urine loss. The strength of the pelvic floor muscles and urethral sphincter, the level of physical activity or high-impact exercise, the amount of fluid intake, or the level of bacteria are just of few of the variables that relate to urinary incontinence. While little information is known about the natural progression of incontinence severity, for women surveyed over a 2-year span, there was an 11% remission rate or resumption of continence.

Risk Factors

Many risks factors, conditions, or causes have been linked to the development of urinary incontinence. Unfortunately, few longitudinal and well-designed studies have been performed to separate the cause and effect for many of the risk factors. Why certain conditions and events such as childbirth and aging affect some women and not others is still unknown. Bump has developed a model (Fig. 48.1) combining many of the known risk factors for the development of urinary incontinence. Which of these factors are most important and how they interact for a particular patient is not known but are areas of current investigation.

FIG. 48.1. Factors related to the development of urinary incontinence. (From Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:723.)

Gender and Age

Urinary incontinence is two to three times more likely to occur in women than in men. This is especially true regarding community-dwelling adults under 60 years of age. Compared to urge incontinence, stress incontinence is more common in younger women and rarely occurs in men. Since childbirth is considered a major risk factor for the development of stress urinary incontinence, it is not surprising that this condition occurs more often in women than in men. But as men and women age, they both have more symptoms of bladder overactivity, urge incontinence, and voiding dysfunction. These symptoms develop such that the gender gap narrows as men and women approach the age of 70.

Brown and colleagues have shown that 12.5% of women under 80 years of age reported daily incontinence and that for every 5-year increment in age beginning at age 80, there was a 30% increase in the prevalence of incontinence. While increasing age is consistently seen as a risk factor for urinary incontinence, the idea that urinary incontinence is a “natural” part of aging is not true. Like other conditions, such as heart disease, hypertension, and arthritis, incontinence is more prevalent as we get older. Like these other conditions, not all older people suffer from incontinence and those who do should be offered treatment and care and not left to “suffer this malady of old age.”

Why urinary incontinence increases with age is not fully understood. With aging, approximately 1% of striated muscle mass is lost each year. Since the sphincter urethra muscle, as well as pelvic floor muscles play important roles in the maintenance of incontinence, it is not surprising that incontinence increases with aging. How aging, menopause, and decreasing hormone levels relate to urinary incontinence and other pelvic floor dysfunctions is poorly understood. Studies evaluating the use of oral combined estrogen replacement therapy have not shown improvement in or prevention of the development of urinary incontinence. Yet clinicians and some patients note improvement in function of the lower urinary tract, especially in decreasing nocturia, when using transvaginal estrogen replacement therapy. Further studies on the effect of estrogen on the blood supply, smooth muscle of the urethra and vaginal submucosa, and collagen content of the anterior vaginal wall are needed to determine the usefulness, correct route and preparation, and dosage of hormone replacement therapy that could be beneficial.

Race

Racial differences in the prevalence and type of urinary incontinence have been reported but remain poorly understood. Fultz and associates reported a urinary incontinence prevalence of 23% in Caucasian women and 16% in African-American women in a national survey of 4,040 community-dwelling individuals over the age of 70. Smaller studies evaluating younger women do not include large enough numbers of African-American, Hispanic, or Asian women to make any conclusions about the prevalence or type of incontinence. In women seeking treatment for incontinence, African-American women appear to have more urge incontinence and detrusor overactivity on urodynamic testing than pure stress incontinence. Whether these differences are related to treatment patterns or true biologic differences is yet undetermined. It does appear, however, that there are racial differences in urethral muscle mass, urethral closure pressures, and urethral hypermobility between continent nulliparous African-American women and Caucasian women. These findings suggest morphologic and physiologic reasons for racial differences in the type of urinary incontinence.

Childbirth

Vaginal childbirth has been seen as the leading inciting factor in the development of urinary incontinence and pelvic floor dysfunction. Yet vaginal delivery does not lead to urinary incontinence in all women and women who have never delivered vaginally or have even been pregnant can develop urinary incontinence and pelvic floor dysfunction. Strong associations have been made between vaginal delivery and stress urinary incontinence. Large population studies have also shown vaginal childbirth is also a risk factor for developing urge incontinence.

Women who deliver by elective cesarean section without ever laboring have a reduced risk of developing urinary incontinence compared to women who deliver vaginally, but a cesarean section is not 100% protective. In addition, the protective benefits appear to decrease after three pregnancies and repeat cesarean sections. Episiotomies, once thought to be protective, have not been shown to decrease or increase the risk of urinary incontinence, either immediately after birth or after several years.

The majority of the damage to the pelvic tissues appears to occur with the first delivery. Other factors associated with increased risk from vaginal delivery include forceps deliveries, prolonged second stage, large-for-gestational-age birth weight, and large head circumferences. Not all of these obstetric factors have been found to be statistically or clinically significant in the literature and their etiologic role in the development of urinary incontinence remains to be determined.

Vaginal childbirth causes damage to the pelvic floor tissues by stretching, tearing, and pressing the soft tissues against the bony pelvis causing anoxia and tissue necrosis. The muscles, nerves, and connective tissues of the pelvis can all be affected and damaged. Studies have shown damage to all of the tissues as measured by prolonged pudendal nerve motor latencies, decreased levator muscle strength, and decreased urethral pressures. Fortunately, with healing and muscle strengthening with Kegel exercises, the majority of the damage can be repaired, and continence regained in the first 6 months after delivery. Long-term pelvic floor trauma secondary to vaginal delivery and aging appear to combine as the major risk factors for urinary incontinence and pelvic floor dysfunction.

Smoking, Exercise, and Obesity

Women who are cigarette smokers or ex-smokers are two to three times more likely to have urinary incontinence than nonsmokers. Whether this association is related to chronic cough and increased abdominal pressure or tissue damage from tobacco toxins is not known.

Physiologically, exercise has many positive and negative effects that may alter the balance between continence and incontinence. Increased abdominal pressure with high-impact exercise may overcome the continence mechanism in some women briefly causing situational episodes of leakage, but does not appear to increase their long-term risks for developing stress incontinence. Exercise that strengthens the lower extremities also strengthens the pelvic floor and enhances the continence mechanism. For the many health benefits, including strengthening the pelvic floor, women should be encouraged to exercise or take daily walks.

Obesity has been shown to be more common in women with both stress and urge incontinence than in continent women. In addition, morbidly obese women who lose weight have shown objective as well as subjective cure of their incontinence. Consideration should be given to surgically managing their morbid obesity over surgically attempting to correct their stress incontinence.

EVALUATION OF URINARY INCONTINENCE

History

The first step in evaluating a patient with urinary incontinence is to pose the question to the patient. Often a brief, directed review of bladder and bowel function can elicit symptoms. Open-ended questions such as “Could you please tell me about problems you are having controlling your bladder?” can be a useful initial approach. If the answer is affirmative for incontinence symptoms then an incontinence evaluation in initiated.

The evaluation begins with more direct questioning concerning the patient's symptoms, timing, and severity of incontinence. Frequently asked questions listed in Table 48.5 can help distinguish the type and severity of a patient's incontinence. Questions aimed at type of protection or pad used and number of pads used in a 24-hour period can indicate the severity of the problem. In addition, questions regarding lifestyle changes such as decreasing fluid intake or avoiding physical activities reflect the impact of incontinence on the patient's quality of life.

If you are having problems with urinary incontinence, please answer the following questions:

1. How long have you had incontinence?
2. How would you describe the severity of your incontinence?
3. Do you lose urine when coughing, sneezing, or laughing?
4. Is your urine leakage associated with a strong urge to go to the bathroom?
5. When you lose urine, is it a small amount, a moderate amount, or a large amount?
6. Do you ever lose urine at night while sleeping?
7. In the last month, how many times did you lose urine?
8. After the episodes of urine leakage do you usually need to change your underpants?
9. What do you usually wear for protection?

TABLE 48.5. *Frequently asked questions*

The presence of symptoms associated with both the storage and the emptying phases of the bladder cycle should be determined. Specific questions should ask about irritative symptoms (urgency or frequency), incontinence (stress or urge), and voiding dysfunction (urinary retention or postvoid fullness). A detailed history of any prior treatment of the genital or urinary tract, including surgeries should be obtained. The surgical history should contain details of any prior procedures for incontinence, including indications, technique, and type of suture used. Any complications (i.e., prolonged catheter use after surgery) or the development of new symptoms (i.e., urinary frequency and urgency following surgery) should be noted.

An obstetric history including route of delivery, episiotomy, lacerations, the use of forceps or vacuum, birth weights, and the length of the second stage of labor can determine the patient's risks associated with childbirth. A history of pelvic cancer therapy should include the dates and findings of any cystoscopic examinations. Other comorbid conditions affecting the lower urinary tract, including cigarette smoking, neurologic and endocrine diseases, as well as family history of urinary incontinence and pelvic organ prolapse may direct the clinician toward one type of urinary incontinence or need for further diagnostic evaluation. Any functional components such as difficult ambulation, declining cognition, or severe fecal impaction or constipation should be addressed prior to further evaluation or treatment.

Medications currently used should be reviewed in detail as many medications have adverse effects on the lower urinary tract (see Table 48.1). Unfamiliar medications should be verified. Diuretics and a-antagonists, two classes of medication commonly used to treat hypertension, may cause incontinence in some women. When incontinence is temporarily related to onset of use or dosage increase, it may be reasonable to use alternative medications that have less effect on the lower urinary tract.

Office evaluation should follow a stepwise progression (Fig. 48.2). Initial evaluation should focus on the severity of urinary leakage and the patient's goals for resolution of the problem. Some women may simply wish to regain sufficient bladder control to participate in certain social or athletic activities, while others desire complete continence under all circumstances. The extent of the evaluation and the proposed therapy should match the patient or her caregiver's expectations and goals.

FIG. 48.2. Evaluation algorithm. (From Fantyl JA, Newman DK, Colling J, et al. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guidelines Number 2, 1996 Update. Rockville, MD: Agency for Health Care Policy and Research, US Dept of Health and Human Services; 1996. AHCPR publication 96-0682.)

Physical Examination

Beyond the standard speculum and bimanual examination, the specific goal of a urogynecologic physical examination is to assess vaginal supports, strength of the pelvic floor, the anatomic position of the anterior vaginal wall, and the stability of the urethrovesical junction (UVJ). The examination for pelvic organ prolapse and the use of the standardized Pelvic Organ Prolapse Quantitative System (POP-Q) can be found in Chapter 45. In addition to noting any prolapse of the vaginal walls, uterus, or vaginal apex, the resting location and mobility of the UVJ with cough or strain is noted. In most cases, the urethral hypermobility can be documented by having the patient strain and the clinician noting prolapse of the distal anterior vaginal wall. If uncertain, and deemed important by the clinician, then a sterile Q-tip may be placed in the urethra or transperineal ultrasound used to document mobility. Not all women with a hypermobile urethra have stress incontinence and not all women with stress incontinence have a hypermobile urethra. African-American women appear to have more urethral hypermobility than Caucasian women, yet they have less stress incontinence because of higher urethral pressures. The importance of noting a hypermobile urethra is useful when considering certain treatment options. Both surgical and nonsurgical techniques that work by stabilizing or supporting the UVJ work best when the urethra is hypermobile allowing for repositioning or stabilization.

Neurologic evaluation of the incontinent female includes assessing intact perineal sensation that primarily represents the S2 dermatome. The bulbocavernosus reflex or anal wink is used to assess the sacral reflexes. A Q-tip swab is gently used to touch the skin overlying the bulbocavernosus muscles in the labia majora or perianally. A positive reflex indicates an intact pudendal nerve and L5-S5 motor neurons causing spontaneous contraction of the external anal sphincter. As with other reflexes, the sign is positive or negative. Hyperreflexia may be seen in upper motor lesions. Unlike the corresponding cremaster reflex in men, approximately 10% of normal, neurologically intact women will not demonstrate this reflex or the response is too weak to see. If, however, in the context of urinary or fecal incontinence or with other neuromuscular abnormalities of the buttocks or lower extremities, the absence of the bulbocavernosus reflex should alert the clinician to possible pathology in the sacral or cauda equina regions of the spinal cord.

A cough stress test should be performed, noting the position of the patient as supine or standing and whether her bladder is full or empty. Documentation of the sign of stress incontinence is adequate for diagnosis in most patients and avoids performing further, more complex and expensive testing.

Other conditions that can be detected during physical exam include hypoestrogenism, levator atrophy, and fecal impaction, which can all affect bladder control. If comorbid conditions such as edema or declining cognitive function are contributing to the patient's incontinence, then an expanded physical examination including mental status assessment, manual dexterity, and ability to ambulate is warranted.

Urinary Diary or Bladder Record

While not always available at the time of the initial history and physical, the urinary diary is an essential part of the of incontinence evaluation (Fig. 48.3). This tool allows the patient to record voided volumes, leakage episodes including amounts and associated activities, and the type and volume of fluid intake. Although a 3- to 7-day diary is optimal, evaluation of the events of a typical 24-hour period can be very helpful clinically. By simply keeping the diary, patients can notice how the amount and types of fluid they drink, as well as when they drink impact incontinence. In addition, the clinician can assess the severity of the leakage and begin to formulate an opinion of the type and etiology of the patient's incontinence and need for further evaluation. Upon review of the diary, the practitioner can suggest simple behavioral interventions such as fluid intake and medication adjustments.

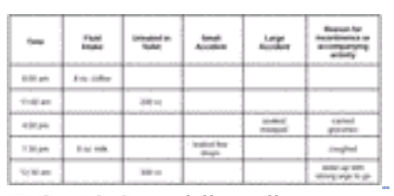

FIG. 48.3. Voiding diary.

Urinalysis and Postvoid Residual Volume

Sterile urine and a normal postvoid residual volume should be documented in all women. This assessment can be performed using a small-gauge catheter within 20 minutes after voiding. While there is no strict definition of a normal postvoid residual, the volume should generally be less than 100 mL. The catheterized urine specimen can then be used to rule out infection. While dipstick methods are available to detect bacteriuria and pyuria, the diagnostic accuracy is variable and dependent on the prevalence of urinary tract infections in that population. Therefore if the dipstick is positive or the patient's symptoms are consistent with a urinary tract infection, obtaining a urine culture is recommended.

Alternatively, an approximation of postvoid residual volume may be obtained with the use of an ultrasound specifically designed for determining bladder volume and using a clean catch urine sample to rule out infection. Infection should be treated and sterile urine should be demonstrated before further incontinence evaluation. If the residual volume is elevated, the test should be repeated on a separate visit. Persistently high residual volume should be evaluated. Conditions affecting bladder emptying such as peripheral neuropathies or pelvic organ prolapse outside the hymen are common etiologies for elevated postvoid residuals. Unlike men who frequently suffer urinary retention due to obstruction by an enlarged prostate gland, women rarely have obstruction unless they have undergone prior surgery for urinary incontinence that is obstructing urine flow.

Stress Test

The stress test is used to observe urinary leakage associated with straining or coughing, and is best performed with a full bladder in the standing position. Often a series of coughs is required to demonstrate incontinence. The patient should be positioned over a pad or paper towel, wrapped with a sheet or gown, and reassured that the physician wants to see urine leakage. Many times patients are embarrassed and reluctant to leak urine in the office setting in front of ther people. Putting the patient at ease and respecting her privacy helps to obtain a positive test and preserves patient dignity. A positive test confirms the sign of stress incontinence. A negative test does not completely rule out stress incontinence, but when performed with a full bladder and in the standing position the diagnosis of stress incontinence is less likely. If the patient also suffers from pelvic organ prolapse, then the prolapse should be repositioned to a “normal” anatomic position with a pessary or large vaginal swabs during the stress test.

Pad Test

A pad test is an objective test used to document the presence and amount of urinary incontinence. The test requires that the patient wear a preweighed pad while she performs activities usually associated with her incontinence. A 1-hour pad test is typically conducted. Generally, the test begins with the patient emptying her bladder and then drinking a known amount of water, typically 500 cc. Alternatively, the bladder can be filled with a set amount or to maximum capacity. The pad is weighed after 1 hour of activity. While pad testing has been found to be reproducible, in terms of objective documentation of incontinence and ability to evaluate pre- and post-treatment incontinence, its use in routine clinical evaluation is limited. A specific use for the pad test is when the clinician is unsure if the symptoms of incontinence

are due to urine loss or secondary to vaginal secretions or sweating. By giving the patient phenazopyridine hydrochloride (Pyridium) to turn her urine orange, a pad test can confirm urine loss.

After taking a careful history, performing a directed pelvic examination including a postvoid residual, ruling out infection, and performing a stress test, an accurate diagnosis can be made on the type of urinary incontinence for approximately 80% of women. Initial management can begin as outlined in Table 48.6.

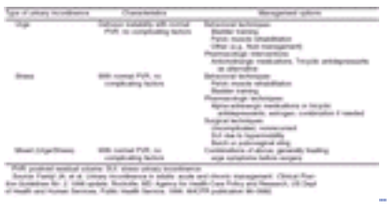

TABLE 48.6. *Management options after basic evaluation*

Specialized Tests

The need and use of specialized tests for the diagnosis and management of patients with urinary incontinence is far from standardized in clinical practice. While some clinicians feel advanced testing is useful, the reproducibility of certain tests such as multichannel urodynamics, leak point pressures, and voiding studies have led many clinicians and expert panels to use specialized testing in selected cases. The Agency of Health Care Policy and Research under the jurisdiction of the United States Department of Health and Human Services has recommended the use of specialized testing according to the guidelines listed in Table 48.7. Clinicians caring for patients with urinary incontinence recognize the difficulties in trying to determine the exact cause of leakage in all patients. When therapies can be used which effectively treat both urge and stress incontinence or there is acceptable cost and morbidity for the individual patient, determining the exact etiology is less critical. However, prior to surgical interventions, because of cost and morbidity, cystometry is recommended to document stress incontinence.

Uncertain diagnosis and inability to develop a reasonable treatment plan based on the basic diagnostic evaluation. Uncertainty in diagnosis may occur when there is lack of correlation between symptoms and clinical findings.
Failure to respond to the patient's satisfaction to an adequate therapeutic trial, and the patient is interested in pursuing further therapy.
Consideration of surgical intervention, particularly if previous surgery failed or the patient is a high surgical risk.
Hematuria without infection.
The presence of other comorbid conditions, such as:
incontinence associated with recurrent symptomatic urinary tract infection
persistent symptoms of difficult bladder emptying
history of previous anti-incontinence surgery or radical pelvic surgery
beyond hymen and symptomatic pelvic prolapse
prostatic nodule, asymmetry, or other suspicion of prostate cancer
abnormal postvoid residual volume
neurologic condition such as multiple sclerosis and spinal cord lesions or injury.

[a]Some patients who meet the criteria may not be appropriate for further evaluation and treatment if such evaluation and/or treatment is not desired by or feasible for the patient.

Source: Fantyl JA, et al. *Urinary incontinence in adults: acute and chronic management. Clinical Practice Guidelines No. 2, 1996 update.* Rockville, MD: Agency for Health Care Policy and Research, US Dept of Health and Human Services, Public Health Service; 1996. AHCPR publication 96–0682.

TABLE 48.7. *Criteria for Further Evaluation of Urinary Incontinence* [a]

If a patient presents with moderate to severe pelvic organ prolapse outside the hymen and has no subjective urinary incontinence, she should be tested for occult or potential stress incontinence. Studies have shown that with the prolapse reduced and straightening of the urethra, incontinence can “occur” in 30% to 50% of patients with prolapse. If urinary incontinence is found, then an antiincontinence surgery should be performed at the time of surgical correction for the patient's pelvic organ prolapse. Which antiincontinence surgery is best for occult incontinence is not known.

Consultation should be considered for cystometric testing and surgical management for patients who have not responded to initial treatments or have failed prior incontinence procedures.

Cystometry Cystometry is the test used to measure the pressure–volume relationship during bladder filling. The main purpose of cystometry is to diagnose or rule out detrusor contractions. A catheter attached to a vertical fluid column, a pressure transducer, or a microtip catheter measures the bladder pressure. Single channel or simple cystometry implies that only the bladder pressure is being monitored during the study. A multichannel or complex cystometry includes a second catheter for monitoring intraabdominal pressure. During a multichannel study, true detrusor pressures are calculated by subtracting the intraabdominal pressure from the bladder pressure. While filling the bladder, the compliance (bladder pressure divided by the infused volume), the first desire to void, maximum bladder capacity, and the presence of detrusor contractions are documented. Stress incontinence is diagnosed with the patient coughing or by performing a Valsalva maneuver and noting urine loss in the absence of a detrusor contraction.
Simple Cystometry or Single Channel Cystometry Performing simple cystometry can easily be done in the office of most gynecologists using a red rubber catheter, a three-way stopcock, intravenous tubing, and sterile water or saline. The patient is placed supine or if possible seated at a 45-degree angle. The sterile catheter is inserted and a postvoid residual volume is obtained. By attaching a three-way stopcock to the end of the catheter, a tube for filling and a tube for measuring detrusor pressures can be used. By taping the pressure tubing vertically to a 100-cm measuring stick taped to an intravenous pole, and then having the zero mark at the level of the bladder, the bladder is filled in 50- to 100-cc increments. After filling, the stopcock is turned off to the filling catheter. The pressure in the tubing represents the pressure in the bladder, including the intraabdominal pressure. The patient is instructed not to talk or perform any maneuvers that will increase her intraabdominal pressure. A rise in the fluid column should then represent a rise in bladder pressure secondary to abnormal compliance or a bladder contraction (Fig. 48.4).

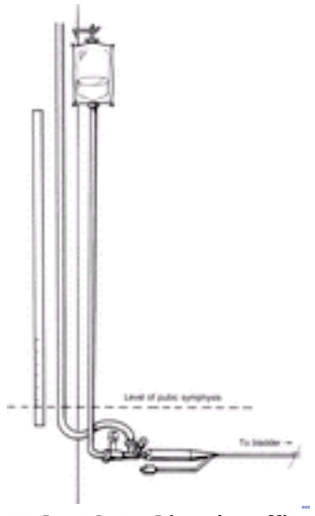

FIG. 48.4. Simple office cystometrogram. The zero mark of a meter stick is aligned with the upper margin of the patient's symphysis pubis, and a Foley catheter is in place for infusion of fluid. (Adapted from the American College of Obstetricians and Gynecologists, Bent AE, ed. *Urogynecologic evaluation, endoscopy, and urodynamic testing in the symptomatic female.* Washington, DC: ACOG Audiovisual Library, 1990.)

An alternative method for simple cystometry uses a specialized filling catheter with a pressure transducer that relays the bladder pressure to a recording device. Several types are commercially available.
Multichannel Urodynamics Approximately 10% of patients require multichannel urodynamic studies for diagnosis and treatment of urinary incontinence. Like all diagnostic tests, the clinician must understand the information gained from the procedure, the accuracy of the measurements, and how the information obtained will alter diagnosis, prognosis, or management of the condition. Multichannel urodynamics, once considered the gold standard for the diagnosis of detrusor overactivity and

stress incontinence, have been questioned regarding their reproducibility and cost-effectiveness in the routine evaluation of urinary incontinence. As outlined in Table 48.7, if initial assessment and treatment are not successful, further evaluation with multichannel urodynamic studies is indicated. Table 48.8 lists the common terms and definitions for urodynamic studies. Multichannel urodynamics are performed using a specialized machine or unit that records the bladder and intraabdominal pressures, subtracts the intraabdominal pressure from the bladder pressure to determine true detrusor pressure, and provides a report. Most units also have the ability to record urethral pressures and electromyography of the pelvic floor or urethra during the multichannel study. When reporting a multichannel cytometric study, the filling medium, rate of bladder fill, and position of the patient during the study should be noted. A typical tracing for a patient with detrusor overactivity is seen in Fig. 48.5. Note the rise in detrusor pressure without a rise in the abdominal pressure that is seen with a cough.

Intravesical pressure is the pressure within the bladder.
Abdominal pressure is the pressure surrounding the bladder and can be estimated from vaginal or rectal pressure.
Detrusor pressure is intravesical pressure that is created by forces in the bladder wall. It is estimated by subtracting the intraabdominal pressure from intravesical pressure.
First desire to void is the feeling during cystometry that would lead the patient to pass urine at the next convenient moment, but voiding can be delayed.
Maximum cystometric capacity is the volume at which the patient feels she can no longer delay micturition.
Detrusor overactivity is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.
Maximum urethral closure pressure (MUCP) is the maximum difference between the urethral pressure and the intravesical pressure.
Abdominal leak point pressure (ALPP) is the intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction.
Intrinsic sphincter deficiency (ISD) refers to urodynamic measures. MUCP ≤20 cm H_2O or ALPP of <60 cm of H_2O, that may indicate poor urethral function. For some surgeons, a diagnosis of ISD may alter the anti-incontinence surgical procedure that is performed.

Source: Abram P, Carodzo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167–178.

TABLE 48.8. *Cystometric definitions*

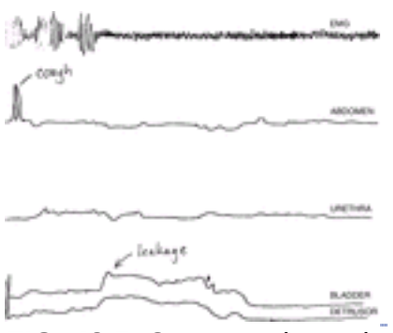

FIG. 48.5. Cystometric tracing.

Uroflow Studies and Voiding Cystogram Uroflowmetry measures the flow rate visually, electronically, or with the use of a disposable unit and is measured in mL per second. An electronically generated flow curve is considered helpful in identifying abnormal flow patterns such as Valsalva voiding (increasing vesicle pressure by pushing rather than having a detrusor contraction). Uroflowmetry does not help diagnose the type of urinary incontinence and is not a routine part of the evaluation of urinary incontinence. A voiding cystometrogram is a uroflow performed with a catheter in the bladder to record bladder pressures. For a patient with urinary retention, a voiding cystogram may help distinguish obstruction from detrusor weakness. A voiding cystometrogram may be useful in the evaluation of patients with elevated postvoid residuals, neurologic conditions such as diabetes that may affect bladder emptying or inability to void after extensive pelvic surgeries, or antiincontinence procedures.
Urethral Pressure Profilometry Urethral pressure profilometry (UPP), a urethral function test, measures resting and dynamic (with cough) pressures in the urethra. Clinically, UPP is used by some clinicians to assess the patient for a weak sphincter or intrinsic sphincter deficiency (ISD). Patients with ISD have been found to have less success with antiincontinence surgeries aimed at repositioning or elevation of the bladder neck and therefore the diagnosis of ISD would determine which surgical procedure was used. Sphincteric function can also be assessed by measuring abdominal or vesical pressure needed to overcome urethral resistance or abdominal or vesical leak point pressure. Clinically, the usefulness of the UPP versus abdominal leak point pressure has not been adequately studied.
Electromyography Both surface and needle electrodes have been used to record urethral sphincter and pelvic floor muscle activity during urodynamic studies. Technically difficult to reproduce, except in a few urodynamic laboratories which have expertise in electromyography (EMG), the clinical usefulness is questionable. The goal of EMG is to evaluate relaxation of the pelvic floor and urethra at the time of voiding. Many patients, while seated in the urodynamics chair with catheters in place and persons in the room, will have difficulty relaxing their pelvic floor and may give a false-positive test for EMG activity and poor relaxation during voiding. Pathologically, patients with detrusor sphincter dyssynergia (DSD) have a detrusor contraction to void but the urethra and periurethral striated muscle contract preventing or decreasing urine flow. DSD is caused by an upper motor neuron injury, most commonly multiple sclerosis.
Cystourethroscopy Cystourethroscopy is not recommended in the basic evaluation of urinary incontinence. For patients with bladder pain, sterile microscopic or gross hematuria, new-onset irritative symptoms without infection, or suspected intravesical foreign body, a cystoscopy is warranted to rule out neoplasia.

TREATMENT OPTIONS

Three major categories of treatment for urinary incontinence include behavioral, pharmacologic, and surgical. Treatment options are often used in combination, such as behavior modification with timed voiding in conjunction with pelvic floor exercises for strengthening the pelvic floor. Realistic expectations for success and any risks of the therapy must be reviewed with the patient before initiating treatment. In choosing treatment for one condition, the potential for exacerbating another condition must be considered. For example, surgery performed to cure minor stress incontinence may dramatically worsen urge incontinence.

Behavioral Techniques

When taught or provided by knowledgeable health care providers, behavioral techniques decrease the frequency of urinary incontinence in most individuals, have no reported side effects, and do not limit future treatment options. Behavioral therapies are most successful when persons can actively participate in their training program, but they can be provided effectively by caregivers for patients with cognitive and motor deficits.

Bladder Retraining Behavioral modification is defined as the analysis and alteration of the relationship between the patient's symptoms and her environment for the treatment of maladaptive voiding patterns. Because most women either decrease their fluid intake or urinate more frequently in order to avoid leakage, behavior modification is helpful in virtually every patient with urinary incontinence. By inquiring about self-directed modifications the patient has made in her diet, fluid intake, or activity level, the practitioner can gain insight not only into the patient's diagnosis, but save time and have a more direct impact by not recommending modifications that the patient has already tried. Simple techniques may be discussed after review of the urinary diary, including adjustments in the type and volume of fluid intake. Older patients frequently have nocturnal diuresis. The diaries of these patients reflect several episodes of nighttime voiding, possibly with urinary loss while en route to the toilet. However, the important diary clue is a large bladder volume—sometimes larger than the patient's first morning voided volume. Rather than adding a nighttime bladder medication, a late afternoon supine rest or leg elevation can help the diuresis. Consuming large volumes of fluid intake, often in an attempt to aid weight loss, is a problem and should be addressed. Women should be counseled to drink and titrate their fluids according to urine color and number of voids. Generally the urine should be a light yellow. Women should aim for six to seven voids in a 24-hour time period. Inadequate hydration may be found in women who restrict intake as a method of controlling their incontinence symptoms. For some women, this may contribute to urgency and frequency as the concentrated urine is more irritative to the bladder than dilute urine. Also, caffeinated beverages increase urinary urgency and frequency and may exacerbate incontinence episodes. Timed voiding is effective for approximately 60% of women with detrusor overactivity. The patient is instructed to void at a specific interval by the clock during waking hours. By examining the voiding diary, a voiding interval that is slightly longer than the current interval that results in leakage is used as a starting time. For example, if a patient is voiding every 30 minutes to avoid leakage, she is encouraged to try and hold her urine for 1 hour and to use the clock to monitor her frequency. Over a period of 6 to 8 weeks, the intervals are gradually lengthened until the patient is able to urinate without leakage at 3- to 4-hour intervals. An alternative technique for women who are going to the bathroom every 30 minutes to 1 hour to avoid incontinence is to add 15 minutes of waiting time to when they feel the first desire to void. By asking the woman to sit and squeeze her pelvic floor when she feels the urge to void and to try and wait 15 minutes before voiding, she can again increase her times between voids to 3- to 4-hour intervals within 6 to 8 weeks. These techniques have significant advantages, including the lack of systemic adverse effects and the minimal cost. It is an ideal initial intervention for many women. Written materials are helpful for optimal understanding and compliance. For women with cognitive impairment or decreased mobility, timed-voiding prompted by a caregiver can also be effective in decreasing the number of incontinent episodes and the amount of leakage. A bedside commode can facilitate voiding and help the patient avoid falls. These behavior modification techniques are often done in conjunction with pelvic floor exercises and have been found to be equal to or more effective than pharmacotherapy for some women with urinary incontinence.
Pelvic Floor Muscle Training Pelvic floor muscle training is defined as “repetitive selective voluntary contraction and relaxation of specific pelvic floor muscles.” Most

women are familiar with the concept of pelvic floor exercises often termed “Kegels” after the gynecologist who first introduced the concept in the 1950s. Women with weakened pelvic floor muscles may benefit from muscle-training protocols. These protocols are helpful for patients with detrusor overactivity or stress incontinence. Muscle rehabilitation aims not only to strengthen but to activate the muscle contraction at the appropriate time. Miller and colleagues have shown that with proper instruction as to the timing of the pelvic floor contraction with a cough or urge to void, women can have immediate success in decreasing their incontinence before any strengthening of the pelvic floor muscles takes place. Like exercises aimed at strengthening other striated muscles, measurable improvements in strength occur after 4 to 6 weeks of training. Patients frequently have difficulty identifying muscles used in pelvic floor contractions and are unaware if they are contracting the right muscles and how to perform the exercises. Assessment as part of the exam for pelvic floor dysfunction can help the patient isolate the right muscles. The examiner places an index finger with light pressure on the posterior fourchette and asks the patient to Kegel, or squeeze her pelvic floor as if she is trying to hold urine or not pass flatus. Another method is to have the patient try to stop her urine flow. This method should only be used as a test and not for performing the exercises. If the patient is able to stop or slow the urine flow then she is squeezing the correct muscles and a strengthening program can be initiated. Women with profound weakness or apparent paralysis generally require a supervised exercise program and biofeedback or electrical stimulation therapy. Biofeedback uses a pressure balloon, surface electrodes that record pelvic floor muscle activity, or another measuring device that, visually or by sound, alerts the patient that she is squeezing the proper muscles. Over time, the patient is able to isolate and contract the muscles without the auditory or visual cue and a formal exercise program can be initiated. Strength can be gained through a variety of exercise programs. There is little scientific evidence to suggest the superiority of any specific muscle-training regimen; however, it is likely that general principles of muscle strengthening apply. Physical therapists and nurses may be helpful in initiating and supervising the rehabilitation program. Simple written or verbal instructions may be sufficient to teach patients how to perform pelvic muscle exercises properly. Performing these exercises supine decreases the gravitational forces and may make the exercise easier for the patient to perform. With improved strength, she may advance to exercising in the upright position. Patients should be instructed to perform 10 to 20 ten-second pelvic floor contractions three or more times per day. A minimum of 30 contractions per day for at least 6 weeks is usually required to achieve a detectable beneficial effect. Too vigorous a program should be discouraged as muscle soreness could result in dyspareunia and abandonment of the exercise program. Older women may need a longer training period. These exercises should be performed indefinitely to prevent recurrence of incontinence. An adjunct to biofeedback and standard pelvic floor exercises is the use of weighted vaginal cones. The cones, weighted 20 to 100 g, are used as part of a structured, progressive, resistive exercise program. Women insert the plastic coated cone into the vagina much like a tampon, and attempt to keep the cone from falling out by squeezing the pelvic floor. The exercise is performed for 15 to 20 minutes once a day. Once a weight has been successfully held for 3 days, the next higher weight is used. For women with stress incontinence, weighted cones have been found to be equal to other pelvic floor exercise programs where patients are monitored closely by nurses or physical therapists. Cones may be preferred by some women because they are done at home, do not require nursing or physical therapy visits, and they are relatively inexpensive. Regardless of the exercise method used, as the muscles are strengthened, the patient must also learn to use her muscles correctly to inhibit urinary urge and reduce stress incontinence episodes. She must learn to contract these muscles firmly in advance of a cough, sneeze, or similar anticipated stress. Strength without timing or timing without strength will result in clinically unsatisfactory results. Once the muscles are strengthened and the patient has learned to squeeze at the appropriate time, the extent of exercise needed to maintain the effect is not fully known. Like many exercise programs, the patient's dedication to the activity likely will diminish with time.

Electrical Stimulation Therapy

Transvaginal electrical stimulation produces a contraction of the levator ani, external urethral sphincter, and anal sphincters, accompanied by a reflex inhibition of the detrusor and is dependent on a preserved reflex arc through the sacral micturition center in order to work. Electrical stimulation with a transvaginal probe reduces detrusor overactivity and stress urinary incontinence in approximately 50% to 70% of affected women. Two randomized trials comparing electrical stimulation to placebo or sham device have been performed. Sand and colleagues, using high frequency probes, reported objective “cure” or improvement in 48% of patients with stress urinary incontinence versus 13% improvement in the control group. Brubaker and co-workers reported on 121 women with urge, stress, and mixed incontinence. Participants used either a sham device or underwent electrical stimulation using a low-frequency, 20-Hz, 2-second to 4-second work–rest cycle for 20 minutes twice daily for 8 weeks. Detrusor overactivity was cured in 49% of women receiving electrical stimulation, but there was no statistically significant change in the percentage with detrusor overactivity in the sham device group. There was no statistical improvement in the women with stress urinary incontinence.

Typically, a transvaginal probe is used once or twice daily for 15 to 20 minutes. Symptom relief generally occurs within 6 to 8 weeks and continues with reduced stimulation (e.g., three times weekly). Like timed voiding and muscle training, this treatment is free of systemic adverse effects. The main drawback is the cost of rental or purchase, which may be out-of-pocket expense for many patients. Many third-party providers and Health Care Financing Administration (HCFA) have approved the use of electrical stimulation therapy for urinary incontinence making the treatment more affordable. Several devices approved by the U.S. Food and Drug Administration are available, and treatment can be home-based or, less commonly, office-based. Women with pacemakers should avoid this therapy unless other options are not available.

Implantable electrostimulators, such as InterStim, are now being used for patients with refractory urge incontinence. Before considering InterStim, all other treatment options should have been used properly, including transvaginal electrostimulation. InterStim requires insertion of a wire electrode, through an incision in the back and placement of a permanent stimulator, to the nerve root of S2, S3, or S4. The nerve root is stimulated and theoretically aberrant afferent signals to the spinal cord are blocked, decreasing bladder overactivity. Improvement of urgency and frequency symptoms ranges from 60% to 83%.

Vaginal and Urethral Devices An increasing selection of vaginal and urethral devices is available and appears to be the fastest-growing type of incontinence therapy. Pessaries modified for use in incontinence provide additional suburethral pressure and are safe and reasonably effective. For some women, the placement of a vaginal tampon may provide adequate urethral support to prevent leakage during physical activities such as playing golf or tennis. Both external and internal urethral barriers are becoming increasingly available. While not optimal for all patients, these devices can provide effective treatment for patients who leak only under known circumstances or perhaps to improve their quality of life while awaiting surgery. External barriers range from patches that fit over the urethral meatus to small suction cups that limit urine loss. Internal urethral barriers are available, but they have the distinct disadvantage of causing urinary tract infections and hematuria. Although effective in preventing urine loss, the devices are less than ideal because of these adverse effects. In addition, many women are not comfortable with the idea of placing something into or over their urethra or are not physically able to do so. The efficacy, cost, comfort, and adverse effects including urinary tract infection and skin irritation for each of these barriers must be considered. More experience is needed before recommendations can be made.

Pharmacotherapy

Detrusor Overactivity or Urge Incontinence No ideal medication for the treatment of incontinence is available, primarily because of the unwanted side effects. In general, drug treatment is used for detrusor overactivity and is aimed at reducing inappropriate detrusor contractions (Table 48.9).

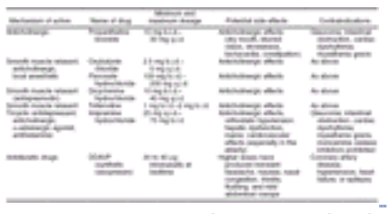

TABLE 48.9. *Pharmacologic therapy for detrusor instability*

Drugs for detrusor overactivity are typically anticholinergic agents. Thus, the adverse effects include xerostomia or dry mouth, blurred vision, drowsiness, and constipation. Narrow-angle glaucoma is an absolute contraindication to the use of this class of medications, and they should be used cautiously in women with cardiovascular disease. While other anticholinergic medications have been used clinically, oxybutynin chloride, propantheline, and tolterodine are the only medications in this class with scientific evidence of efficacy for treating detrusor overactivity. Oxybutynin chloride is available in generic formulations and in a longer-acting, once-a-day nongeneric formulation. Tolterodine, available in a once- or twice-a-day dosing form, may have fewer adverse effects when compared to generic oxybutynin chloride. Because of the high side-effect profiles, the medications should be started at very low doses and increased according to the patient's symptoms of incontinence and adverse reactions. The medications can be self-titrated over a period of 6 to 8 weeks with written instructions. Since constipation is a common comorbid condition in the elderly, recommending a stool softener when initiating therapy should be considered. Long-term compliance with incontinence medications is poor and usually ranges from 40% to 50%. This low compliance should be considered when selecting this mode of therapy and follow-up should be scheduled. The effectiveness of pharmacotherapy is poor in women whose incontinence is related to insensible loss (leakage that occurs without the patient's knowledge).
Stress Incontinence Medications that stimulate a-receptors are used to increase urethral tone in an effort to reduce stress incontinence episodes. These medications stimulate a-receptors throughout the body (e.g., in the cardiovascular system) and may cause hypertension. Phenylpropanolamine and pseudoephedrine are the first-line pharmacologic therapy for women with stress incontinence. Women with mixed urinary incontinence may benefit from imipramine hydrochloride, a tricyclic antidepressant. This medication offers a combination of anticholinergic medication for detrusor suppression and a-receptor sympathomimetic activity to increase urethral pressure.
Estrogen The role of oral or vaginal estrogens in the management of overactive bladder or stress incontinence remains unclear. Prospective studies have shown little effect of oral combined estrogen/progestin therapy on lower urinary tract function, including prevention or improvement in urinary incontinence. Meta-analysis of prior studies has shown some improvement in nocturia secondary to estrogen therapy in postmenopausal women. While many clinicians feel strongly that preoperative transvaginal estrogen therapy improves surgical outcome and tissue healing, further evaluation is needed.

Surgical Management

Surgical management of urinary incontinence has been reported since the early 1900s. With an aging United States population, there will be greater demand for surgical and nonsurgical treatment of incontinence. Estimates indicate the demand for services will increase 10.9% for women between the ages of 30 to 58 years and 80.7% for those between 60 to 89 years by 2020. Although hundreds of operations have been described, today there are basically three types of procedures used: a suburethral plication, a shelf or repositioning type of procedure, or a pubovaginal sling. The large number of reported procedures indicates that no single type of operation will cure all patients. Table 48.10 presents the studies that have included objective testing and highlights the handful of studies that have been prospective, randomized, controlled trials. Based on the clinical findings in each individual patient, the surgeon must select the procedure or combination of procedures that will most likely alleviate the condition. Selection of the antiincontinence procedure is determined by many factors including need for other concomitant abdominal or vaginal procedures to correct pelvic organ prolapse, history of prior repairs, urethral hypermobility, and overall health and surgical risks for the patient.

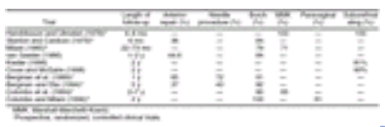

TABLE 48.10. *Urinary incontinence procedures: objective cure rates*

Significant limitations in reviewing data on the surgical treatment of stress incontinence have been encountered. There is no standardized pre- or postoperative evaluation for the surgical treatment of stress incontinence. Variable lengths of follow-up, inconsistent outcome criteria, and reporting biases of operating surgeons make comparison of many clinical series nearly impossible. The 1996 revision of the Agency for Health Care Policy and Research Urinary Incontinence Clinical Practice Guidelines summarized that “the surgical literature is deficient in standards for describing the patient population, the type of incontinence, the method for accurate diagnosis, the techniques of the surgical procedure, or the outcome in different domains.” In 1997, the American Urologic Association completed a comprehensive, evidence-based review of the surgical literature on the treatment of stress incontinence. Minimal criteria for follow-up interval and reporting outcomes resulted in the elimination of over half the reported clinical series from the database. There were no standardized pre- and postoperative evaluations and uniformity in the terminology describing the surgical procedures. Limited, poorly defined outcome measures (e.g., “dry”, subjective vs. objective variables, “improved”—1 pad/day vs. 3 pads/day) with little accuracy in morbidity rates made comparison of the surgical literature impossible.

Although our understanding of the pathophysiology of stress incontinence is incomplete, most accept the current concepts of urethral hypermobility and intrinsic sphincter dysfunction as causes, whether alone or in combination. Einhorning believed that the proximal urethra descended beyond the pelvic diaphragm and thus beyond the sphere of influence of the abdominal cavity, and restoration of continence required the urethra be drawn back within the abdominal cavity. Reexamination of the anatomy of the female pelvis from both a structural and functional perspective has led to the current concept that poor support of the proximal urethra as a result of relaxation or detachment of the anterior vaginal wall is responsible for the hypermobility associated with stress incontinence. It is recognized that this is an incomplete explanation since the majority of women with hypermobility do not have stress incontinence. Thus, there must also be some abnormality in the function of the urethra in women with stress incontinence. Whether this dysfunction is a primary neurologic defect or muscular defect is not yet determined, but there is strong evidence that denervation plays an important role. Snooks and co-workers demonstrated that the denervation effects of vaginal birth and subsequent pudendal neuropathy are significantly associated with GSI.

A subset of women develop stress incontinence despite excellent support of the UVJ. The term “intrinsic sphincter deficiency” (ISD) was created to describe this condition. ISD is a weakness or defect in the intrinsic urethral sphincter, resulting in stress incontinence, and is generally considered a more severe type of stress incontinence which emphasizes decreased urethral sphincter function rather than urethra position or mobility. Whether there is an actual physiologic difference in these “types” of stress incontinence or their underlying pathophysiology is unknown. This distinction may be artificial, looking at the same problem of neuromuscular dysfunction along one continuous spectrum.

Traditionally, from a surgical standpoint, the distinction between the two types of stress incontinence has been used to determine the type of surgical procedure performed—colposuspension or pubovaginal sling. Hypermobile stress incontinence has generally been managed with the “urethral hammock” support using a colposuspension such as a Marshall-Marchetti-Krantz (MMK), Burch, or paravaginal repair. The surgical procedure's goal is to elevate and stabilize the UVJ.

Patients with ISD have been found to have lower success rates following retropubic urethropexies when compared to patients with urethral hypermobility and a better functioning urethra. Thus pubovaginal sling procedures employed to treat ISD are designed to restore compression and coaptation of the damaged urethral sphincteric mechanism.

While some surgeons continue to surgically treat these “types” of stress incontinence differently, many surgeons, both urologists and gynecologists, are increasingly using a pubovaginal sling for all patients with stress urinary incontinence. Because of the reported durability, the pubovaginal sling, in increasing numbers of practices, is being performed for patients with hypermobile stress incontinence without ISD. Cross and associates performed pubovaginal slings on such patients with a cure rate of 93% reported at 22 months.

In 1996, a review by Black found four prospective studies done to compare colposuspension with sling procedures. None reported a difference in cure rate although all had substantially less than 50% power to detect a significant difference and all defined surgical success differently. Only one study analyzed complication rates and found a statistically significant higher risk of complications after a sling operation including elevated postvoid residual urine, entry into the bladder, and uterine prolapse. One large retrospective trial suggested that colposuspension may be more effective than sling procedures (95% vs. 79%). Marinkovic and colleagues, in a retrospective review of 18 women having a Burch colposuspension and 18 women undergoing a pubovaginal sling, found that the Burch group had twice the number of postoperative complications, with comparable success. In contrast, Enzelsberger showed significant increases in postoperative voiding dysfunction in patients after pubovaginal sling (13%) that was not observed in Burch patients. Thus, there is no convincing evidence that the effectiveness of colposuspension and sling procedures differ. The differences may be in the complication rates for the two procedures. However, less than 150 patients have ever been included in prospective studies concerning these two surgeries. Two large, prospective trials comparing Burch colposuspension and pubovaginal sling are underway and should help determine the best procedure.

Suburethral Plication/Anterior Colporrhaphy While most surgeons have abandoned the suburethral plication as an antiincontinence procedure, for a select group of patients, the Kelly-Kennedy plication is appropriate. Dr. Howard Kelly from Johns Hopkins University was the first to describe this operation in 1913. The technique has changed very little from his original description. Through an anterior vaginal incision, the vesicovaginal space is dissected bilaterally to the pubic rami. A series of plicating mattress sutures of either permanent or delayed-absorbable material are then placed beneath the UVJ and then subsequently, in any significant pubocervical fascial defect, below the urethra and bladder. Although Dr. Kelly reported a more than 90% subjective success rate with his anterior vaginal repair, subsequent success rates in the literature have ranged from 31% to 69% with 1- to 5-year follow-up. One noteworthy exception to these figures, however, is two studies from Dr. R. Peter Beck of Canada. In his original series of 105 patients reported on in 1982, a 90% subjective cure rate was described. In a follow-up paper published in 1991, similar outcome numbers were provided for over 500 patients. Dr. Beck attributed much of his success to the use of delayed absorbable polyglycolic suture instead of chromic cat gut suture. Anterior vaginal repair remains indicated in the treatment of a cystocele caused by a central fascial defect. Concomitant suburethral plication may be a reasonable choice in the prevention of potential or occult stress incontinence for patients having vaginal reconstruction for pelvic organ prolapse. The most appropriate indication for a suburethral plication is in conjunction with an obliterative procedure, such as when complete or LaForte colpocleisis is performed. These patients, generally older with poorly functioning detrusor muscles or detrusor overactivity, are at risk for urinary retention or worsening of incontinence from detrusor contractions if a more durable antiincontinence surgery is performed. A suburethral plication may be the best antiincontinence surgery for these patients. Their incontinence may not be “cured”, but the low morbidity balances the higher risks of urinary retention or overactive bladder. Success in these cases is defined by improved quality of life from prolapse surgery and hopefully a reduction in urinary incontinence and avoidance of self-catheterization. Complications include hemorrhage, vaginal foreshortening, and suture misplacement in the bladder, urethra, or ureter. Thus, follow-up cystoscopic evaluation is recommended to assess for potential injury to the lower urinary tract.

Retropubic Urethropexy Retropubic urethropexy (RPU) is used by many surgeons as their primary repair for stress incontinence. The first RPU, described in 1949, the Marshall-Marchetti-Krantz (MMK) procedure has had success rates ranging from 70% to 90%. After entry to the retropubic space is achieved, the urethra is identified along its course to the bladder neck. One to three pairs of sutures, usually nonabsorbable, are placed on each side and close to the urethra through the pubocervical fascia. These are then fixed to the fibrocartilage of the symphysis pubis. Because the angle of elevation is more acute and centrally placed than with a Burch procedure, the potential exists for the patient to have an increased risk of bladder neck obstruction. Voiding dysfunction occurs in 5% to 20% of cases. The rate of subsequent osteitis pubis is approximately 2%. In 1961, Dr. John Burch of Nashville, Tennessee described a new fixation point for the RPU sutures, namely Cooper's ligament. Through a Pfannenstiel incision, the retropubic space is entered. With the surgeon's nondominant hand in the patient's vagina, the Foley catheter is pulled down to the UVJ. While gently retracting the bladder medially, the paravaginal tissues are identified and, if necessary, gently cleaned off at the UVJ and midurethra extending approximately 2 cm lateral to the urethra. Seeing the white surface of the vaginal submucosal layer in contrast to the yellow bladder helps identify

the vagina. A full thickness figure-of-eight of permanent suture is placed at the UVJ and midurethra on both sides. Cooper's ligament is identified, and both arms of the sutures are brought through the ligament, with the midurethral sutures most caudad (Fig. 48.6). The sutures are tied while elevating the vagina so that the urethra is repositioned parallel to the floor. Overcorrection should be avoided; suture bridges are the norm. Cystoscopy, transurethrally or through the bladder dome, teloscopy, is then performed to assess the integrity of the lower urinary tract. Consideration for placement of a suprapubic catheter is reasonable, especially if the patient is predisposed to postoperative voiding dysfunction.

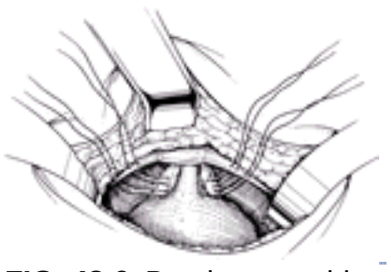

FIG. 48.6. Burch retropubic urethropexy. Sutures are placed lateral to the urethrovesical junction and lateral to the midurethra and brought to the Cooper ligament bilaterally. (Adapted from Tanagho EA. Colpocystourethropexy: the way we do it. *J Urol* 1976;116:751.)

Objective cure rates for the Burch RPU range from 70% to 90%. Complications include ureteral damage (usually from overcorrection or kinking, not direct trauma) and bleeding from the adjacent large veins of Santorini. Enterocele formation following colposuspension has been reported in 3% to 17% of patients, leading most surgeons to perform a uterosacral ligament plication or cul-de-sac obliteration for patients predisposed to pelvic organ prolapse. The prevalence of postoperative detrusor overactivity is 5% to 18%. Postoperative management is similar to that for other abdominal surgical procedures. It is usually possible to allow patients to have oral intake soon after the operation, because the peritoneal cavity was not entered. The bladder is drained continuously for the first 1 or 2 postoperative days. If used, the suprapubic catheter is occluded and patients are asked to indicate when they feel that the bladder is full. They are then allowed to void, and the amount of urine remaining inside the bladder is measured by the nursing personnel. If transurethral catheter drainage has been used, the bladder can be filled retrograde until the patient feels full. The catheter is then removed and the patient is asked to void. The voided amount is measured using a hat placed in the toilet. By subtracting the voided amount from the amount instilled in the bladder, the postvoid residual can be determined. The catheter should be replaced or the suprapubic catheter should be left in until the patient is able to void adequately with small amounts of residual urine (<100 mL or <25% of the total volume in the bladder) consistently for three voids. The patient can also be taught clean, intermittent self-catheterization to perform until her postvoid residuals are adequate. Most patients can void adequately within 72 hours. Some literature suggests that the Burch procedure has fewer complication rates than the MMK. Columbo and colleagues randomized 80 patients with stress incontinence to receive either a Burch or an MMK. Although the cure rates were equal, patients who underwent an MMK were more likely to have detrusor overactivity and voiding dysfunction postoperatively.

Laparoscopic Bladder Neck Suspension The laparoscopic approach to correcting stress incontinence has been described with increasing frequency since the early 1990s. Reports by expert laparoscopic surgeons who perform the Burch procedure identical to the open technique report similar success rates to the open procedure. Reports where techniques are altered, such as one suture used on each side rather than two, or only one arm of the suture being brought through Cooper's ligament have shown significantly more failures. The applicability of this technique demands that the procedure be performed in exactly the same way as an open Burch. Complications with the laparoscopic technique include injuries to nearby structures at the time of surgery and are more frequent than with open dissection. This is most likely due to the learning curve. Most skilled laparoscopists cite a learning curve of 10 to 20 procedures.

Paravaginal Repair Paravaginal repair is another retropubic procedure used for the correction of stress incontinence. The abdominal paravaginal repair was first described by Burch, in his initial attempts to surgically support the UVJ. Due to poor results, Burch modified his procedure, elevating the sutures from the endopelvic fascia to Cooper's ligament rather than the arcus tendineus fasciae pelvis (ATFP). Cullin Richardson reintroduced paravaginal repair as a procedure to correct paravaginal (lateral) defects in anterior vaginal wall support. Although others have suggested that the procedure may also be used as an antiincontinence surgery, closer examination of the procedure performed indicates that the investigators combined Burch stitches to the Cooper ligament with paravaginal stitches to the ATFP. The only randomized, prospective study comparing the Burch procedure to a pure paravaginal repair, with pre- and postoperative objective follow-up, indicates that the paravaginal repair yields inferior cure rates, 75% versus 100%, in treating stress incontinence. The paravaginal repair should be considered a procedure for correcting anterior lateral vaginal wall defects and not as an antiincontinence procedure.

Suburethral Slings Suburethral sling procedures have been described since the early 1900s. In 1942, Aldridge was the first surgeon to use strips of autologous rectus fascia, placing it under the bladder neck and affixing it to the anterior abdominal wall. Traditionally, suburethral slings have been performed for recurrent stress incontinence, for patients with risk factors for surgical failure such as chronic pulmonary conditions like asthma, or for patients who perform physically demanding activities that cannot be modified. The more common indication is for ISD with or without urethral hypermobility. There has also been a trend in performing primary sling procedures in patients with hypermobile stress incontinence based on the high failure rates of other procedures, particularly, anterior repair and needle suspensions. Suburethral sling procedures may use autologous materials or foreign materials to support the UVJ. Autologous materials such as fascia lata may be obtained from the leg, or rectus fascia from the anterior abdominal wall has also been used. Synthetic materials such as Marlex and Mersilene have been used for suburethral slings with success. Allograft fascia has been used with varying success rates depending on tissue source and processing. Surgeons continue to search for the ideal sling material. While autologous materials have fewer long-term complications such as erosion or infection, the harvesting of grafts increases operative time and potential for morbidity. The technique of a suburethral sling procedure basically involves placement of either a tissue or synthetic graft under the bladder neck and fixation of the material to an abdominal site. A graft measuring approximately 8- to 10-cm long by 2-cm wide is either harvested or cut from the synthetic material and tagged at the corners with permanent suture. The vaginal portion of the procedure begins with a vertical or U-shaped incision made along the anterior vaginal wall, and entry into the retropubic space is accomplished. The UVJ is identified by gently pulling on an indwelling Foley catheter. The sling itself will be sutured such that two-thirds of the 2-cm–wide sling are under the urethra and one-third is under the trigone (Fig. 48.7).

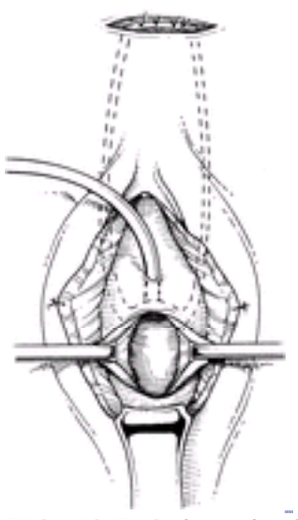

FIG. 48.7. Suburethral sling procedure. After dissection of the anterior vaginal wall, the sling is anchored underneath the urethrovesical junction, and the arms are brought to the anterior rectus fascia, where they are similarly anchored. (Adapted from Horbach N, Blanco J, Ostergard DR, et al. A suburethral sling procedure with polytetrafluoroethylene for the therapy of genuine stress incontinence in patients with low urethral closure pressure. *Obstet Gynecol* 1988;71:648.)

A short suprapubic incision is made to the level of the anterior rectus fascia. A stab wound is made through the rectus fascia 2.5 cm lateral to the midline just above the symphysis. A uterine packing forceps or suture carrier is passed through this incision down into the vagina, guided by the surgeon's index finger. The arm of the sling is grasped and withdrawn up to the anterior rectus fascia. The procedure is repeated on the opposite side. At this point, a cystoscope is introduced into the bladder to ascertain whether or not perforation of the bladder has occurred and urethral function remains normal. The sling is then secured at the UVJ using fine absorbable suture. The sling is then gently elevated until there is no slack. The most important step in the procedure is paying careful attention to not to pull the sling too tight. The sling functions as a backstop, not by occluding the urethra. Experienced surgeons know that loose is better than tight. While various techniques including Q-tip angles and cystoscopy have been used to try and “standardize” sling tension, none have proven useful. The sling is sutured first to the rectus fascia. The anterior vaginal wall is approximated and the anterior abdominal wall incision is closed. Postoperative care and bladder management is the same as described for colposuspension. Complications of the suburethral sling procedure include the possibility of erosion of the sling material into the vagina or the anterior abdominal wall with sinus tract formation. Occasionally, slings must be removed because of this problem. Slings may also be removed from patients who develop marked obstruction and who do not want to use self-catheterization on a permanent basis. Success rates for sling procedures range from 85% to 90%. Reasons for failure include inaccurate placement at the bladder neck, inadequate sling tension, poor tissue graft, or inadequate fascial attachment. The most common complication and the reason many surgeons avoid sling procedures is postoperative voiding dysfunction. Failure to void after the procedure occurs in up to 20% of patients. Although there are procedures designed to remedy this situation (i.e., sling release or modification), the best method is prevention by assuring that the sling is not placed too tightly in the first place. Some patients may be able to modify their urination by changing positions such as leaning forward or standing. As long as the patient is not having serious sequelae such as pain or urinary tract infections, treatment may remain conservative. The patient may very well be willing to accept some voiding difficulty in exchange for being dry. If however, the patient cannot spontaneously void by 6 weeks after surgery, sling revision should be offered. In most cases, the sling can be cut transvaginally and the patient does not develop recurrent incontinence.

Tension-free Vaginal Tape In 1995, a modification of the pubovaginal sling, the tension-free vaginal tape (TVT), was introduced. Developed by Petros and Ulmsten in

Sweden, the TVT differs from the traditional pubovaginal sling in that the sling is placed at the midurethra and not the UVJ, and the sling material is a 1-cm–wide mesh of Prolene that is held in place by friction and not sutures. The procedure, designed to be performed under local or regional anesthesia, allows the patient to cough with a full bladder during sling adjustment. The sling is elevated to the level where urine leakage stops and is not made any tighter. For women with hypermobility and a normal functioning urethra, an objective cure rate of 90% has been reported after a 5-year follow-up. For a small group of women with ISD, cure rates of 74% with additional improvement in 12% with a 4-year follow-up have been reported. Immediate complications, including bleeding and bladder perforation, are similar to other series for pubovaginal slings. Voiding dysfunction appears to be less than for traditional pubovaginal slings, but is probably related to having a looser sling. As more surgeons have adapted the loose sling technique to traditional sling placement, the voiding dysfunction in more recent series is also decreasing. Long-term complications, including graft erosion, are unknown. While Prolene appears to have properties that are more favorable for vaginal placement than other meshes, it is likely that there will be a 1% to 3% erosion rate. Longer follow-up and careful reporting of outcomes will determine the use of TVT in the management of stress urinary incontinence.

Transurethral Collagen Injections Although initially thought to be a significant breakthrough in treating patients with severe incontinence, periurethral bulking agents have a less than 50% long-term success rate. However, for some patients this is a reasonable surgical alternative to more invasive procedures. The patient best suited for a bulking agent is one who has ISD, an immobile bladder neck, excessive surgical risk, and who has undergone multiple antiincontinence procedures. Short-term cure rates approach 70% to 90%. Periurethral collagen injections are not indicated in women with urethral hypermobility, because cure rates are only 20% to 25% in this group of women. The most commonly used substance for bulking is gluteraldehyde cross-linked bovine collagen. Because of potential allergies, a patient must have a negative reaction to a collagen skin test weeks before surgery. The procedure can be done in the physician's office or in an outpatient setting with local anesthesia. A zero-degree operative cystoscope with a spring-mounted injection needle is employed. Once the bladder neck is visualized, a site approximately 1 to 2 cm distal to it is selected for needle insertion. Injections are performed at the 3 o'clock and 9 o'clock positions in an attempt to close the bladder neck. Usually, 5 to 7 cc of material will be sufficient. The patient is asked to cough to observe for leakage. Injections can last 3 months to several years. Most patients require multiple injections given 2 to 3 months apart, followed by a general improvement lasting 6 months to 1 year. This method is probably best used by obstetrician–gynecologists who specialize in the treatment of incontinence.

Artificial Urinary Sphincters Few treatment centers implant artificial urinary sphincters in women, mostly because of the high complication rates. The ideal patient has ISD but no scarring at the bladder neck. Failure of a sling procedure or collagen injections may prompt the surgeon to consider this surgery. The sphincter is placed using a combined abdominal/vaginal approach. The sphincter is placed around the urethra, with the reservoir in the retropubic space and the pump in the labia majora. The active sphincter mechanism is not activated for 6 weeks until healing has taken place. The device maintains closure of the bladder neck until patient activation of the device evacuates the cuff for several minutes to allow voiding. Complications include infection, device erosion, or pump failure.

SELECTING THE APPROPRIATE SURGICAL PROCEDURE FOR STRESS INCONTINENCE

Selection of a surgical procedure for a given patient is based on the operating surgeon's impression of the clinical complaints, the physical examination findings, and cystometric values. Objective urodynamic assessment of the patient is only required if the surgeon is going to base the choice of surgical procedure on specific objective findings such as the urethral closure pressure or the bladder pressure needed to overcome the urethra. If however, the surgeon will perform a pubovaginal sling, for all patients with stress incontinence regardless of urethral function, then urodynamic testing in not indicated.

Traditionally, if a patient's urethral pressure has been considered normal, greater than 20 cm H_2O, a retropubic urethropexy of the Burch type is preferred. If the urethral pressure is less than 20 cm H_2O, a suburethral sling procedure should be considered. In both circumstances, it is assumed that inadequate support of the UVJ is present, as indicated by a Q-tip test that is greater than 30 degrees from the horizontal during straining. If the UVJ is well supported, as indicated by a Q-tip deflection on straining of less than 30 degrees from the horizontal, the patient is less likely to respond to either of the aforementioned procedures, and other surgical means may be indicated for treatment. Options for treatment of intrinsic sphincter deficiency and a supported bladder neck include an artificial sphincter, periurethral injection, or an obstructive sling. With the latter choice, the patient needs to be informed of the extremely high probability that lifelong self-catheterization may be required to empty the bladder.

Much discussion has taken place regarding the different procedures used to manage stress incontinence in regard to efficacy and long-term success. Unfortunately, most studies in the literature have lacked objective pre- and postoperative assessment and therefore an objective measurement of cure. Table 48.10 shows the studies that have included objective testing and highlights the handful of studies that have been prospective, randomized, controlled trials.

SUMMARY

Many women of all ages have urinary incontinence. Unfortunately, many women still do not seek treatment. All clinicians who care for women should ask about bladder function and reassure patients that many successful treatments are available. After asking the question, the clinician should work with the patient to determine the type and severity of her incontinence and the impact her urine leakage is having on her life. Evaluation should be directed at ruling out treatable causes such as urinary tract infections, fluid overload, or medications that affect fluid balance or lower urinary tract function. Bladder testing with cystometry should be considered before surgical treatment to be sure the patient suffers from stress incontinence and not detrusor overactivity that may be made worse or have no improvement after surgery. Treatment should be based on the patient's expectations, ability to use behavioral techniques, side effects of therapies, cost, and success for treating her condition.

SUMMARY POINTS

- Urinary incontinence is a common condition affecting women. Many successful treatment options are available.
- Diagnosis of lower urinary tract conditions, particularly urinary incontinence, cannot be made based on symptoms alone. A systematic approach including history, physical examination, voiding diary, assessment of postvoid residual, and ruling out infection begin the assessment.
- A positive stress test demonstrates the sign of stress urinary incontinence.
- Multichannel urodynamic studies are indicated for approximately 10% of women to help make the diagnosis of the type of urinary incontinence. Clinicians who specialize in urinary incontinence use multichannel urodynamics to test more patients because of the complexity and prior failed treatments in women referred for subspecialty care.
- Selection of the appropriate surgical procedure for the correction of stress incontinence should be based on urethral function, the presence or absence of urethrovesical junction (UVJ), hypermobility, and the need for other surgical procedures for pelvic organ prolapse.
- Retropubic urethropexy procedures, specifically the modified Burch procedure, offer the best long-term support of the UVJ and cure of incontinence with the least morbidity.
- Intrinsic sphincter deficiency should be considered in patients with severe leakage with minimal activity or those with recurrent incontinence, a history of radical pelvic surgery, or radiation. Options for therapy include periurethral injection of bulking agents or artificial sphincter in patients with a well-supported UVJ, or a suburethral sling when UVJ hypermobility is present.
- Detrusor overactivity should be looked for in every patient with urinary incontinence, most importantly prior to any surgical antiincontinence procedure. It is best treated with bladder retraining, electrical stimulation therapy, or anticholinergic medications.

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Chapter 49

Arthur F. Haney

Leiomyomata

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Postoperative Pelvic Adhesions
Medical Suppression
Myolysis
Uterine Artery Embolization
Recurrence of Leiomyomata Following Myomectomy

Leiomyomata represent the most common gynecologic tumors and are responsible for approximately 300,000 hysterectomies per year. They can cause a variety of symptoms, including menometrorrhagia, dysmenorrhea, pelvic pain, infertility, preterm birth, and compression of adjacent pelvic viscera. Paradoxically, large subserosal leiomyomata may be totally asymptomatic. These tumors are often multiple, are almost always benign, and represent gonadal steroid–responsive aberrant clonal expansions of individual myometrial cells. Leiomyomata are more common in African-American women and have a nonmendelian inheritance pattern with up to a 50% recurrence rate after myomectomy. Treatment of patients with leiomyomata should be undertaken only to address a specific clinical problem and the therapy choice depends on the goal of therapy, with hysterectomy most often used for definitive management and myomectomy when preservation of childbearing potential is desired. Intracavitary and selected submucous leiomyomata can be removed by hysteroscopic resection and, although laparoscopic myomectomy is technically feasible, the risk of uterine rupture during subsequent pregnancy is potentially greater with the endoscopic removal of intramural leiomyomata. Although gonadotropin-releasing hormone (GnRH) agonist–induced hypogonadism can reduce the volume of leiomyomata by up to 50%, the severe side effects and prompt reenlargement after discontinuance make this approach useful only for short-term goals such as: (a) shrinking an intracavitary tumor prior to hysteroscopic resection, (b) preoperatively correcting anemia, or (c) reducing the overall size of the uterus to facilitate surgery. Nonextirpative approaches, such as myolysis and uterine artery embolization (UAE), are being evaluated and may prove useful options for carefully selected women if proven safe and efficacious in long-term follow-up studies. The impact of these nonextirpative options on fertility and pregnancy has not been determined. Ultimately, if the genetic basis for fibroid development or the molecular mechanism(s) of myometrial proliferation are better understood, additional nonsurgical therapeutic interventions may be forthcoming.

INTRODUCTION

Uterine leiomyomata are by far the most common benign tumors of the female genital tract and likely the most common soft tissue tumors of all. Approximately 300,000 hysterectomies and 20,000 myomectomies are performed annually in the United States because of symptoms caused by leiomyomata. These tumors can attain very large size with few if any symptoms and, alternatively, small leiomyomata may cause massive uterine bleeding, marked abdominal distension, and disabling dysmenorrhea. Although representing one of the most frequent indications for gynecologic surgery, the incidence of leiomyomata far exceeds the frequency of clinical problems, with estimates of as high as 50% of women having at least one identifiable fibroid at menopause. Understanding what is known regarding the pathophysiology, genetic risk predisposition, and natural history of leiomyomata is invaluable for the practicing clinician.

CLINICAL PICTURE

Leiomyomata come to clinical attention for a variety of reasons, and the symptoms (Table 49.1) depend upon tumor size and location (Fig. 49.1). It is unusual but not rare for fibroids to become symptomatic before a woman reaches age 30. Excessive menstrual bleeding (menorrhagia) leading to anemia, debilitating dysmenorrhea, generalized pelvic pain, or symptoms of pressure on the adjacent pelvic viscera my occur, but pain other than dysmenorrhea is typically a late symptom. Vaginal bleeding apart from the expected menses, despite being heavy, is not typically a sign of uterine fibroids and usually indicates an underlying endocrine abnormality such as anovulation. Furthermore, the typical scenario is not a sudden heavy bleeding episode, but rather a gradual increase in menstrual bleeding that parallels the growth of the fibroids. Leiomyomata occasionally undergo rapid enlargement during pregnancy with central avascular necrosis, the so-called *red degeneration*, resulting in extreme pain requiring hospitalization and narcotics. As the size and number of the leiomyoma increase, particularly with single large subserosal leiomyomata, the adjacent pelvic viscera may become compressed, resulting in urinary frequency, constipation and, occasionally, dyspareunia. Rarely, when the fibroids are large and fill the pelvis or grow laterally from the midportion of the uterine body, they can compress the ureters and cause hydronephrosis (Fig. 49.2). Intracavitary fibroids often are on a vascular pedicle and may be extruded through the cervix, appearing as a necrotic mass. Rarely, large uterine leiomyomata will become entrapped in the pelvis when the expanding tumors are juxtaposed against the promontory of the sacrum and cause the cervix to descend in the vagina and occasionally appear at the introitus. This is particularly true when a woman with large serosal leiomyomata conceives and the tumors, as well as the gravid uterus, enlarge rapidly and can become incarcerated in the pelvis. Although fibroids can be present and cause symptoms at any age after puberty, they typically do not become a clinical problem until the early to mid-30s. With a rising age at which women first attempt pregnancy, this increasingly represents a difficult management problem which did not exist a generation ago when simple hysterectomy was the frequent curative choice. Preserving reproductive potential while relieving symptoms is the challenge today, with the rising age at first pregnancy increasing the likelihood that leiomyomata will develop prior to completing childbearing.

Menorrhagia
Dysmenorrhea
Pelvic Pressure (Pressure on Adjacent Pelvic Viscera)
Urinary frequency
Constipation
Dyspareunia
Infertility
Repetitive Pregnancy Loss
First trimester
Second and third trimester (preterm labor)
Abdominal distension

TABLE 49.1. *Symptoms of leiomyomata*

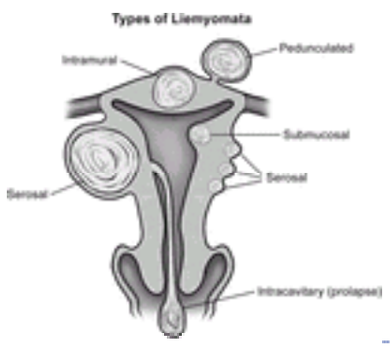

FIG. 49.1. Possible locations of leiomyomata. This schematic diagram illustrates the many locations at which leiomyomata may develop. Symptoms related to heavy vaginal bleeding generally are greater when the leiomyomata are in close proximity to the endometrial cavity, with serosal tumors that can attain large size with virtually no change in menstrual bleeding. Fibroids can develop anywhere in the uterus, with the cervix having proportionally fewer because of its lower complement of myometrial cells.

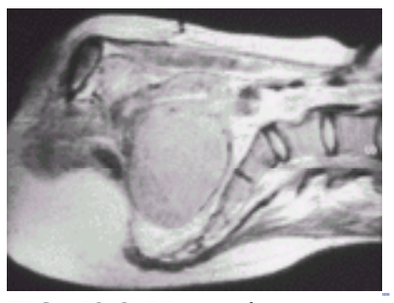

FIG. 49.2. Magnetic resonance imaging of leiomyomata. This magnetic resonance image demonstrates a large leiomyoma arising from the posterior aspect of the uterus and filling the entire pelvis. It directly contacts the promontory of the sacrum.

Anatomic Features

Leiomyomata represent benign sex steroid–responsive smooth uterine muscle tumors originating as clonal expansions of individual myometrial cells. The histology is virtually indistinguishable from normal myometrium, except for a circular whorling pattern with the cellularity and mitotic activity being highly variable. The number of mitoses per high-power field is usually low, and increased numbers are critical to the risk of malignancy. Assessing the number of mitoses is typically part of the pathologic evaluation when fibroids are removed. There are often interspersed areas of fibrosis and occasional calcification, especially after pregnancy-induced degeneration and in postmenopausal women. Leiomyomata typically grow in a spheric or nodular fashion with a relatively distinct demarcation from the surrounding normal myometrium, reflecting their clonal origin.

Leiomyomata can arise from anywhere in the myometrium (see Fig. 49.1) and may be single or multiple, with occasional women having very large numbers of fibroids. When the cell of origin is near the serosal surface, the path of least resistance to expansion is to bulge outward into the peritoneal cavity, termed a *serosal* or *subserosal fibroid.* Serosal tumors can grow very large without symptoms, because they virtually represent external appendages to the uterus. When a tumor is very superficial, this can result in a pedunculated fibroid, with a pedicle narrower than the tumor diameter containing the vascular supply. Occasionally, a pedunculated tumor will become detached from the uterus completely and derive its blood supply from an adjacent site. This is likely the result of pressure necrosis of the interface between the tumor and the adjacent viscera, or torsion of the pedicle and attachment at the new site during healing. When the myometrial cell of origin is deep within the myometrium, an intramural fibroid develops. These are associated more commonly with menorrhagia and dysmenorrhea, with the normal prostaglandin-mediated uterine contractions resulting in higher intrauterine pressures and failing to constrict the vessels feeding the endometrium during menses. If the myometrial cell of origin is near the endometrium, a submucosal tumor will develop and these are very likely to be associated with menorrhagia and dysmenorrhea, even at a relatively small size. When clonal expansion occurs in a cell immediately under the endometrial layer, the tumor may protrude into the endometrial cavity, and an intracavitary tumor on a pedicle may develop. Intracavitary tumors can cause severe symptoms despite their small size. With uterine contractions, the fibroid's stalk may elongate, extruding the fibroid through the cervix, typically associated with significant cramps and sanguineous vaginal discharge. Compression of the vascular pedicle may cause aseptic necrosis and the degenerating tumor becomes secondarily infected, making it appear similar to a necrotic cervical cancer. Although cervical fibroids can occur, they are infrequent, paralleling the small number of myometrial cells within the cervix. However, because of their proximity to the bladder, urinary symptoms typically can be very distressing.

There is virtually no neovascularity within fibroids, and individual leiomyomas derive their vascular supply from the vessels on the periphery of the tumor at the interface with the normally vascularized myometrium. Although fibroids are stimulated by sex steroids, the vascular supply is more likely to be the limiting factor for the growth of individual tumors. Often the uterine blood vessels are visibly enlarged because of the increased metabolic requirements of the uterus containing leiomyomata. However, the anatomic relationship of the vessels to the surrounding viscera is not altered, despite enlarged vascular pedicles. Collateral vascular channels are comparably engorged and represent a challenge to the surgeon if they are not considered in the surgical approach. Not surprisingly, this increased vascularity may increase the blood loss with any extirpative surgery, even if performed by the most experienced surgeon. When rapid fibroid growth does occur, such as is observed occasionally during pregnancy, the vascular demands of the tumor may exceed the capability of the vasculature. The leiomyoma then undergoes aseptic necrosis and, reflecting the peripheral nature of the vascular supply, the center of individual tumors undergoes degeneration with the outer layers relatively spared. This is initially described as *red degeneration* and later, as the devitalized central tissue is replaced by fibrosis, described as *hyalinized degeneration*, and ultimately may become calcified. It is not unusual to find marked calcium deposits in leiomyomata which have long ago undergone degeneration and were never symptomatic.

Influence of Sex Steroids

There is little doubt that the growth of leiomyomata is related to exposure to sex steroids, because they (a) are not noted prior to puberty, (b) typically regress after menopause, (c) possess sex steroid receptors (estrogen and progesterone), (d) often enlarge dramatically during pregnancy when estrogen and progesterone levels are very high, and (e) can be made to shrink with medically induced hypogonadism. Clearly, the uterus, like other secondary sex organs such as the breasts, enlarge with exposure to the higher levels of ovarian steroids produced at puberty. However, this growth is programmed and should cease once reaching the appropriate development, despite continued exposure to sex steroids throughout the reproductive lifespan.

There is no evidence that higher or aberrant patterns of ovarian steroid secretion of estrogens, progestins, or androgens contribute to the development of leiomyomata. However, myomatous tissue has the same number of estrogen receptors but a higher number of progesterone receptors than the adjacent normal myometrium. This, coupled with the observations that mitoses within myomas are more frequent in the luteal phase of the cycle and that progesterone up-regulates several growth factors, suggests that progesterone is causally involved somehow in either myomatous development or growth. Because estrogen stimulates the synthesis of progesterone receptors in other reproductive tissues, a more complex relationship among the two dominant female sex steroids and leiomyomata is likely present. Additionally, some data indicate that the development of fibroids may be related to postpubertal weight gain, which may relate to endogenous nonovarian estrogen production. Despite these observations, there is no consensus on the specific roles of the various sex steroids aside from a general positive relationship with development of leiomyomata.

Oral contraceptive use has not been associated with an increased incidence of leiomyomata or more rapid recurrence or progression. Treatment of postmenopausal women with hormonal replacement therapy occasionally, but not consistently, allows continued growth of existing leiomyomata. There is no evidence, however, that if leiomyomata are not present, they will develop in response to hormone replacement therapy after menopause. For clinical purposes, withholding hormone replacement therapy for fear of stimulating leiomyomata in otherwise appropriate candidates is not appropriate, given its well-documented benefits. Special note should be made of postmenopausal women with breast cancer treated with tamoxifen, because this compound has both estrogen agonist and antagonist activity, which has the potential

to influence the pattern of fibroid growth. Undoubtedly, gonadal steroids are important in the development or growth of leiomyomata and, as more selective estrogen, progestin, and androgen response modulators become available for clinical use, their impact on the development or growth of leiomyomata will become apparent. Potentially, some of these agents will be found therapeutically useful.

GENETIC INHERITANCE PATTERN

It has been estimated that more than 40% of first-degree female relatives of women with leiomyomata will develop fibroids sometime during their lifetime. These will not necessarily be symptomatic, and the number and location are not predictable. Although leiomyomata are common in all races, African-Americans appear to have a somewhat higher incidence than women of other ethnicities, despite being a common disease in women of all ethnicities. African-American women undergoing hysterectomies have increased numbers of and larger fibroids, and it has been estimated that nearly 90% of uteri removed from these women for clinical symptoms contain leiomyomata. Regardless of ethnicity, leiomyomata are, by far, the commonest genital tract tumors and remain the most frequent indication for gynecologic surgery. This familial pattern seems most consistent with a multifactorial genetic inheritance pattern, rather than simple mendelian genetics, which is modified by confounding cofactors, such as the impact of gonadal steroids. Aside from the disease's apparent familial, age, and ethnic associations, there is little clinical predictability for an individual woman. Given the high prevalence of leiomyomata, virtually all women are at risk for developing them in their latter reproductive years.

Molecular Mechanisms and Genetic Dysregulation

Leiomyomas represent monoclonal neoplasms, in which etiologic genetic mutations in individual tumors are highly likely. Cytogenetic studies of individual leiomyomas reveal that approximately one third have some type of chromosomal aberration, but these are not consistent among individual leiomyomata, even among fibroids in the same woman, further supporting the clonal nature of leiomyomata. The most common aberrant patterns are translocations between chromosomes 12 and 14, deletions of the short arm of chromosome 7, and rearrangements of the long arm of chromosome 6. It is not clear whether there is real clinical relevance to these differences in the rate of tumor growth, recurrence rates, and responses to various therapies. Interestingly, when tumors have translocations between chromosomes 12 and 14, they are more likely to be larger myomas, whereas deletions of the long arm of chromosome 7 are found more often in smaller myomas. Although there are no consistent alterations in gene expression noted in leiomyomata, the transcription-factor high-motility group A2 is up-regulated in leiomyomata with expression of the 12;14 chromosome translocation. These observations imply that, despite similar histologic appearance and benign growth characteristics, there may be several molecular mechanisms by which these tumors develop, with correspondingly different clinical implications.

Undoubtedly, individual myometrial cells become neoplastic as a result of a complex interaction of factors including genetic mutations, endogenous sex steroid production–stimulating growth, reproductive patterns and, potentially, medicinal hormonal exposure after menopause. Molecular geneticists have noted abnormal expression of a variety of genes leading to altered growth factors and steroid receptors in individual leiomyomata, but there remains no single predominant molecular mechanism or group of mechanisms underlying their development and growth. Although this molecular dysregulation may explain the propensity to grow disproportionately to the normal pattern of myometrial growth throughout life, the molecular evidence does not suggest a progression from benign leiomyomata to leiomyosarcoma. Undoubtedly, the mechanism of clonal expansion of individual myometrial cells involves the interplay of gonadal steroids and aberrant expression of autocrine, paracrine, and endocrine growth factors. During the coming years, this molecular puzzle undoubtedly will be better understood but will just as likely prove to be very complex, without a single abnormality responsible for most leiomyomata. Clarifying the pathophysiologic mechanism(s) of growth of this most common of neoplasias should provide opportunities for better predicting the clinical course, genetic inheritance, as well as optimal prevention and therapeutic strategies for individual women.

Impact of Leiomyomata on Reproduction

The impact of leiomyomata on the ability to reproduce remains difficult to define in clinical terms useful for individual patients (Table 49.2). Clearly, the most logical approach for women with leiomyomata is to attempt to conceive and elect treatment only if they encounter difficulty. There is general agreement that intracavitary and submucosal leiomyomata are likely to cause infertility by preventing implantation, comparable to the effect of an intrauterine device. Fibroids within the endometrial cavity or impinging on the cavity contour can be detected by hysterosalpingography, sonohysterography, or hysteroscopy, and their removal can be expected to improve fertility. With intramural leiomyomata, a relationship to infertility is less certain and all other potential causes should be considered before concluding that the leiomyomata are causal. Intramural leiomyomata have been associated with a reduced pregnancy rate following assisted reproductive technology (in vitro fertilization and gamete intrafallopian transfer, known collectively as *ART*), indicating they may interfere with implantation. Given the time, expense, and complicated nature of ART, it is prudent to remove intramural fibroids in carefully selected infertile women before they undergo ART, when other therapeutic options have failed and no other cause is identified. Whether postoperative adhesions form after myomectomy is of lesser importance under these circumstances, because the oocytes will be retrieved transvaginally, regardless of whether adhesions involving the adnexae are present. The most important issue is that the couple be given the highest chance of success with ART, given the stress, expense, and time involved.

Impaired Implantation
Submucous
Intracavitary
Enlarged uterine cavity volume
Impaired Tubal Transport
Obstruction
Distension

TABLE 49.2. *Mechanisms of infertility with leiomyomata*

Although fibroids can be found anywhere in the myometrium, when they arise adjacent to the entry of the fallopian tubes into the uterus there is concern about occluding a tube or altering its function. This rarely occurs, likely due to the relatively slow growth of leiomyomata and the distensibility of soft tissues such as the fallopian tubes. However, because oocyte capture by the ciliated epithelium of the fimbria is necessary for fertilization, growth of fibroids near the distal end of the oviduct, which increases the distance between the surface of the ovary and the tubal ostia, theoretically can reduce the chance of conception. For this to be considered a problem, however, both fallopian tubes would need to be affected similarly. This is an infrequent circumstance, and a myomectomy should be performed to improve tubal function only when the uterine fibroids visibly distort the ovarian tubal anatomy bilaterally and after all other possible infertility factors have been excluded.

Whether leiomyomata are associated with a higher risk of first-trimester pregnancy loss, preterm labor, or intrauterine growth restriction is much more controversial. The impact of fibroids in each patient is critically dependent on location, not simply size or number. Clearly, many women with large myomatous uteri deliver infants without difficulty, while in others, fibroids may compromise the ability of the endometrial cavity to accommodate a growing fetus or the maternal vascular adaptation necessary for normal placental function. Complicating this picture is our inability to predict which women with leiomyomata will experience rapid enlargement of their fibroids during pregnancy. An abruption may occur rarely when the placental bed overlies an enlarging fibroid. Lower segment fibroids have the potential to obstruct labor, and a classic cesarean section occasionally is required when the presenting part cannot be applied directly to the cervix. If the leiomyomata are extremely large and intramural in location, preconception removal or other management of the fibroids may be considered, but the potential benefit must be weighed carefully against the complications of the procedure. There simply is no predicting which women will encounter problems and which will not. Clinical judgment will be sorely taxed to make correct decisions in the absence of a previous adverse clinical outcome. Overall, term delivery rates following myomectomy for symptomatic leiomyomata in an unselected patient population vary from 40% to 50%. The need to perform a cesarean section following myomectomy needs to be considered in any risk–benefit analysis.

LEIOMYOSARCOMA

Rarely, a leiomyosarcoma is encountered that is clinically indistinguishable from simple leiomyomata, but these are typically in older postmenopausal women, with the average age well over 60. The diagnosis often is suggested by enlargement of the uterus after menopause in the absence of any hormone replacement therapy. Uterine fibroids present prior to menopause may enlarge when the gonadal steroids are replaced, but this is not common and does not represent a frequent enough problem to preclude the use of any type of hormone replacement therapy. A leiomyosarcoma is not thought to develop from a preexisting leiomyoma, rather it arises de novo, with the factors leading to this rare cancer obscure. Rapid growth is not a very ominous sign of malignancy, because this is a common occurrence in women with leiomyomata before menopause. No physical findings or unique imaging differences can reliably distinguish leiomyomata from leiomyosarcoma. The diagnosis of a leiomyosarcoma typically is based on histology, not gross appearance. Degenerating leiomyomata may have unusual and varied features, including necrosis and central liquefaction. The histologic changes suggesting malignancy include increased numbers of mitoses, cellular pleomorphism, and thrombotic degeneration within the tumor. Many fibroids are very cellular but without other characteristics suggestive of malignant potential. Typically, more than 10 mitoses per high-power field suggests a risk that the tumor is malignant, between 5 and 10 represents a “cellular” or actively growing fibroid, and below 5 is usual for the typical myoma. Because of the difficulty accurately characterizing the number of mitoses by frozen section microscopy, the intraoperative diagnosis of a leiomyosarcoma is difficult to make with confidence and permanent sections usually are required. When a leiomyosarcoma is diagnosed following surgery, a second procedure for extirpation of any remaining pelvic organs and lymph node sampling for staging usually is required to plan optimal management. Leiomyosarcomas are estimated to account for 0.1% of all uterine tumors, but 1.7% of women undergo hysterectomy for leiomyomata during their seventh decade of life. For practical purposes, leiomyomata always should be

considered benign in premenopausal women and rarely malignant in elderly women, but with the caveat that all excised specimens should undergo careful pathologic examination.

DIAGNOSTIC STUDIES

The vast majority of leiomyomata are detected on pelvic examination performed for routine health maintenance or because of a gynecologic symptom, such as increasing dysmenorrhea, menorrhagia, or pelvic pressure. The uterus typically is enlarged and irregular on bimanual examination. It is important to distinguish leiomyomata from other pelvic masses such as ovarian tumors. This is done most easily with an endovaginal or abdominal ultrasonographic examination, because the leiomyomata appear solid by sonography, with acoustic impedance similar to that of the normal myometrium. Other imaging techniques, such as computerized tomography or magnetic resonance imaging, can prove useful in selected circumstances (see Fig. 49.2, Table 49.3). Indeed, it must be appreciated that detecting an unrelated but clinically important adnexal mass may be difficult when there is a large leiomyoma. Unless the tumor has been stable on pelvic examination for many years in women in the latter reproductive years and beyond, some diagnostic imaging modality is warranted to ensure that the abnormal physical examination findings reflect leiomyomata and not another type of pathology with a greater potential for malignancy. Other imaging modalities, such as computerized tomography or magnetic resonance imaging, can distinguish leiomyomata from adnexal pathology, but they are much more expensive and time consuming and yield no more useful information than simple office sonography.

Endovaginal ultrasonography
Sonohysterography
Hysterosalpingography
Hysteroscopy
Computerized tomography
Magnetic resonance imaging

TABLE 49.3. *Diagnostic techniques*

The proximity of the leiomyomata to the endometrial cavity usually can be demonstrated by taking advantage of the acoustic differences between normal myometrium, fibroid tumors, and the endometrial cavity. The endometrial stripe is a reliable marker of the endometrial cavity, and a smooth continuous endometrial stripe with normal underlying myometrium between the cavity and any fibroids suggests that palpably detectable fibroids are primarily in a subserosal location. Simultaneously injecting saline into the endometrial cavity while performing an endovaginal ultrasonographic examination (sonohysterography) improves the delineation of submucous and intracavitary leiomyomata. However, it is not possible to distinguish an endometrial polyp from an intracavitary myoma with any imaging technology.

The closer the fibroid is to the endometrial cavity, the greater the likelihood and severity of dysmenorrhea and menorrhagia. Additionally, distortion of the endometrial cavity increases the probability of difficulty in achieving and maintaining a pregnancy. Hysterosalpingography often is undertaken if infertility is present concurrently, because this technique can identify intracavitary tumors or an otherwise normal endometrial cavity enlarged by stretching of the normal myometrium around leiomyomata (Fig. 49.3). This radiographic technique has the added advantage of determining tubal patency. Removal of leiomyomata will not improve the likelihood of conception unless an enlarged endometrial cavity, an irregular endometrial ontour, or an intracavitary defect is present. Increasingly, office hysteroscopy is being used when tubal patency is not an issue, because this technique allows clear differentiation between leiomyomata and other intracavitary pathology, such as endometrial adhesions, uterine septae, and endometrial polyps.

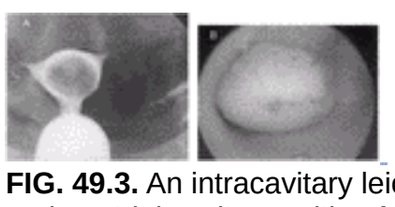

FIG. 49.3. An intracavitary leiomyoma. **A:** A hysterosalpingogram using a water-soluble contrast medium demonstrates a large, smooth filling defect within the endometrial cavity resulting from an intracavitary fibroid. The mass effect on the study is nonspecific, and only direct visualization can confirm that it is caused by a fibroid. **B:** The hysteroscopic view of this intracavitary leiomyoma.

Another disease involving the myometrium, adenomyosis, occasionally can be difficult to distinguish clinically from leiomyomata, and imaging studies may not be helpful. This disease process represents functional endometrial glands and stroma within myometrium, with these cells presumably infiltrating into the underlying myometrium from the endometrium. This is an infiltrative process, which is found immediately adjacent to the endometrial cavity and parallels the contours of the endometrial cavity. It is always continuous with the endometrium but not necessarily present in all subendometrial areas. Frequently, a marked fibrotic reaction is present around the isolated endometrial cells within the myometrium, presumably because of the irritation caused by menstrual shedding in the midst of the muscle. When the process is localized, these fibrotic areas may be difficult to distinguish on palpation from leiomyomata and the true diagnosis made only with surgery. Leiomyomata typically have a clear demarcation from the underlying myometrium, whereas a nodule of adenomyosis has a very indistinct infiltrating border which makes complete surgical removal virtually impossible. Adenomyosis tends to have more variability in shape, but the two pathologic entities occasionally may be indistinguishable by any of the available imaging techniques and the diagnosis made only after excision of the lesion. Magnetic resonance imaging is useful in differentiating adenomyosis from leiomyomata, because it better delineates the borders of the intramyometrial pathology; however, this is not used routinely preoperatively because of the expense involved. Like endometriosis, adenomyosis may be associated with an elevation in serum CA-125, but this is a nonspecific serum marker and cannot be used alone to diagnose adenomyosis.

Because most leiomyomata are identified only after symptoms are present and treatment carries considerable risk and expense, development of an inexpensive screening tool with reasonable sensitivity and specificity would be a major clinical advance. There are no laboratory markers which detect leiomyomata which are too small to cause symptoms or be palpated on pelvic examination. Detecting small leiomyomata in women with a familial risk would be very helpful, because it would assist in determining their true prevalence, better define the natural history, identify risk factors, and lead to earlier medical intervention, potentially reducing the need for surgical excision.

PREVENTING DEVELOPMENT, PROGRESSION, AND RECURRENCE

The ultimate goal of understanding the pathophysiology of leiomyomata is to prevent their occurrence in both genetically susceptible women and those without a family history. With further insight regarding the molecular mechanism(s) of growth, it may be possible to identify medicinal approaches to interfere with the molecular pathway(s) and reduce the risk of development, progression, and recurrence of leiomyomata. This will be particularly useful for women at risk of leiomyomata because of a strong family history, those with previous myomectomy, and women with leiomyomata approaching menopause who can anticipate spontaneous regression once ovarian function ceases. Additionally, understanding the impacts of childbearing, lactation, the various forms of steroidal contraception, and estrogen and hormone replacement therapy on the development, progression, and recurrence of leiomyomata should help optimize clinical recommendations. There are few, if any, predictors of the development of leiomyomata, aside from a family history. Endocrine markers such as early puberty, late menopause, parity, oral contraceptive use, and hormone replacement therapy of any kind are not correlated with either the development or the recurrence of fibroids after myomectomy.

TREATMENT

When to Treat

Although fibroids are responsible for a large number of gynecologic surgeries, management of these benign tumors requires the same risk–benefit analysis as any other therapeutic decision. Often, a prostaglandin synthetase inhibitor or oral contraceptives will relieve the symptoms. Although an increasing variety of options exist, it is important that the management be goal directed to alleviate specific symptoms. Simply identifying leiomyomata does not imply that they will continue to grow, become symptomatic, or require management. Occasionally, however, it may be appropriate to remove asymptomatic large leiomyomata in an effort to prevent anticipated problems before attempting pregnancy. Similarly, when a woman has intracavitary or large submucous myomas but has not attempted to conceive, it is likely, but not unequivocal, that removal of her fibroids will improve her chances. Removing myomas which cause significant distortion of the endometrial cavity in an infertile population will improve the likelihood of pregnancy and the maintenance of early pregnancy. Large tumors which fill the pelvis can impinge on the pelvic sidewalls, causing hydronephrosis, and their removal is critical. However, therapeutic intervention generally should be focused on the alleviation of symptoms, and observation is all that is necessary in the vast majority of asymptomatic women.

The growth characteristics of individual leiomyomata remain highly unpredictable, because many leiomyomata have limited growth potential and, thus, may remain static in size until the sex steroid levels decline at menopause, when they shrink. Paradoxically, some leiomyomas have already undergone rapid growth, aseptic necrosis, or replacement by fibrosis without symptoms and will not shrink after menopause. Although many fibroids may enlarge gradually, causing symptoms well before the anticipated regression at menopause, the growth pattern is so varied that there are simply no predictive characteristics helpful in identifying which women will need intervention and which will not.

The symptoms caused by leiomyomata vary, depending on the size, number, and location of the tumors, and can include dysmenorrhea, menorrhagia, increased abdominal girth, pelvic pressure (frequent urination or constipation), and pelvic pain with physical activity or intercourse. Dysmenorrhea and menorrhagia are more frequently linked than other symptoms. When the dysmenorrhea or menorrhagia is mild, nonsteroidal antiinflammatory agents and oral contraceptives are often useful, and the symptoms may improve sufficiently to avoid further intervention. In most cases, a therapeutic medical trial is indicated before proceeding to more aggressive medical or surgical options. When dysmenorrhea and menorrhagia are caused by leiomyomata, they are typically of secondary onset and worsen gradually in severity paralleling the enlargement of the tumors.

Location of the fibroids is critically important; the closer they are to the endometrial cavity, the greater and earlier the symptoms. Intramural, submucosal, and intracavitary fibroids are far more likely to cause dysmenorrhea and menorrhagia than intramural or subserosal myomas. Severe symptoms may warrant intervention at a relatively small size, particularly for an intracavitary or submucosal fibroid. Typically, the closer to the serosal surface the fibroids are located, the larger the size will be attained before symptoms occur. Indeed, some extremely large leiomyomata will not be associated with any symptoms aside from increased abdominal girth. This explains why many patients with extremely large leiomyomata are either minimally symptomatic or asymptomatic, while those with small submucosal or intracavitary fibroids may have dramatic bleeding and pain. Because of the proximity of the bladder, the most frequent symptom associated with a large subserosal or pedunculated myoma is frequent urination, comparable to what women experience during pregnancy. Rarely, compression of the colon against the sacrum may cause difficulty with defecation, although this is infrequent and, more often than not, feelings of constipation are not relieved completely by removing or shrinking the leiomyomata. As the tumors enlarge, these pressure symptoms intensify and ultimately may require medical or surgical intervention.

Selecting the Appropriate Therapy

When clear indications for therapy are present, the most critical questions which must precede a decision are as follows: (a) Is future reproduction is desired? and (b) How soon can menopause be anticipated? Because a simple hysterectomy represents a definitive cure, this is an attractive option for many symptomatic women when maintenance of reproduction is not desired, menopause is not imminent, and more conservative measures have failed to alleviate the symptoms (Fig. 49.4). This also requires an assessment of the woman's individual preferences, as well as her surgical and anesthetic risks. Clearly, women view extirpation of the uterus in their own social, cultural, and religious contexts, and removal of any genital structure cannot be viewed as inconsequential, even if there is no wish to preserve reproductive capacity. As a result, many women wish to preserve the uterus independent of reproduction, and they should be provided with all the therapeutic options and their choices respected. When the preservation of reproductive capacity is desired, a myomectomy is the primary choice. However, because the recurrence risk of symptomatic leiomyomata is high, myomectomy should be viewed as providing a disease-free interval and the women encouraged to attempt to reproduce as soon as is reasonable. As a result, many women without reproductive desires are interested in other, less well-established options such as UAE or myolysis, which may reduce the symptoms and retain the uterus.

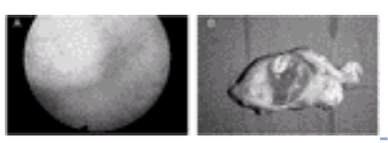

FIG. 49.4. Submucous leiomyoma. **A:** A submucous fibroid visualized at hysteroscopy is from a woman with a history of menometrorrhagia unresponsive to medical management with NSAIDs and oral contraceptives. Although the tumor protrudes into the endometrial cavity, most of it is still within the underlying myometrium. **B:** The hysterectomy specimen which demonstrates the submucous myoma responsible for the excessive vaginal bleeding.

Extirpative Surgery for Leiomyomata

The mainstay of management for symptomatic leiomyomata is surgical, either hysterectomy or myomectomy, depending on the woman's desires regarding childbearing (Table 49.4). Given the risks inherent with all surgical procedures, the decision to proceed with any surgery should be based on a personalized clinical risk–benefit assessment, with the pivotal issue being future reproduction. Virtually no woman with leiomyomata need be faced with the painful choice of having to endure the symptoms in order to maintain reproductive potential versus relieving symptoms at the price of terminating reproductive options. A myomectomy is virtually always an option, even if a large number of fibroids are present or the tumors are very large or both. The uterus functions well in pregnancy after a myomectomy, despite the impact of multiple incisions. Although improvements in surgical technique, particularly minimally invasive surgery, have the potential to improve the benefits for women with symptomatic leiomyomata, comparative clinical trials of the various surgical approaches are urgently needed.

Endoscopic Techniques
Laparoscopically assisted supracervical hysterectomy
Laparoscopically assisted total hysterectomy
Myomectomy
Abdominal Approach
Supracervical hysterectomy
Total hysterectomy
Myomectomy
Vaginal Approach
Hysterectomy
Myomectomy

TABLE 49.4. *Extirpative options*

Hysterectomy

When childbearing is not desired and the symptoms are severe enough to warrant treatment, a simple hysterectomy often is chosen, because it relieves the symptoms permanently, prevents recurrence, provides permanent contraception, and improves the quality of life as measured by questionnaires, presumably by eliminating further vaginal bleeding. An infrequently considered and poorly appreciated additional benefit is making hormone replacement therapy after menopause much simpler, with estrogen replacement without progestin the favored option. The decision to proceed with removal of the uterus should be based on a risk–benefit decision weighing the severity of the symptoms with the personalized surgical risk, and not on a concern that the leiomyomata might be malignant. The surgical approach, either abdominal or vaginal, should be individualized, based on the size and location of the fibroids, the degree of uterine descensus, the woman's habitus, and whether or not an oophorectomy is being considered or other pathology is present. The available techniques are an abdominal hysterectomy, vaginal hysterectomy, or a laparoscopically assisted hysterectomy.

Preservation of the cervix in appropriately selected women is an increasingly popular option. The myometrium is the portion of the uterus at risk for growth of leiomyomata and, because the cervix is composed primarily of fibrous tissue, the potential for the development of leiomyomata in a retained cervix is extremely low. The structural ligamentous support for the cervix and vaginal apex remains intact when the cervix is retained with, at least theoretically, lower rates of vaginal prolapse. Additionally, a major portion of the surgical morbidity associated with hysterectomy by any technique relates to the surgical dissection necessary for removal of the cervix. This morbidity is avoided when choosing a supracervical hysterectomy, without risk of recurrence or the need to add a progestin to a hormone replacement regimen. The risk of subsequent cervical dysplasia is very low in this age group, and it is managed easily on an outpatient basis if it occurs, with the same methods used if the fundus is still in place. However, when choosing to retain the cervix, the continued need for screening cervical cytology should be emphasized.

The risks of complications with a hysterectomy are significant and, when prospectively documented, are approximately 17% with abdominal hysterectomy, 23% for vaginal hysterectomy, and 19% for laparoscopically assisted hysterectomy. The risk of complications is apparently higher when the hysterectomy is done for fibroids. The complications include the usual problems associated with abdominal operations but, specifically, hemorrhage and injuries to the bladder and ureters. The risk of ureteral injury is 7 times greater with the vaginal approach, likely secondary to the limitations in visualization of the anatomy when operating through the vagina. Despite these concerns, hysterectomy is associated with a high level of patient satisfaction, even if there are surgical complications.

Hysteroscopic Myomectomy

With improvements in endoscopic surgical technology, most intracavitary and a substantial number of submucous leiomyomata can be resected via surgical hysteroscopy in an ambulatory setting. If the tumor protrudes completely into the endometrial cavity via a stalk, such as a completely intracavitary myoma, a hysteroscopic resection is by far the most cost-effective method of removal. This does require an experienced hysteroscopic surgeon and should not be attempted unless the requisite skill is available. When a submucosal leiomyoma is predominately within the endometrial cavity, most are similarly amenable to removal via hysteroscopic resection. However, if despite protruding into the endometrial cavity, the bulk of the tumor is still contained within the underlying myometrium, a hysteroscopic approach will likely not prove successful and, indeed, can prove hazardous if the surgeon does not recognize the depth of the myoma. In this circumstance, extreme caution should be exercised when resecting a submucous fibroid, and resorting to an abdominal procedure should not be perceived as a failure but rather should be considered the safest option.

A hysteroscopic myomectomy typically is performed using a hysteroscopic resectoscope comparable to that used for transurethral prostate resection. It is inserted through the cervix, the endometrial cavity distended with a nonconductive media, and the leiomyoma resected by electrical loop excision. The fragments are removed with the effluent of the distending media through an inflow–outflow system. Careful preoperative selection of patients is required to ensure safe, effective removal in an ambulatory setting. Preoperative shrinkage of the leiomyoma with a gonadotropin hormone–releasing hormone agonist often may be helpful and affords a reduction in the height of the surrounding endometrium. Preoperative atrophy of the endometrium, to provide a clear operative field without resorting to complete pituitary down-regulation, can be accomplished with a 10-day preoperative course of a progestin (20 mg/day of medroxyprogesterone acetate) or an androgen (danazol 800 mg/day). Care must also be taken to avoid excessive intravascular absorption of the distending medium, which can result in fluid overload, electrolyte imbalance, or a bleeding diathesis, depending upon the type of medium.

Abdominal Myomectomy

When symptomatic leiomyomata are not completely within the endometrial cavity but in an intramural location, an abdominal surgical approach usually is required. With infrequent exceptions, a low transverse incision yields adequate surgical exposure. Rarely, a vaginal myomectomy can be performed with proper patient selection, but this clinical situation is rare and requires a high degree of surgical skill. The goal of a myomectomy is to remove all the identifiable leiomyomata with the least possible alteration of the reproductive tract. There are numerous surgical techniques but, in general, the myometrium is incised, the myoma dissected from the surrounding myometrium, and the incision closed in layers with absorbable suture to ensure hemostasis and myometrial integrity (Fig. 49.5). Entry into the endometrial cavity is not associated with any significant morbidity, but it is essential not to place sutures though the endometrial cavity wall as if it is a layer to close. Because the distance to the opposite endometrial surface is small, approximating the myometrium underlying the endometrium to the corresponding opposite side is all that is necessary. Cervical fibroids can represent a significant surgical challenge because of their proximity to the bladder and ureters, as well as the difficulty attaining hemostasis. Similarly, parasitic fibroids can be difficult to remove depending on their vascular supply (Fig. 49.6).

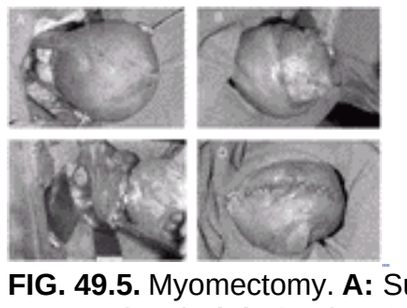

FIG. 49.5. Myomectomy. **A:** Surgical exposure of a large uterus containing an intramural leiomyoma is depicted. The fibroid is dissected from the underlying myometrium in **(B). C:** The uterine incision is extended down into the cavity and the fibroid is removed. The myometrium is reapproximated in layers **(D)** and the uterine muscle wall closed.

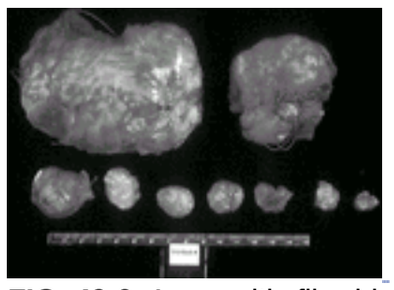

FIG. 49.6. A parasitic fibroid. A large tumor has become parasitic to a loop of small bowel, deriving its blood supply from the new vascular source. This typically happens only with large posterior or fundal tumors and is more common when they are pedunculated. The mechanism is felt to be pressure necrosis and revascularization during healing of the necrosis of the bowel wall.

Because myometrium is extremely well supplied with vasculature, significant intraoperative blood loss is encountered frequently. Myomectomy at the time of an operative delivery is particularly hazardous because of the increased vascularity of the myometrium associated with pregnancy. Careful surgical technique, applying a tourniquet around the lower uterine segment to compress the uterine arteries, intramyometrial injection of vasospastic agents such as vasopressin, and employing an intraoperative blood scavenger system can reduce the net blood loss. These steps, coupled with the preoperative correction of anemia, storage of autologous blood, and mild overhydration to reduce the amount of red blood cell loss per unit of blood lost, have reduced dramatically the need for homologous transfusion. Rarely, if ever, is a hysterectomy necessary because of intraoperative blood loss when a myomectomy is undertaken. Caution should be exercised when using the injection of intramyometrial vasopressin, because uterine incisional bleeding after the metabolism of the vasopressin may result in unappreciated blood loss which, even if it does not put the patient at a hemodynamic risk, increases the time required for resolution of the postoperative anemia and may complicate efforts to reduce adhesion formation. During the immediate postoperative interval, it is common that women with multiple uterine incisions experience febrile morbidity unrelated to any demonstrable infection. Whether this is related to a tissue reaction from the relatively large surgical area of the uterine incision(s) or a response to hemorrhage within the myometrium is not clear, but it is a benign occurrence, and antibiotic therapy should be reserved for women with clinical findings suggesting infection.

Once the myometrium has sustained a surgical incision involving a significant portion of the uterine wall, an elective cesarean section generally is recommended as the route of delivery. When a myomectomy incision is repaired properly, the likelihood of a dehiscence during pregnancy is very remote, estimated to be approximately 0.002%. The incisions required for myomectomy are not similar to the low transverse uterine incisions used for most cesarean sections; rather, it is more comparable to the fundal incision used in a classic cesarean section. Furthermore, the endometrial cavity does not need to be entered for there to be concern regarding the integrity of the uterine wall during labor. Following a myomectomy, the couple should wait 2 to 3 months before attempting pregnancy, to allow complete healing of the uterine incisions and to minimize the potential for myometrial scar disruption before labor. This recommendation is based on the clinical experience with the rate of dehiscence of classic cesarean section scars which involve the contractile part of the uterus. Because the myomectomy incision is comparable in location, it has an impaired ability to withstand the force of a prolonged labor without rupture, a catastrophic occurrence for both the mother and fetus. The selection of women for an operative delivery should be based on the depth and extent of the myomectomy incision and the adequacy of the incisional repair, because the risk of uterine rupture is not well defined in the modern era but appears to be lower than when a cesarean section has been performed. Further data regarding circumstances following an abdominal myomectomy under which a vaginal delivery does not represent an increased the risk to the mother and fetus will likely not be forthcoming. As a result, an elective cesarean section is usually the preferred route of delivery for most women with a previous abdominal myomectomy.

Laparoscopic Myomectomy

Improvements in endoscopic surgery allow myomectomy to be accomplished via the laparoscope. It is clear that pedunculated, serosal, and superficial intramural leiomyomas can be removed via laparoscopy, but the surgery is lengthy, technically difficult, and should be undertaken by only the most experienced endoscopic surgeons. Furthermore, because only clearly obvious leiomyomata can be removed via laparoscopy, this therapy should be undertaken only when removal of a specific tumor can be anticipated to relieve the symptoms. Many smaller intramural fibroids will not be identified by this technique, so it is anticipated that a higher rate of subsequent symptomatic leiomyomata can be anticipated. Endoscopic closure of the uterine incisions is also technically difficult, and there have been several reports of spontaneous uterine rupture after laparoscopic myomectomy. This is additionally disconcerting, because this may occur during pregnancy prior to the onset of labor, as

early as 33 weeks of gestation. This is distinct from that observed with abdominal myomectomy, when the risk of uterine rupture is felt to be limited primarily to the labor process. This suggests that even with careful attention to incision closure by skilled endoscopic surgeons, uterine rupture should be major risk factor considered in choosing the endoscopic approach. In the absence of long-term safety studies, selection of laparoscopic myomectomy for patients desirous of pregnancy should be done very carefully. By contrast, when the symptoms can be attributed to an isolated fibroid in a woman not desirous of childbearing, a laparoscopic myomectomy performed by an experienced surgeon can be a reasonable option.

Recurrence of Leiomyomata Following Myomectomy

There appears to be a genetic basis for the development of leiomyomata. Even when all of the palpable leiomyomata have been removed by myomectomy, the rate of recurrence and persistence with continued growth has been variably reported as high as 30%, depending on the number of tumors present and the length of follow-up. Indeed, between 10% and 25% of women undergoing myomectomies require another surgical procedure within the next decade. There is a suggestion that a delivery after a myomectomy may reduce the likelihood of recurrence, but this has a relatively small impact. Virtually all the data regarding *recurrence* or, more properly termed, *development of new leiomyomata* has been derived from women undergoing myomectomy with all the palpable fibroids removed. Obviously, small tumors may remain, and this will be impossible to separate from new clonal expansion of isolated myometrial cells or from persistence of small nonpalpable tumors not identified during surgery.

Some women who have symptoms but lack absolute evidence of existence of fibroids have undergone one of the newer nonextirpative therapies such as myolysis or UAE. The “recurrence” of fibroids has not been assessed in these women. Obviously, if leiomyomata are felt responsible for symptoms following a therapeutic procedure during which they are not removed, it will be impossible to distinguish persistence from the development of entirely new fibroids. It may be more appropriate to consider the frequency and time to recurrence of symptoms rather than simply when and at what interval fibroids are again present. If the newer techniques are applied mainly to women close to menopause, this may be a nonissue considering the natural loss of the stimulation by gonadal hormones. However, if younger women elect the nonextirpative therapies, only long-term comparative trials will yield useful discriminating information. Given the climate favoring broader nonextirpative options, such studies are needed urgently to assist women with therapeutic decision making.

In general, the size, location, or histologic pattern of the myomas have limited predictive ability for recurrence rates. The size of individual myomas may be of greater predictive value, because it appears that extremely large fibroids have a lower recurrence rate after myomectomy than do smaller tumors, despite an overall smaller volume of leiomyomata. It is not clear if the cytogenetic abnormalities have any predictive value for recurrence. The number of leiomyomata may be important in predicting recurrence, with women having single large tumors less likely to have subsequent fibroids detected than women with multiple, particularly smaller diameter, fibroids (Fig. 49.7).

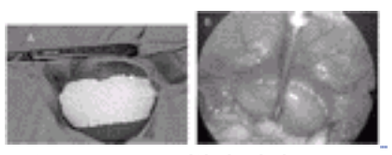

FIG. 49.7. Multiple leiomyomata excised at myomectomy. Many individual fibroids of different sizes and shapes can be encountered within the same patient. Some are very large and obvious, while others may be small and difficult to palpate.

The time of follow-up affects the risk of a clinical recurrence, with the longer the interval of observation correlated with the greater the apparent recurrence risk. It is no surprise that the younger the woman is when fibroids are detected, the greater the likelihood of recurrence after myomectomy. When leiomyomata do recur, it is typically 3 to 5 years following the myomectomy, giving most women an opportunity to reproduce before fibroids are again present. When fibroids are noted in a shorter time frame, it is more likely that not all the myomas were removed. Although too few endoscopic myomectomies are available to reach a meaningful conclusion, it can be anticipated that higher recurrence rates will be observed, because it is difficult to identify all the tumors present without direct palpation of the uterus. Similarly, when a GnRH agonist is used preoperatively, the leiomyomata usually shrink and some smaller tumors might become too small to be detected at surgery, only to reemerge as symptomatic or palpable fibroids relatively quickly. As with the myolysis procedures, these “recurrences” may simply represent the persistence of tumors. Many small leiomyomata with the potential to enlarge simply will not be identified visually because they are intramural and deep within the myometrium. Undoubtedly, the technical skill to remove all the leiomyomata by any procedure is critically important and will influence the rate of apparent persistence or recurrence.

The methodology used to identify recurrent myomas will undoubtedly influence the recurrence rates. If clinical symptoms lead to evaluation, palpation will detect a larger tumor than will routine surveillance by transvaginal ultrasonographic examination. Other imaging techniques such as magnetic resonance imaging or computerized tomography, although rarely used for routine monitoring, would probably detect small fibroids before clinical symptoms develop and thus influence the apparent recurrence rate. If a clinically significant recurrence does occur, the typical time frame for the return of symptomatic fibroids after abdominal myomectomy is 3 to 5 years. Women with a single large leiomyoma appear to have lower recurrence rates than those with multiple intramural tumors. Women clearly should be counseled that when all the palpable myomas are removed during abdominal myomectomy, an interval free of symptoms and the opportunity to reproduce is provided, but it does not “cure” an inherited predisposition to the their development. No long-term data are available regarding the recurrence or persistence risks with experimental myolysis procedures or UAE, but when such data are available, clinical decision making will need to incorporate these findings.

Postoperative Pelvic Adhesions

A major complication of any myomectomy is postoperative adhesions. These can involve viscera adherent to the uterine incision sites, as well as de novo adhesions at nonsurgical sites, generally attributable to the unavoidable peritoneal trauma associated with surgery. The frequency of postoperative adhesions following myomectomy exceeds 50% and can result in reduced fertility, pain, or bowel obstruction. Interestingly, endoscopic surgery has not reduced the rate of postoperative adhesions at the site of the surgery, but it does appear to reduce the de novo adhesion rate. Careful surgical technique to minimize the degree of surgical trauma, confining the incisions to the anterior uterine surface so as to prevent contact with the bowel and adnexal structures, and covering the posterior uterine incisions with surgical barriers have been advocated to minimize the rate of postoperative adhesions. The materials used as adhesion prevention barriers are quite varied and include oxidized regenerated cellulose that is degraded by leukocytes; polytetrafluoroethylene, a nonreactive permanent material which is typically removed several weeks following surgery after the peritoneum has reconstituted itself (Fig. 49.8); and a hydrolyzable barrier composed of a combination of hyaluronic acid and carboxymethylcellulose. All of these materials have their advantages and disadvantages, and few comparative studies are available. In the only direct comparative study, fewer postoperative adhesions were associated with the use of the barrier composed of polytetrafluoroethylene versus oxidized regenerated cellulose. Improvements in surgical barrier technology, other systemic or intraperitoneal medicaments, and alternative surgical strategies will undoubtedly be forthcoming to help reduce the rate of postoperative adhesions.

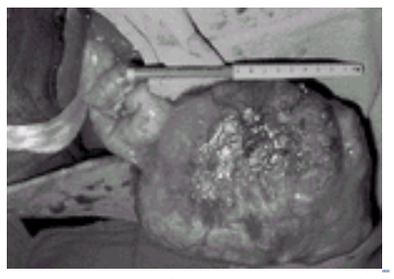

FIG. 49.8. Placement of a barrier of polytetrafluoroethylene at the time of myomectomy. To reduce the risk of adhesion formation between the visceral peritoneum of the uterus and the tubes and ovaries, a permanent barrier composed of polytetrafluoroethylene is anchored over the uterine incision with permanent sutures **(A).** The barrier is removed several weeks later via laparoscopy. **B:** The appearance of the uterine incision a year after the barrier was retrieved at a laparoscopy done for unrelated reasons. Note the healed uterine incision does not have any adhesion and represents an optimal surgical result.

Nonextirpative Management of Leiomyomata

When removing fibroids is not appropriate, either because of patient choice or when confounding medical problems exist, a nonextirpative approach should be taken. A variety of options exist (Table 49.5) including medical suppression, in situ destruction of the myomas, or depriving them of their vascular supply. These approaches all suffer because long-term data are lacking and because the fibroids themselves, although regressed, are not removed. However, with the onset of menopause, the

tumors can be anticipated to regress spontaneously, so a temporizing measure may suffice to relieve symptoms permanently.

Myolysis
Cryotherapy
Monopolar electrocautery
Bipolar electrocautery
Diathermy
Contained laser
Uterine Artery Embolization
Bilateral uterine artery cauterization
Medically Induced Hypogonadism
GnRH agonist
GnRH agonist with "add-back" therapy

GnRH, gonadotropin-releasing hormone.

TABLE 49.5. *Nonextirpative options*

Medical Suppression

Many medicinal agents have been considered for the management of leiomyomata including estrogen antagonists, progesterone antagonists (RU-486), androgens (danazol), and pituitary down-regulation with GnRH agonists. However, only suppressing ovarian steroid production and creating a state of hypogonadism with GnRH agonists has been demonstrated to reduce the size of leiomyomata and relieve symptoms to such a degree as to be clinically useful. Although the volume of the leiomyomata typically decreases by 35% to 50%, this is somewhat misleading. Physicians consider a reduction in the diameter of a fibroid to be the most clinically useful measure of shrinkage, and the diameter decreases far less than the total volume as determined using imaging measurements. Unfortunately, most leiomyomata rapidly return to the pretreatment size upon discontinuance of GnRH agonist therapy, and the return of symptoms parallels the enlargement. Prolonged hypogonadism may cause central necrosis of large cellular tumors and permanently reduce the size of individual fibroids. However, few data address this possibility or the circumstances under which it might occur. As a result, the reexpansion of the fibroids to their pretreatment size is the most likely clinical outcome, when ovarian function resumes after discontinuing the GnRH agonist.

Hypogonadism cannot be sustained for a prolonged interval because of the significant side effects, such as vasomotor hot flashes, accelerated bone loss, genital tract atrophy, and loss of the cardiovascular benefits of estrogen. Approximately 1% of the bone mass is lost per month after the onset of hypoestrogenism, and the hot flashes and genital tract atrophy can be very debilitating. Although most of the bone mass is regained if the therapy is limited to 6 months in young women, longer intervals or use in women closer to menopause may result in a permanent loss of age-adjusted bone mineral density. In an attempt to alleviate the severity of the hypogonadal symptoms, the simultaneous administration of low doses of estrogen and progestin simultaneously with GnRH agonists, the so-called *add-back regimens*, have been advocated. Although these regimens certainly relieve the hypoestrogenic symptoms and prevent bone loss, they have yet to be demonstrated to be as efficacious as GnRH-agonist therapy alone and do not offer any other objective benefit. The GnRH agonist with add-back approach will require a substantial amount of long-term data demonstrating a meaningful clinical benefit before it is considered a viable therapeutic option.

The important question to ask is "What is the goal of medical suppression?" The most important reason for using a GnRH agonist is to stop excessive vaginal bleeding and improve the hemogram prior to surgery, or to temporarily stop the bleeding and delay surgery in order to correct other medical problems posing an increased surgical risk. It is important to recognize that there is an initial action of the GnRH agonist that lasts 2 to 3 weeks before attaining the hypogonadal state. Hence, the bleeding may worsen transiently before stopping, and GnRH agonists are of little use for acute management of bleeding problems. Although reduced surgical blood loss and shortened operative time by preoperative use of a GnRH agonist often are espoused as benefits, scant data support these contentions. Indeed, the softening of small intramural leiomyomata by the hypogonadism may be a detriment. It may be virtually impossible to palpate them during a myomectomy and perhaps even make those identified more difficult to remove by reducing the surgeon's ability to demarcate clearly the boundary between normal myometrium and the fibroid. Given the variation in blood loss with surgery, it will be very difficult to demonstrate reduced intraoperative blood loss with GnRH-agonist pretreatment. Until convincing clinical data are available, the use of GnRH agonists for other than for preoperative correction of anemia will remain controversial.

Myolysis

There have been many attempts to induce therapeutic necrosis of cells within the center of a fibroid, such as myolysis, and thereby to shrink the tumor size, relieve symptoms, and prevent progressive growth of the tumors. These strategies typically involve repeatedly inserting a surgical probe of some sort into the tumor, typically at laparoscopy, and then causing tissue injury by the means of the following: (a) monopolar or bipolar electrocautery, (b) laser hyperthermia, (c) fiber laser vaporization, (d) diathermy (heat-generating ultrasonography), or (e) cryotherapy. All of these techniques require substantial operative time, result in a variable amount of cellular injury within the fibroid, and occasionally injure a portion of the normal myometrium, as well. Aseptic necrosis may cause significant pain during the immediate posttreatment interval, comparable to that observed with degeneration of leiomyomata seen in pregnancy. Long-term data for the efficacy of the various myolysis techniques are lacking, particularly with respect to the normalcy of subsequent pregnancy, safety, and persistence or recurrence rates. As a result, myolysis should be considered experimental until these issues are clarified by well-designed, long-term comparative trials.

Uterine Artery Embolization

When menorrhagia is the primary clinical symptom and either the surgical risk is judged unacceptable or the patient declines extirpative surgery, therapeutic UAE has been advocated to deprive leiomyomata of blood supply, induce necrosis, and reduce the volume of blood loss (Fig. 49.9). Importantly, there is no dominant vascular pedicle to individual fibroids, so bilateral embolization of both uterine arteries is required to reduce the blood supply to the leiomyomata. The procedure involves cauterizing the femoral artery on one or both sides and identifying the uterine arteries. An embolic agent is then infused to induce clotting and to obstruct blood flow to the uterus. This approach has been used in women with otherwise uncontrollable postpartum hemorrhage and palliatively for women exsanguinating from locally eroding advanced cervical cancer. In those clinical situations, the uterine arteries are the primary vascular supply to the bleeding sites involved, and occluding them reduces this vascular supply. UAE has been employed successfully under these circumstances with comparatively little morbidity relative to the other available options, such as emergency surgery. Based on its success for acute genital tract bleeding, UAE has been promoted actively by interventional radiologists as a primary therapy for virtually any symptoms attributable to fibroids.

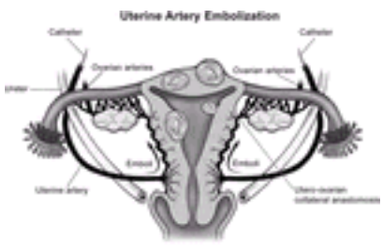

FIG. 49.9. The technique of uterine artery embolization. This schematic diagram demonstrates the technique used to inject emboli into the uterine arteries and deprive the normal myometrium as well as the leiomyomata of blood supply. Note that the uterine arteries have collateral connections with the ovarian arteries and provide a pathway for potential embolization to the ovarian vasculature.

With leiomyomata, the situation is nonemergent and significantly different from postpartum hemorrhage or an eroding cervical cancer. The vascular supply to the myomatous uterus varies significantly from woman to woman, with a large aberrant blood supply developing from normally minor collateral vasculature. UAE, by the nature of the technique, deprives the normal myometrium, as well the tumors enclosed within the uterus, of its blood supply. The technique's success depends on a large differential requirement of blood supply to the fibroids compared with that to the surrounding myometrium. Several case series of carefully selected women with leiomyomata have demonstrated a resolution of the menorrhagia ranging from 65 to 90%, but virtually no data are available for the efficacy for other symptoms attributable to leiomyomata, such as dysmenorrhea, pressure on adjacent viscera, and pelvic pain. The impact of UAE on the size of fibroids is not as well documented, with estimates ranging from 30% to 50%, comparable to the reduction seen with GnRH-agonist management. The leiomyomata typically shrink but, because they are not removed, not always enough to eliminate symptoms such as dysmenorrhea, pelvic pain, and pressure on adjacent viscera.

Although the benefits of UAE for stopping massive bleeding in women with postpartum hemorrhage and with eroding cervical cancer are obviously lifesaving, the long-term safety and efficacy in women with fibroids remain to be demonstrated. This is particularly true for women wishing to retain fertility, whose increased uterine blood flow during pregnancy is a normal physiologic adaptation, critically important to the survival and normal development of the fetus. Few pregnancies have been reported, because most women undergoing UAE are over 40 years of age and not desirous of further childbearing. No information is available regarding intrauterine growth restriction, abnormal placentation, or the value of a cesarean section to prevent uterine rupture during pregnancy or labor. As with an abdominal myomectomy,

the risks involved are likely to be related to the number, size, and location of the fibroids being treated.

Another concern for women wishing to retain their fertility is ovarian function. Because there are substantial anatomic collateral connections between the uterine and ovarian vasculature, it is possible for the embolic agents to enter the ovarian vasculature, reduce blood supply to the ovary, and cause premature ovarian failure. The overall rate of ovarian failure is between 5% and 10%, with most of these women being over age 40 at the time of the UAE. However, because the surgical removal of one ovary does not result in earlier menopause, many oocytes may be lost without causing premature menopause. Women may also experience postprocedure amenorrhea when ovarian function is normal, indicating loss of the integrity of the endometrium, which is also of concern regarding fertility. It is imperative that controlled trials with long-term follow-up be performed in order to counsel accurately women with childbearing desires as to the results to be attained with UAE.

UAE has been widely touted as avoiding the risks of abdominal surgery, causing less pain, and requiring less recovery time than surgical extirpation. However, the aseptic necrosis often causes such intense abdominal pain that women undergoing UAE are hospitalized routinely for parenteral narcotic administration for 24 to 48 hours. If intracavitary or submucous myomas are present, the avascular necrosis following UAE may result in prolapse of the degenerating myoma through the cervix, necessitating surgical removal. A postembolization syndrome can develop, similar to that observed after a myocardial infarction, manifested by a flulike syndrome with general malaise, elevated temperature, and leukocytosis. This is difficult to distinguish from an infection and usually is treated with antibiotics. Sepsis can occur, but whether is secondary to an ascending infection or from another source is not clear.

As the number of women undergoing UAE increases, serious acute complications necessitating hysterectomy, and even including death, are being reported. Until randomized comparative trials with long-term follow-up are available demonstrating a benefit of UAE over surgery in a defined clinical setting, this technique will remain a controversial addition to our therapeutic armamentarium. UAE should be considered primarily for women with unacceptably high surgical risks or those women without reproductive desires who do not want surgery. It should be undertaken with the understanding that, although UAE may relieve symptoms, it is not without the risk of serious complications, including death, and that no data are available regarding recurrence rates and long-term complications such as premature ovarian failure.

Another nonextirpative option is the laparoscopic cauterization of both uterine arteries to reduce the flow of blood to the myomatous uterus. As with UAE, the theoretic value is to reduce the vascular supply to both the normal myometrium and the leiomyomata and, thus, cause tissue schemia, with the uterus tolerating this to a greater degree than the myomas. Also like UAE, this therapy has not been assessed adequately in large long-term trials, but in a few highly selected patients it has reduced the symptoms attributable to the leiomyomata. This must be considered an experimental therapy, and its clinical application should await the results of randomized clinical trials with long-term follow-up.

SUMMARY POINTS

- Leiomyomata represent the most common gynecologic tumors and can grow to impressive size, despite being almost invariably benign in the reproductive age group.
- Fibroids cause a variety of gynecologic symptoms and account for a substantial proportion of gynecologic surgery.
- Although some insights into the molecular mechanisms responsible for growth of leiomyomata have been gained, much remains to be learned about this gynecologic tumor, because no consistent molecular mechanism of tumor growth has been identified.
- The therapeutic choices focus on extirpation, with hysterectomy most often used for definitive treatment and myomectomy when preservation of reproductive potential is desired, albeit with a significant recurrence risk.
- Medical therapy focused on hypogonadism is successful for temporarily treating symptoms, but the leiomyomata rapidly return to the pretreatment size upon discontinuance, and this approach does not represent a long-term treatment nor eliminate the risk of recurrent symptoms.
- Newer techniques of UAE and myolysis have not yet been evaluated adequately in comparative clinical trials to establish accurately their risks and long-term recurrence rates, particularly their impact on future reproduction.
- Until a better understanding of the factors involved in initiating leiomyomata growth is achieved, management will remain focused primarily on the surgical relief of symptoms.

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Chapter 50

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Disorders of the Breast

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Breast cancer remains the most common cancer in women, and is second only to lung cancer as the leading cause of cancer-related death in the United States. It is estimated that in 2003 there will be 211,300 new cases of breast cancer diagnosed. The lifetime risk among women of developing breast cancer is 12.5% (1 in 8); the lifetime risk of dying from breast cancer is 3.6% (1 in 28). Although breast cancer remains a serious health concern in the United States as well as in other countries, breast cancer mortality is declining in the U.S. and in other industrialized countries. This decline is thought to be secondary to increased use of mammographic screening and early detection of breast cancer.

Obstetricians and gynecologists are commonly the primary care physicians for many women. According to the American College of Obstetricians and Gynecologists (ACOG), the diagnosis of breast disease, as well as the education of women on breast self-examination, and their referral for mammographic screening, is central to the obstetrician/gynecologist's role in women's health care.

This chapter presents an overview of breast cancer screening, benign and malignant conditions of the breast, and the role of the obstetrician/gynecologist in the diagnosis of and education of women about breast disease.

ANATOMY OF THE BREAST

The adult breast lies between the second and sixth ribs in the vertical plane and between the sternal edge (medially) and midaxillary line (laterally). The average breast measures 10 to 12 cm in diameter and is 5 to 7 cm in thickness. It is concentric, with a lateral projection into the axilla named the *axillary tail of Spence*.

The breast consists of three major structures: skin, subcutaneous fatty tissue, and breast tissue (parenchyma and stroma). The skin contains hair follicles, sebaceous glands, and eccrine sweat glands. The glandular breast is divided into 15 to 20 segments (lobes) that are separated by connective tissue and converge at the nipple in a radial arrangement. These lobes are made up of 20 to 40 lobules, which in turn consist of 10 to 100 alveoli (tubulosaccular secretory units). Five to ten major

collecting milk ducts drain each segment and open at the nipple into subareolar lactiferous sinuses.

A superficial pectoral fascia envelops the breast; the undersurface of the breast lies on the deep pectoral fascia. Between these two fascial layers are fibrous bands, Cooper suspensory ligaments, which provide support for the breast. The space between the deep layers of the superficial fascia of the breast and the deep investing fascia of the pectoralis is the retromammary bursa.

The epidermis of the nipple (mammary papilla) and areola is pigmented and wrinkled and consists of keratinized, stratified squamous epithelium that contains smooth muscle fibers in dense connective tissue. These fibers are responsible for the erection of the nipple. Two receptor-type nerve endings (Ruffini-like bodies and end bulb of Krause) are present on the nipple and are associated with the tactile reception of stretch and pressure.

The areola has no hair follicles; it has sebaceous glands (at its margin), apocrine sweat glands, and accessory areolar glands (Montgomery glands) that open on the surface of the areola as small elevations called Morgagni tubercles.

The blood supply of the breast is mostly from superficial vessels. The principal blood supply is derived from the internal thoracic (mammary) and lateral thoracic artery and their tributaries. The posterior intercostal arteries of the second to fourth intercostal spaces also give off tributaries, the mammary branches.

The superficial veins follow the arteries and drain through perforating branches of the internal thoracic vein, tributaries of the axillary vein, and perforating branches of posterior intercostal veins. The veins anastomose circumferentially around the nipple, which is named the circulus venosus.

EPIDEMIOLOGY OF BREAST CANCER

Risk Factors and Assessment

Age The incidence of breast cancer increases with age. Age is the most significant risk factor for breast cancer.
Family History Hereditary breast cancers account for 5% to 10% of all breast cancers and are thought to be attributable to highly penetrant mutations in breast cancer–susceptibility genes. Two such tumor-suppressor genes, *BRCA1* and *BRCA2*, have been well characterized. Breast cancer has also been noted to occur in association with other cancers such as in the Li-Fraumeni syndrome and Cowden syndrome.
Personal History A patient's history of prior breast biopsy is important. Although the number of breast biopsies undergone does not increase a woman's risk of breast cancer, certain pathologic entities do play a role. Atypical ductal or lobular hyperplasia and lobular carcinoma in situ are considered markers of increased risk of developing invasive breast cancer. A personal history of breast cancer increases the risk for development of another breast cancer. Women treated for breast cancer are at risk for the development of a contralateral breast cancer. Various studies have shown this risk to be between 0.5% and 1% per year. In addition, patients treated with breast conservation (lumpectomy and radiation therapy) are at risk for an ipsilateral recurrence. In these women, this risk could be 10% or higher at 10 years post-treatment.
Reproductive History Early menarche, late menopause, and nulliparity are thought to be risk factors for breast cancer. Age at first pregnancy is also thought to be a relative risk (RR) factor for breast cancer. Early age at first pregnancy is often associated with a lower risk for breast cancer; pregnancy by the age of 30 may reduce risk by up to 30%, and a full-term pregnancy by the age of 20 reduces risk by 50%. Breast-feeding has been reported to reduce risk of breast cancer, and the greatest effect is seen when cumulative times exceed 24 months. The effect of menopause as it relates to breast cancer risk has been examined. Late menopause poses an increase in risk of breast cancer. Bilateral oophorectomy before natural menopause has been reported to reduce risk of breast cancer.
Exogenous Hormone Use The role of exogenous estrogens in the promotion of breast cancer is still controversial. Studies of oral contraceptives (OCP) and hormone replacement therapy (HRT) have yielded conflicting results. Studies of HRT and breast cancer risk indicate that women who are currently using HRT are at increased risk for breast cancer development. A meta-analysis of the largest studies, however, suggests that the increased risk is only about 10%. Women who have taken HRT in the past but are not currently using HRT are not at increased risk. Long-term use of HRT (>10 years) has been associated with relative increase in breast cancer risk, and the highest risk was noted in those patients using HRT with progestins (RR =1.41). Of note, multiple studies have shown that patients who develop breast cancer while on HRT have smaller, less aggressive cancers and a lower risk of death from breast cancer. Recently, results from the Women's Health Initiative randomized controlled trial were reported. Between 1993 and 1998, 16,609 women with an intact uterus were randomized to receive combination HRT (0.625 mg/day conjugated equine estrogens and 2.5 mg/day medroxyprogesterone acetate) versus placebo. The planned duration of the trial was 8.5 years; however, the data and safety monitoring board of the committee recommended halting the trial because the incidence of invasive breast cancer had exceeded the stopping boundary that had been set at the initiation of the trial. This occurred after a mean of 5.2 years of follow-up. The increased risk of breast cancer reported hazard ratio was 1.25 (95% confidence interval [CI], 1.00-1.59). There was also a reported increased risk of coronary heart disease (HR 1.29; 95% CI, 1.02-1.63), stroke (HR, 1.41; 95% CI, 1.39-3.25). Beneficial effects included decreased risk in colorectal cancer (HR, 0.63; 95% CI, 0.43-0.92) and hip fracture (HR 0.66; 95% CI, 0.45-0.98). Based on the data and safety monitoring board did not recommend stopping the estrogen-alone arm in women who had had a hysterectomy. Results of this part of the study are anticipated in 2005. The annual increased risk for an individual woman is still relatively small. The increased risk for breast cancer is apparent after four years of HRT use. The American College of Obstetricians and Gynecologists (ACOG) stresses the importance of addressing the reasons for initiating or continuing on HRT. It is no longer recommended to prevent heart disease in healthy women (primary prevention) or to protect women with preexisting heart disease (secondary prevention). In addition, it is no longer recommended solely for prevention of osteoporosis. HRT is highly effective in treating vasomotor symptoms with limited effective alternative therapies. In this setting, short-term use (<5 years) can be considered as data on short-term use does not show an increased association with breast cancer. In the past, most studies addressing OCP use and breast cancer risk concluded that there was a significant increase in risk associated with OCP use. However, the majority of studies regarding OCP use and breast cancer risk have demonstrated little association with breast cancer incidence rates. In women who have used OCP for extended periods of time (>10 years), a minimal, nonsignificant increase in breast cancer cases has been reported, seen most commonly in the group of women who began using OCP at a young age (<20 years). Past or present use of OCP at the time of diagnosis of breast cancer does not affect mortality from breast cancer. The presence of a family history of breast cancer does not appear to further increase the risk of breast cancer associated with either OCP or HRT use.
Prior Exposure to Radiation Therapy Exposure to ionizing radiation such as occurs in treatment with mantle radiation for Hodgkin's disease poses a risk for breast cancer. This is noted 7 to 10 years after completion of radiation therapy. The cumulative probability of breast cancer at age 40 approaches 35% in these women. The risk of breast cancer associated with radiation exposure decreases with increasing age at exposure.
Other Factors Breast cancer is more frequent in Jewish women than in non-Jewish women and in black women than in white women. Asian women have a low incidence of breast cancer. Japanese women show lower rates of breast cancer than white women. Although postmenopausal breast cancer is less common in Japanese women who have migrated to Western countries than among the general populations of these countries, after two or three generations, the incidences of breast cancer in these women approaches that of white women. The Western diet, with the increased intake of animal fat, has been implicated in these studies. Alcohol consumption has been reported to increase breast cancer risk in a dose-related manner. Women who drink approximately one drink per day have slightly elevated risk of breast cancer over nondrinkers. This risk is significantly higher with moderate to high alcohol consumption (two to five drinks per day).

Relative Risk

Relative risk (RR) is a ratio that depicts the likelihood over time of an event's occurrence in a study population relative to that in a reference population. It is often used to quantify risk factors for breast cancer. Absolute risk is a percentage that depicts the likelihood over time of the occurrence of an event. For rare events, these two are the same, but for common events they are not. It is best to discuss risk with patients in terms of absolute rather than relative risk.

Several models exist to estimate a woman's risk of breast cancer. The Gail model, developed for use in the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) Breast Cancer Prevention Trial, is available from the National Cancer Institute and provides a measurement of absolute risk over time for breast cancer. However, in familial-type hereditary cases, it underestimates the risk of breast cancer by overlooking age at onset, bilaterality of disease among affected family members, and breast cancer in nonfirst-degree relatives (Table 50.1).

Factor	Relative risk
Family history of breast cancer	
First-degree relative	1.8
Premenopausal first-degree relative	3.0
Postmenopausal first-degree relative	1.5
Premenopausal first-degree relative (bilateral breast cancer)	9.0
Postmenopausal first-degree relative (bilateral breast cancer)	4.0–5.4
Menstrual history (age in years)	
Menarche before age 12	1.7–3.4
Menarche after age 17	0.3
Menopause before age 45	0.5–0.7
Menopause from age 45–54	1.0
Menopause after age 55	1.5
Menopause after age 55 with >40 menstrual years	2.5–5.0
Oophorectomy before age 35	0.4
Anovulatory menstrual cycles	2.0–4.0
Pregnancy history	
Term pregnancy before age 20	0.4
First term pregnancy at age 20–34	1.0
First term pregnancy after age 35	1.5–4.0
Nulliparous patient	1.3–4.0
Noninvasive breast disease	
Atypical lobular hyperplasia	4.0
Lobular carcinoma in situ	7.2
Other neoplasm	
Contralateral breast cancer	2.0–10.0
Cancer of the major salivary gland	4.0
Cancer of the uterus	2.0

Source: Marchant DJ. *Breast disease.* Philadelphia, Baltimore: WB Saunders, 1997:119, with permission.

TABLE 50.1. *Risk factors for breast cancer*

BRCA1 and BRCA2 *BRCA1* and *BRCA2* are breast cancer–susceptibility genes that have expanded our knowledge of familial breast cancer. Linkage studies done in 1990 in early-onset breast cancer families led to cloning of the *BRCA1* gene at the University of Utah in Salt Lake City in 1994. The *BRCA1* gene consists of 22 coding exons distributed over approximately 100 kb of genomic DNA on chromosome 17q21. It is thought to be responsible for approximately 45% of early-onset hereditary breast cancers, and nearly 90% of hereditary ovarian cancers in families with a high incidence of breast and ovarian cancers. Two specific mutations, *185delAG* and *5382insC*, are present in approximately 1% and 0.25% of the Ashkenazi Jewish population, respectively. They are thought to be founder mutations (i.e., an altered gene or genes seen with a high frequency in a population originating from a small ancestral group, one or more of the founders of which were carriers of the mutant gene). *BRCA2* was isolated on chromosome 13q12-13 in 1995. The *BRCA2* gene is composed of 26 coding exons distributed over approximately 70 kb of genomic DNA. This gene appears to account for 35% of families with early-onset breast cancer. It confers a lower risk of ovarian cancer compared with breast cancer. A single mutation, *6174delT*, is found in approximately 1.4% of the Ashkenazi Jewish population. Together, both *BRCA1* and *BRCA2* mutations are found in approximately 1 in 40 Ashkenazi Jewish individuals. For both genes, the estimated penetrance is 70% to 90% for breast cancer by age 70, but the risk of breast cancer by age 50 may be lower for *BRCA2* mutations. The likelihood of a patient having a *BRCA1* or *BRCA2* mutation is dependent on certain factors such as age at the time of diagnosis of breast or ovarian cancer and the number and age of first- and second-degree relatives in the same parental lineage and ethnicity with breast or ovarian cancer. The parental lineage can be either maternal or paternal. The American Society of Clinical Oncology issued guidelines for recommending genetic testing for families with high probability (>10%) of having a mutation for *BRCA1* (Table 50.2).

Three or more kindred with breast cancer < age 50
Two or more breast cancers and one or more ovarian cancer diagnosed at any age
Sister pairs with two breast cancers, two ovarian cancers, or a breast and an ovarian cancer, all diagnosed < age 50

TABLE 50.2. *American Society of Clinical Oncology (ASCO) guidelines for recommending genetic testing for families with high probablility (>10%) of having BRCA1 mutation*

Identification of patients with a high-risk family history should be referred for genetic counseling and testing. The decision to undergo genetic testing is a complex one, as it can affect an individual's personal, psychological, social, financial, and ethical well-being. Women who have a negative genetic test should still be considered at risk on the basis of age, environment, or other genetic factors or unknown mutations.

HISTORY AND PHYSICAL EXAMINATION

Obtaining a thorough history, including a family history and information on menstrual status, pregnancies and lactation, hormone use, prior breast surgeries and trauma, is essential. In addition, ascertaining whether the patient performs breast self-examinations, as well as the presence and characterization of nipple discharge or a breast mass is important.

Bilateral breast examination is best performed right after menstruation and prior to ovulation. At this time, breast engorgement and tenderness is less likely to be present. A multipositional breast examination should be performed, including examination in the upright and supine positions (Fig. 50.1 and Fig. 50.2). Breast retraction and subtle changes in the skin and nipple may be missed if the patient is examined in only one position. Examination should be performed with hands at sides, elevated above the head, and finally, with the arms tensed at the waist (contracting the pectoralis muscles). Attention is directed toward the supraclavicular area and axilla. Digital palpation is performed beneath the lateral pectoralis muscles into the axilla itself.

FIG. 50.1. A: Inspection of patient with arms at sides. **B:** Inspection of patient with both arms raised. **C:** Inspection of patient with hands at waist, pectoral muscles contracted.

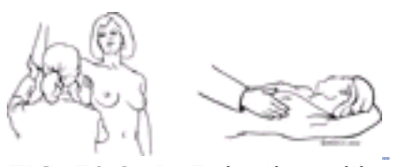

FIG. 50.2. A: Palpation with patient upright, with support of ipsilateral elbow; axillary nodes and also supraclavicular nodes examined. **B:** Palpation of breast with patient in supine position.

The second phase of the breast examination is conducted with the patient in the supine position. Digital palpation is carried out using the index and middle fingers and applying varying amounts of pressure with the flats or pads of the fingers. A thorough examination systemically covers the entire breast and chest wall. The examination can be done in a clockwise direction or by rows (stripwise). It is important to carefully examine beneath the nipple–areolar complex and within the axilla.

An inflammatory appearance of the breast should raise suspicion of an inflammatory carcinoma. The classic appearance of inflammatory breast cancer includes a red, swollen breast with skin edema (“peau d'orange”). The breast is generally not tender. If the inflammation persists following a short course of antibiotics to rule out cellulitis, biopsy of the breast and skin is warranted. Inflammatory breast cancer is often a clinical diagnosis, and a benign skin biopsy should not dissuade the clinician from undertaking further evaluation and treatment. Any asymmetric skin changes or changes of the nipple–areolar complex should arouse suspicion. Paget disease of the nipple is the presence of intraductal or invasive cancer involving the nipple and should be excluded by a nipple biopsy of the abnormal area following a mammogram.

It is important to instruct patients in the technique of breast self-examination. Physician-directed discussion on breast self-examination is the most effective approach. Physicians have the opportunity to reinforce what is normal versus abnormal to patients during the examination.

If no abnormal findings are noted on examination, it is critical to document negative findings. The date of the last mammogram, discussion of cancer screening, and plans for follow-up should also be recorded.

Hormones (HRT or OCP) should not be renewed without a documented annual breast examination or mammography if indicated. A great deal of litigation results from failure to diagnose breast cancer. The Physician Insurers Association of America's breast cancer claims study, conducted in 1988, determined that 75% of successful malpractice lawsuits involved primary care physicians with practices in family medicine, internal medicine, or obstetrics and gynecology. It is important that the medical

chart include careful documentation, since approximately one third of the cases reported in the Physician Insurers Association of America's study resulted from inadequate documentation.

MAMMOGRAPHY

The primary goal of mammography is to screen asymptomatic women to help in detection of breast cancer at an early stage. In general, a routine screening mammogram consists of a mediolateral oblique (MLO) view and a craniocaudal (CC) view of each breast. With modern low-dose screening, the dose is less than 0.1 rad per study (for comparison, a chest x-ray delivers 0.025 rad per study). The effectiveness of screening also varies depending on the density of the breast.

Breast composition may be one of four patterns of increasing density:

1. almost entirely fat
2. scattered fibroglandular densities
3. heterogeneously dense
4. extremely dense.

The greater the breast density, the lower the sensitivity of the mammogram. Because some palpable cancers are invisible on mammography, a negative study cannot always exclude cancer. It is important to note that the false-negative rate for mammograms is 10% to 15% and that a normal mammogram does not eliminate the need for further evaluation of a dominant mass in the breast. If the clinical examination is suspicious, a negative mammogram should not delay further investigation.

Mammographic screening in women 40 years or older has reduced mortality by 20% to 30%. The efficacy of screening mammography in decreasing breast cancer mortality has been demonstrated in numerous studies. In the 1960s, the Health Insurance Plan of Greater New York performed a study of physical examination and mammography in a study group of 30,756 women and a control group of 30,239 women between the ages of 40 to 64 years. At 10-year follow-up, the study group had a 30% decrease in breast cancer mortality compared with the control group.

A total of eight large randomized trials on mammographic screening have been conducted. Six of the eight trials revealed a statistically significant reduction in mortality with mammographic screening. The reduction in mortality was not as evident among women between the ages of 40 and 49 compared with women over 50 years of age. The relative mortality reduction appears later in women between the ages of 40 and 49 at randomization compared with women 50 years of or older. It is also likely that the small numbers of women between 40 and 49 years of age in the existing randomized trials may have contributed to this difference.

In a meta-analysis of eight randomized, controlled trials of mammographic screening, a statistically significant 18% reduction in mortality in women aged 40 to 49 was noted. Combined data from five Swedish trials yielded a statistically significant mortality decrease of 29% (Table 50.3).

Trial	Relative risk (95% CI)
Malmö	0.96 (0.68–1.35)
Canada	1.08 (0.84–1.40)
Göteborg	0.55 (0.31–0.95)
Stockholm	0.73 (0.50–1.06)
Kopperberg	0.58 (0.45–0.76)
Östergötland	0.76 (0.61–0.95)
New York	0.79 (0.64–0.98)
Edinburgh	0.87 (0.70–1.08)

CI, confidence interval.

TABLE 50.3. *Randomized population-based mammography trials*

A re-analysis of the meta-analysis excluded six of the eight studies because of issues related to randomization methods used and other factors in these trials. This re-analysis questioned the risk reduction offered by mammography and resulted in much controversy. The risk reduction associated with mammography continues to be an area of debate within the medical community.

Screening Interval

For several years, there has been a significant debate about the appropriate age at which to commence mammographic screening. In 1997, the American Cancer Society (ACS) and the National Cancer Institute (NCI) modified the guidelines for mammographic screening for women between the ages of 40 and 49, recommending regular mammograms for women in this age group. The recommended intervals differ: the ACS recommends a yearly mammogram starting at age 40, while the NCI recommends a mammogram every 1 or 2 years. The ACOG recommendations on mammography are similar to the NCI guidelines.

Annual screening mammography may commence earlier than age 40 in a few special circumstances (Table 50.4).

TABLE 50.4. *Screening guidelines for women under age 40*

BI-RADS

In the past, a lack of uniformity in mammography terminology and reporting often led to confusion as to the malignant nature of a lesion. In 1994, the Mammography Quality Standards Act was passed by Congress and is administered by the Food and Drug Administration (FDA). It requires that mammography facilities monitor the results of their breast cancer–detection programs, including the number of recommended biopsies, and the size, number, and stage of cancers detected. The American College of Radiology (ACR) Breast Imaging Reporting and Data System uses a terminology and lexicon system called *BI-RADS* for reporting abnormalities seen on mammography (Table 50.5). This standardized reporting system—the Breast Imaging Reporting and Data System—was developed in 1995. Each category leads to a fixed assessment and specific management recommendations.

BI-RADS categories	Assessment
0	Need additional imaging evaluation—assessment is incomplete
1	Negative
2	Benign finding
3	Probably benign finding—short interval follow-up suggested
4	Suspicious abnormality—biopsy should be considered
5	Highly suggestive of malignancy—appropriate action should be taken

Source: American College of Radiology. *Illustrated breast imaging reporting and data system (BI-RADS)*, third ed. Reston, VA: American College of Radiology; 1998.

TABLE 50.5. *American College of Radiology (ACR) BI-RADS assessment categories*

In addition, associated findings such as skin or nipple retraction, skin thickening, skin lesions, axillary adenopathy, and the presence of architectural distortion should also be reported.

The predictors of malignancy for the BI-RADS categories are 0% to 2% for category 3 and approximately 98% or greater for category 5.

Category 4 is less predictable. Liberman and colleagues and Orel and colleagues have placed the risk of malignancy for this category around 30%.

The ACR is working on a new edition of the BI-RADS classification system that, in particular, will attempt to provide data on category 4 in terms of risk of malignancy. According to the ACR, in the forthcoming edition of BI-RADS, category 4 will be divided into three subdivisions—low, medium, and high—in an effort to better guide clinicians and to get meaningful data about this category (personal communication, July 2002).

Diagnostic Mammography

Abnormalities found on mammographic screening may need further evaluation with additional mammography views or other imaging modalities such as ultrasound or magnetic resonance imaging (MRI). In some screening programs, the mammograms are reviewed by the radiologist as they are performed, and if additional views are needed, they are performed on the same day. In other programs, if additional studies are required, the patient is called back for them at a later date. In several studies, the frequency of “call-backs” has ranged from 5% to 11%.

Mammographic Lesions

A “mass” is defined as a space-occupying lesion seen in two different projections. If a possible mass is seen on only one view, it is called a “density” until its three-dimensionality is confirmed. A description of the shape and the margins of the lesion are also necessary. The highest frequency of carcinoma is noted in masses that have an irregular shape or spiculated borders. These lesions are associated with pleomorphic calcifications that appear discontinuous and linear in distribution. This discontinuous linear pattern suggests irregular filling of a duct with abnormal cells.

Microcalcifications

The BI-RADS lexicon describes calcification morphology (shape) and distribution. Calcifications may be scattered or clustered, coarse or fine, old or new. Comparison with prior mammograms is often necessary (Table 50.6).

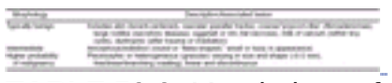

TABLE 50.6. *Morphology of microcalcifications and associated lesions*

Breast Ultrasound and MRI

Breast ultrasonography can be used to distinguish between solid and cystic masses in the breast. It can be used to evaluate a focal mass identified on a mammogram or a palpable mass. It is also used as an adjuvant for biopsy. Because of its low specificity, it is not thought to be a good modality for screening. It cannot replace mammography, as it has no ability to detect microcalcifications. Ultrasound can complement mammography in young women with dense breasts (which limits the accuracy of the mammogram).

Presently, MRI has no role in breast cancer screening. MRI has a high sensitivity in the diagnosis of breast cancer, ranging from 86% to 100%, but a low specificity 37% to 97%. Because of this low specificity it is of limited value in screening. It is an expensive test that requires intravenous contrast and the technology for performing biopsy under MRI guidance is not widely available. Current uses include evaluation of breast implants for rupture, evaluation of pectoralis involvement with extensive breast cancer, and evaluation of post-lumpectomy bed fibrosis. Research into the use of MRI for screening of patients with dense breasts is under investigation. Future uses may include evaluation of occult breast cancers and evaluation of multifocal disease in those patients who are considering breast conservation.

DIAGNOSTIC EVALUATION

Palpable Mass

The workup of a patient with a dominant mass should include a bilateral mammogram. In addition to gaining valuable information about the characteristics of the mass, a secondary purpose in this setting is to screen the normal surrounding breast and the contralateral breast for nonpalpable mammographic abnormalities (densities or calcifications). Evaluation of a palpable mass is important to determine whether the mass is cancerous even if the mammogram is negative.

Fine-Needle Aspiration or Biopsy

Fine-needle aspiration (FNA) can be extremely useful in providing a cytologic analysis of a palpable breast mass. Many palpable thickenings and all dominant masses should be considered for FNA as it can differentiate between solid and cystic masses. In addition, FNA can diagnose and treat simple cysts and provide cellular material for cytologic analysis. The FNA should be performed after radiologic examination because the resultant hematoma could mask an underlying abnormality.

The breast is prepped with alcohol; with the physician facing the patient, the lesion is stabilized with the physician's opposite hand. Usually, a 21-gauge or 25-gauge needle on a 10-cc syringe is used. Approximately 3 cc of air is aspirated into the syringe to facilitate expulsion of the contents onto the slide following the procedure. The needle is introduced into the lesion, and suction is applied on the syringe (Fig. 50.3A, Fig. 50.3B and Fig. 50.3C). If the mass is cystic, the fluid is completely evacuated and the lesion should completely disappear. The syringe is withdrawn and the fluid is discarded if it is serous and nonbloody. The patient should return in 4 to 6 weeks for reexamination.

FIG. 50.3. Aspiration biopsy. **A:** Mass. **B:** Stabilizing the lesion. **C:** Aspirating.

If the lesion encountered is not cystic or suspected to be solid, an FNA biopsy can be performed in the same manner. After insertion into the lesion, multiple passes (10–15) through the lesion with changes in direction allow extensive sampling and create a “feel” for the mass (carcinomas are usually hard and gritty). The goal of sampling is to obtain material in the hub of the needle, not to fill the syringe. Care should be taken to release the suction before withdrawing the needle to prevent aspiration into the syringe. The sample is then ejected onto a glass slide, gently smeared with another slide and placed in sterile jars containing 95% ethanol for transport to the cytology lab. Alternatively, it can be placed in a specimen jar containing cytofixative. The needle should be removed from the syringe, the medium

aspirated into the syringe, the needle replaced, and the medium then ejected into the jar.

An FNA requires a cytopathologist experienced in breast pathology. The false-negative rate can range from 3% to 35% depending on the expertise of the aspirator and the cytopathologist, the size of the lesion, the location within the breast and the cellular composition of the lesion. Negative findings of an FNA in the presence of a suspicious mass should not preclude further diagnostic evaluation. A diagnosis of atypical cells following an FNA warrants a surgical biopsy. Any mass remaining after aspiration of a cyst should be excised. Similarly, a cyst that recurs in the same location after one or two aspirations should be excised.

The false-positive rate of an FNA is less than 1%, but in the United States most surgeons will not perform definitive surgery (i.e., a mastectomy or axillary dissection) without a prior surgical biopsy, core-needle biopsy, or frozen-section diagnosis at the time of surgery. An FNA that is positive for adenocarcinoma could, however, provide a preliminary diagnosis and guide subsequent management.

Patients with palpable solid masses can have a biopsy of the mass in the office with use of a Tru-cut 14-gauge biopsy device. The breast is prepped sterilely and a local anesthetic is used to infiltrate the skin. A small nick is made in the skin with a scalpel to accommodate the biopsy instrument. A core biopsy of the solid mass is obtained. The instrument has a “firing” range and therefore should be kept parallel to the chest wall to avoid penetrating trauma. The specimen is placed in formalin and sent to pathology. It is believed that if the specimen “floats” in the solution, it is likely nondiagnostic fat. Tumor specimens will have a grayish appearance and will typically “sink” in the solution.

Needle-Localization and Excision

Needle localization is a technique that allows surgical excision of a lesion that is nonpalpable. The technique uses a hook-wire system to target the lesion, and image guidance can be provided by mammogram, ultrasound, and in some cases MRI. In mammography-guided needle localization, coordinates of the lesion are obtained by placing the breast in an alphanumeric grid. The needle is inserted and, when adequate placement is noted, the hook wire is deployed and the needle removed. Two mammographic views are then obtained.

The mammography films are available intraoperatively and show the relationship between the lesion and localizing hook. Excision with needle localization allows the surgeon to minimize the amount of breast tissue removed by following the needle to the targeted lesion. After removal, a specimen radiograph is obtained to ensure that successful removal of the lesion has been performed. Radiologists and surgeons experienced in needle localization and excisions report only 0.2% to 0.3% of lesions missed with this approach. The specimen radiograph helps to ascertain the lesion was not missed.

Image-Guided Percutaneous Breast Biopsy

With the current advancements available in breast imaging, percutaneous image-guided breast biopsy is increasingly being used as an alternative to surgical biopsy. Percutaneous biopsy methods differ with respect to the method of imaging guidance and the tissue-acquisition device used. The use of image-guided percutaneous biopsy has advantages over surgical excision for the diagnosis of breast lesions. It is less invasive and because less tissue is removed, it will result in less scarring on subsequent mammograms. Regardless of whether the diagnosis is benign or malignant, the patients who have percutaneous biopsies will undergo fewer operations. In addition, in cases of malignancy, the discussion and surgical treatment plan can be streamlined. The choice of which image-guided modality to use depends on the lesion. Stereotactic biopsy is best for calcifications. If a lesion is seen on ultrasound, it is best to use that modality, since it is easier to use and has been reported to be less costly.

Stereotactic Biopsy

Stereotactic biopsy uses specialized mammography equipment to calculate the location of a lesion in three dimensions. Stereotactic biopsy can be performed with the patient prone on a dedicated table or with the patient sitting in an upright unit. An automated core needle or directional vacuum-assisted biopsy probe is used to obtain the tissue specimens. Multiple tissue specimens are obtained for pathologic analysis. Many reports in the medical literature state the procedure has a sensitivity of 70% to 100% and a specificity of 85% to 100%. The greatest success is noted in reports using 14-gauge core needles, as well as in those with increased numbers of specimens obtained. In mass lesions, it is likely that five core samples may be adequate for accurate diagnosis; however, ten or more core specimens may be required in cases of calcifications.

Ultrasound-Guided Biopsy

The use of ultrasound imaging for percutaneous biopsy of lesions seen on ultrasound has certain advantages. For example, it requires no specialized equipment, no radiation exposure, and has the ability to sample areas that may be inaccessible with stereotactic biopsy (such as the axilla). A 14-gauge automated needle is used, and real-time imaging allows accurate positioning. Multiple tissue core samples are sent for pathologic analysis.

Tissue-Acquisition Devices

Available tissue-acquisition devices include fine needles, automated core needles, directional vacuum-assisted probes, and biopsy cannulas. Excellent results have been obtained using the 14-gauge automated needle for biopsy of masses under ultrasound or stereotactic guidance. Most centers use larger tissue-acquisition devices instead of fine needles, because of accuracy of tissue diagnosis when a larger volume of tissue is obtained. Compared with the automated needle, the vacuum device acquires larger samples of tissue, has a higher frequency of retrieval of calcifications, and may provide more accurate lesion characterization. Accurate placement of a localizing clip through the biopsy probe is necessary to facilitate subsequent localization if needed.

Surgical Excision/Breast Biopsy

The ACOG has stopped short of recommending that open biopsy be performed by every obstetrician and gynecologist.

A biopsy can be performed on an outpatient basis under local anesthesia in the majority of patients. It is important to choose the appropriate incision and location (Fig. 50.4). Unless the lesion is close to the nipple or suspected to be a fibroadenoma, the incision should be made in close proximity to the mass and not circumareolar. The surgeon should keep in mind the possibility of subsequent mastectomy when placing the incision. Many times, the biopsy is part of the treatment. The specimen should be adequately oriented for margin analysis by the pathologist and also sent for the appropriate markers such as estrogen-receptor (ER) and progesterone-receptor (PR) status and HER2/ *neu*. Orientation of the specimen is important, as a reexcision of a close or involved margin may need to be performed.

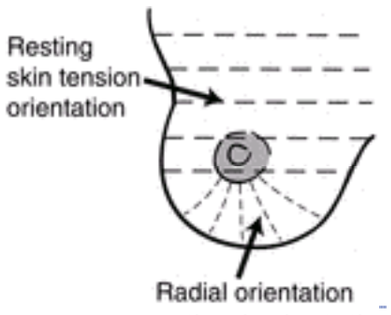

FIG. 50.4. Optimal orientation of biopsy incisions.

The incision should be closed with fine suture material, with a subcuticular closure. Hemostasis needs to be ascertained prior to closing and is usually achieved with electrocautery. Weck clips can be placed in the cavity bed if a diagnosis of breast cancer is known and breast conservation is planned. No particular immobilization is required but a good support bra is recommended to minimize hematoma and induration.

BENIGN BREAST CONDITIONS

Fibrocystic Changes

Fibrocystic change is the most common benign breast condition in women. It is a result of fluctuating hormone levels, and most common in premenopausal women between the ages of 20 and 50. It is often associated with pain and tenderness (mastodynia) and tends to be bilateral. Most women will report symptoms during the premenstrual phase of the cycle.

Pain is due to breast stromal edema, ductal dilation, and associated inflammatory response. An increase in breast size is also frequently reported. The differential diagnosis for breast pain includes other conditions affecting the anterior chest wall such as intercostal neuralgia, myalgia, and chronic costochondritis. Women with large pendulous breasts will have associated stretching of Cooper ligaments and associated breast pain.

Etiologic factors are still inconclusive. The ingestion of foods and medications containing methylxanthines has been implicated through an inhibition of 3'5'-cyclic adenosine monophosphate (cAMP) phosphodiesterase and 3'5'-cyclic guanosine monophosphate (cGMP) phosphodiesterase. This inhibition will lead to accumulation of increased amounts of cAMP and cGMP. High levels of cAMP and cGMP have been detected in patients with fibrocystic change. In some studies, reduction of dietary methylxanthines has been associated with symptomatic subjective reduction in pain, tenderness, and palpable nodularity. Other studies, however, have failed to show an effect from decreased consumption of dietary methylxanthines.

Fibrocystic change is not a risk factor for cancer in the majority of women. Histologically, there are two changes noted with fibrocystic change: nonproliferative changes and proliferative changes. The nonproliferative changes include cystic changes with formation of microcysts (2 mm or less in size), macrocysts, and fibrosis.

Proliferative Changes

Proliferative changes include hyperplasia and adenosis. Hyperplasia is proliferation of ductal epithelium, which results in layering of the cells. Atypia may be associated with this proliferation. If atypia is noted, this confers a five fold increase in breast cancer risk for the patient. Hyperplasia with atypia is the only fibrocystic change associated with an increased risk factor for breast cancer. If atypia is noted on a core biopsy, a surgical excision of the area is recommended, as it is thought that there is a 50% chance of finding a coexistent carcinoma.

Adenosis is also a proliferative lesion, caused by changes in the acini in the distal mammary lobule. Sclerosing adenosis refers to the dense, fibrotic tissue surrounding these small ducts. These lesions may present as a palpable mass in women in their 30s and 40s.

A papilloma can result from this ductal proliferation. Papillomas are papillary lesions with a branching fibrovascular core surrounded by epithelium. These lesions are associated with serosanguineous nipple discharge in 25% to 50% of presentations. Ninety percent of the time, there is a small palpable mass adjacent to the areola. Intraductal papillomas are rarely associated with carcinoma, but require surgical excision to rule out the possibility of misdiagnosis of a malignancy.

Management of fibrocystic changes includes regular physical examinations, appropriate imaging, and supportive measures. Recommendations for use of a good support bra may be helpful, especially in physically active women. Dietary restrictions of methylxanthines may produce subjective improvement in 65% of patients. The use of vitamins A and E has been reported in some studies to be helpful. Diuretic therapy during the premenstrual period has been reported to provide temporary relief, and requires cyclical use. Fluid retention is a result of cyclical hormonal stimulation.

Oral contraceptives suppress symptoms of fibrocystic changes in the majority of patients (70%–90%). Symptoms often recur after discontinuation. Other medications such as danazol (17a-norethisterone) in doses of 100 to 400 mg per day should be reserved for patients in whom other agents have been ineffective. Their side-effect profile can lead to poor compliance. A 3- to 6-month course can provide significant reduction in symptoms, and its effect can last several months after its discontinuation.

Fibroadenoma

Fibroadenomas are benign fibroepithelial tumors and are the second most common benign lesion of the breast. They are the most common lesion found in women under the age of 25. They will persist during the menstrual years of a woman's life, but regression after menopause has been reported. Patients typically present with a mobile, smooth, painless, palpable mass. Ultrasound examination, along with physical examination, can help in making the diagnosis. Mammographically, fibroadenomas may appear as round, oval, or lobulated masses with circumscribed margins. In older women, they can have a rim of coarse calcifications. FNA will reveal benign ductal epithelial cells and elongated dense stromal cells. Microscopically fibrous tissue composes most of the fibroadenoma. Carcinoma arising in fibroadenomas is rare.

Fibroadenomas can be followed without the need for complete surgical excision. This can be achieved with physical examination or ultrasound examination if they are not palpable. However, surgical excision should be performed if:

- the mass continues to enlarge
- the results of FNA or core biopsy are inconclusive or yield atypia
- the patient desires surgical excision.

Phyllodes Tumor

Phyllodes tumors are uncommon, slow-growing fibroepithelial tumors. Previously referred to as cystosarcoma phyllodes, this name contributed to confusion in understanding this entity. Although very similar to a fibroadenoma, the stromal component is hypercellular with increased pleomorphism and mitotic activity. Phyllodes tumors can occur in women of any age, but more commonly occur in premenopausal women.

Malignant behavior in phyllodes tumors is rare in premenopausal women. Malignant phyllodes tumors are noted when there is a combination of increased mitotic activity, invasive borders, or marked pleomorphism. Incomplete excision is a major determinant for local recurrence. Treatment is total surgical excision with a wide margin of healthy tissue.

Superficial Thrombophlebitis

Superficial thrombophlebitis is also known as Mondor disease of the breast. It is an uncommon benign inflammatory process. It can occur spontaneously, but usually is associated with breast trauma, breast surgery, or pregnancy. It is a thrombophlebitis of the thoracoepigastric vein, which drains the upper-outer quadrant of the breast. Patients present with acute pain and a linear, tender fibrotic band with skin retraction over the distribution of the thoracoepigastric vein.

Treatment is conservative, with analgesics and application of heat. The condition resolves in 1 to 3 weeks. Skin retraction superficial to the area of inflammation can remain if the inflammation is extensive. Biopsy is not necessary.

Mastitis

Mastitis usually occurs in relation to lactation. It can occur in nonpuerperal periods in association with galac-torrhea. Skin organisms, *Staphylococcus aureus*, and *Streptococcus* species may cause infection of the nipple and breast ducts. Presence of milk in the ducts is an excellent medium for infection.

Women with mastitis may continue to breast-feed. Antibiotic therapy with dicloxacillin sodium (250 mg q.i.d.) or penicillin G is indicated. If there is no response, an abscess that may require surgical drainage must be excluded. Inflammatory carcinomas can mimic mastitis, and if no resolution of infection is noted despite continued antibiotics, a skin biopsy may be indicated.

Galactoceles are milk-filled cysts. They are usually tender and present after the abrupt termination of breast-feeding. Aspiration of the cyst is often necessary for symptomatic relief. If reaccumulation occurs, however, surgical excision may be required to avoid infection.

Duct Ectasia

Duct ectasia is a condition usually occurring in perimenopausal or postmenopausal women. Patients present with a tender, hard erythematous mass adjacent to the

areola in association with burning, itching, or a sensation of pulling in the nipple area. A thick greenish-black discharge may be present. Histologic evaluation of the area shows dilate, distended terminal collecting ducts obstructed with inspissated lipid-containing epithelial cells and phagocytic histiocytes. This process tends to occur in a segmental fashion extending from the involved nipple area to adjacent ducts. Occasionally, as a result of this infection, a small abscess forms at the base of the nipple. Treatment is excisional biopsy.

Younger women can present with inflammation of the ducts in the region of the nipple, which may produce fissures and fistulae with connection from the nipple ducts to the skin at the edges of the areola. Prior periductal mastitis leads to the squamous epithelium of the terminal dilated portion of the collecting ducts to undergo squamous metaplasia. Keratin is formed in the duct, accumulates, and can cause an abscess at the base of the nipple. Excision of the area usually is necessary.

Fat Necrosis

Fat necrosis is a relatively uncommon benign condition occurring as a response to breast trauma. Patients present with a hard mass that can mimic a carcinoma. The irregular mass is palpable and may involve skin retraction. Multiple calcifications can be seen on mammography.

The histology is active chronic inflammatory cells, with lymphocytes and histiocytes predominating. In the later stages, a collagenous scar is noted, with “oil cysts” or free lipid material released by lipocyte necrosis. Fat necrosis does not increase the risk of carcinoma, and its clinical importance is in the differential diagnosis of a carcinoma.

Nipple Discharge

Nipple discharge has been reported in 10% to 15% of women with benign breast disease and in 2.5% to 3.0% of those with carcinoma. The discharge is classified according to its appearance as milky, green, bloody, serous, cloudy, or purulent. The drainage should be classified according to whether it is unilateral, bilateral, or spontaneous, or recurrent. This information is obtained at the time of a thorough history and physical examination. For example, if the drainage first appeared in the patient's bra or nightgown on awakening, this finding is significant. The presence of a mass should also be investigated. The risk of cancer is increased when the discharge is unilateral from a single duct, occurs in a postmenopausal patient, or when a mass is present.

Unilateral, Spontaneous Nipple Discharge In cases of unilateral, spontaneous nipple discharge, several causes are included in the differential. The most common cause of nipple discharge is mammary-duct ectasia, which produces a multicolored (green, yellow, white, brown, gray, or reddish brown) nipple discharge. The reddish-brown discharge is often mistaken for a blood discharge. It is thought to be due to an increase in glandular secretions, with the production of an irritating lipid fluid that can produce a nipple discharge. Guaiac of the discharge can help to diagnose whether it is bloody. The next most common cause of a multicolored, sticky nipple discharge is nonpuerperal mastitis. The persistent type involves inflammation in deeper portions of the breast; the transient types are associated with periareolar inflammation. If the inflammation develops into an inflammatory mass, surgical excision and drainage are necessary. Medical management with local care, avoidance of all nipple manipulation, and nonsteroidal antiinflammatory agents and an antistaphylococcal antibiotic is often successful when infection is suspected. Bloody nipple discharge warrants surgical evaluation. Intraductal papillomas are the most common cause of bloody nipple discharge. During the breast examination, physicians should look for an associated periareolar mass. The examination consists of gently and carefully palpating the subareolar region to identify the pressure point that produces the discharge. It is important to reproduce the discharge and demonstrate the breast quadrant from which it emanates. All significant nipple discharges warrant referral for tissue biopsy. Although a mass is usually present when the discharge is due to cancer, there is no palpable mass in 13% of cancers with nipple secretions. Bloody discharge occurring in the third trimester of pregnancy however may be regarded as physiologic and does not require intervention unless persistent for several months after delivery. There are no contraindications to breast-feeding in these patients. In addition, physicians should not rely solely on the cytology of the discharge because there is an 18% false-negative rate and a 2.6% false-positive rate with standard cytology alone. Galactography (injecting radiopaque contrast into the discharging duct and then performing mammography) offers better visualization of small intraductal papillomas but cannot differentiate between benign and malignant lesions. A surgical procedure is still necessary. Mammography has a 9.5% false-negative rate and a 1.6% false-positive rate for detecting cancer in patients with a nipple discharge.

BREAST CANCER

Natural History

The most common site of origin of breast cancer is the upper-outer quadrant (38.5%), central area (29%), upper-inner quadrant (14.2%), lower-outer quadrant (8.8%), and the lower-inner quadrant (5%). These percentages correlate with the amount of tissue that is present in these quadrants. Metachronous bilateral carcinoma of the breast has been observed in 5% to 8% of patients.

Metastasis to the ipsilateral axilla is the most common route of spread. Metastasis to the internal mammary nodes is more frequent with inner-quadrant lesions and is more likely to occur when involvement of the axillary nodes is also present.

Pathology

Ductal Carcinoma in Situ Ductal carcinoma in situ (DCIS) is an abnormal proliferation of malignant epithelial cells within the mammary ductal–lobular system without invasion into the surrounding stroma. It is classified as a heterogenous group of lesions with different growth patterns and cytologic features. Classification of DCIS has traditionally been based on architectural pattern. The most common types are comedo, cribriform, micropapillary, papillary, and solid.
Paget's Disease Paget's disease is involvement of the nipple with intraductal carcinoma. In absence of a palpable mass, invasive carcinoma occurs in less than 40% of cases. The malignant cells are large and pale-staining and are seen in the basal layer and upper portions of the epidermis. Diagnosis is made through a nipple biopsy.
Lobular Carcinoma in Situ Foote and Stewart initially described lobular carcinoma in situ (LCIS) in 1941 as a noninvasive lesion arising from the lobules and terminal ducts of the breast. LCIS is characterized by a solid proliferation of small cells with round to oval nuclei that distort the involved spaces in the terminal duct–lobular units. Three important features of LCIS are:

1. It is usually an incidental microscopic finding that is not detected clinically or by gross pathologic examination.
2. It is multicentric, and the associated cancer may be ductal or lobular.
3. The risk for subsequent cancer is the same for both breasts.

It is unfortunate that Foote and Stewart chose the name they did, as it has led to a great deal of confusion over the past several decades. LCIS is a marker for breast cancer risk and is not a malignant finding.
Invasive Duct Carcinoma Invasive duct carcinoma is the most common group of malignant mammary tumors and comprises 65% to 80% of all mammary carcinomas. Included in this group are special subtypes: Tubular, medullary, metaplastic, mucinous (colloid) papillary, and adenoid cystic carcinoma. Each subtype constitutes only 1% to 2% of all invasive breast cancers, except medullary carcinoma, which constitutes 7%, and the rare adenoid cystic carcinomas, at less than 0.1%. Many of these subtypes, such as tubular and medullary carcinomas, carry an excellent prognosis. Metaplastic carcinomas, however, often have an aggressive behavior. These tumors are characterized by the presence of homologous (epithelial) or heterologous (mesenchymal) elements. Two types have been described: Squamous and pseudosarcomatous metaplasia. Invasive duct carcinoma not otherwise specified (NOS) is a generic term that includes tumors that may express more than one element of the specific forms of duct carcinoma.
Infiltrating Lobular Carcinoma Infiltrating lobular carcinoma has been reported to constitute 10% to 14% of invasive carcinomas. These carcinomas are characterized by uniform cells with small, round nuclei and limited cytoplasm. The presence of intracytoplasmic mucin vacuoles often gives the cells the appearance of signet-ring cells. The cells tend to grow circumferentially around ducts and lobules with a linear arrangement. This pattern is referred to as “Indian-file” or targetoid growth. There is often an associated desmoplastic stromal reaction.

Inflammatory Carcinoma

Inflammatory carcinoma is characterized by cutaneous findings present with an underlying invasive carcinoma. Usually the invasive tumor is a poorly differentiated infiltrating duct carcinoma. Upon microscopic evaluation, skin involvement often reveals tumor emboli in dermal lymphatics with an associated lymphocytic reaction in the dermis.

Metastases from Extramammary Tumors

The most common primary site of an occult extramammary tumor is the lung. Other primary sites include the ovaries, uterus, kidneys, and stomach. In those previously diagnosed, melanoma, prostate, cervix, uterus, and urinary bladder are the most common sites. Metastatic ovarian cancer may simulate papillary or mucinous

carcinoma of the breast. A workup and history are often helpful in difficult cases. Often, identification of an in situ component helps to provide definitive evidence of a mammary origin.

Biologic Markers/Prognostic Factors

Axillary Lymph Node Status The most important prognostic factor is nodal status. The presence of metastasis, as well as the number of lymph nodes involved, is significant and correlates with local failure and distant metastases. It is predictive of overall survival.
Tumor Size Tumor size correlates with the incidence of lymph node metastases. The size of the tumor is also important, even in the absence of lymph node involvement. Patients with tumors less than 1 cm in size, or with good histologic types measuring less than 3 cm, do very well.
Histologic Grade Histologic grade also correlates with breast cancer outcome. Poorly differentiated tumors have been associated with more aggressive behavior.
Estrogen Receptors/Progesterone Receptors The hormone receptors can be measured by immunohistochemical (IHC) studies using monoclonal antibodies directed against the receptors. Positivity correlates with response to antihormonal agents as well as better prognosis.
HER2/neu HER2/ *neu* is an oncogene whose protein product may function as a growth factor receptor. It can be detected by IHC demonstration of the protein product or by gene amplifications. Overexpression or amplification has been shown to correlate with a poor prognosis; however, the studies differ with regard to the method of detection used, as well as the interpretation of results. HER2/ *neu* has been used as a predictor of response to certain chemotherapeutic agents. Particularly, increased-response, doxorubicin-based therapy has been reported in the treatment of patients with positive nodes and overexpression of HER2/ *neu*. Herceptin (trastuzumab) is a humanized anti-HER2 antibody against the extracellular domain of the 2-neu oncoprotein. Its use in the metastatic setting has been reported to demonstrate an increase in response rate and prolongation of disease-free and overall survival.
p53 A tumor-suppressor gene, *p53* has a protein product that is a nuclear transcription factor with many functions, including regulation of the cell cycle and apoptosis. Most clinical studies have used IHC to study protein expression. Accumulation of p53 protein has been reported to correlate with reduced survival in some studies.

STAGING OF BREAST CANCER

Staging of Breast Cancer Using the Tumor–Node–Metastasis (TNM) System

The American Joint Committee on Cancer (AJCC) determines staging of breast cancer. The AJCC staging system is a clinical and pathologic staging system based on the tumor–node–metastasis (TNM) system. The new updated AJCC staging system (2002) incorporates sentinel node staging. It distinguishes micrometastasis from isolated tumor cells on the basis of size and histologic evidence of malignant activity. In the current AJCC staging system, supraclavicular lymph node metastasis is now classified as N3 disease, rather than M1 disease, as in the old system (Table 50.7, Table 50.8).

TABLE 50.7. *American Joint Committee on Cancer Staging for breast cancer*

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mic.
Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within four months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

TABLE 50.8. *Stage by tumor, node, metastasis (TNM)*

TREATMENT OF BREAST CANCER

Mastectomy

William Halsted performed a radical mastectomy in 1894. The guiding principle at this time was centered on the belief that cancer originates in the breast and spreads in a stepwise fashion first to the regional lymph nodes, and then to distant sites. Removal of all the breast tissue, pectoral muscles, and axillary contents was the standard surgical treatment. Over the next several decades, two simultaneous trends existed. One involved less-radical surgery, which included removal of the breast and axillary contents, but preserved the pectoral muscles and more skin. This was described by Patey and Dyson in 1948, and is the modern-day modified radical mastectomy. The other trend involved more extensive surgery, the extended radical mastectomy, which included en-bloc removal of the internal mammary chain at the time of radical mastectomy. Subsequent randomized trials failed to show a survival advantage with the extended radical mastectomy when compared with the radical mastectomy.

Breast-Conservation Therapy

The shift toward less radical surgery at the time of mastectomy occurred for several reasons. As earlier diagnosis of breast cancer with smaller tumors and less involvement of pectoral muscles occurred, the need for radical procedures decreased. In addition, even with radical mastectomy not all patients were cured, and although regional recurrences were low, patients died of distant disease. The morbidity of the radical mastectomy was well documented, including lymphedema, immobility of the shoulder, and disfigurement. A shift to breast conservation followed the same trends. The initial trials with radiation therapy using radium implants at the Princess Margaret Hospital in Toronto had promising results.

This led to randomization studies comparing breast-conservation therapy with mastectomy. Table 50.9 lists randomized trials that compared radical and modified radical mastectomy in stage I and stage II carcinoma of the breast.

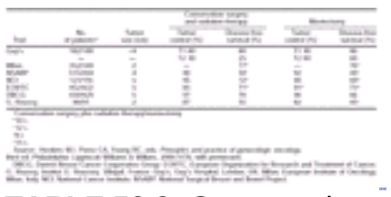

TABLE 50.9. *Conservation surgery and irradiation in Stage I and II carcinoma of the breast: Results of randomized comparisons with radical or modified mastectomy*

In breast-conserving surgery, a wide local excision is performed with excision of the tumor and a 1- to 2-cm rim of normal tissue. This excision is referred to as “lumpectomy” or a “tumorectomy.” This differs from a quadrantectomy, in which a resection of the tumor with the overlying skin and the involved quadrant of the breast is performed. The six randomized trials differed with respect to the type of wide local excision performed as well as tumor size in the patients who were randomized. In the Milan trial, a quadrantectomy was performed. In the Insitut Gustave Roussy trial, the “tumorectomy” performed was removal of the tumor and a 2-cm margin of normal tissue. In the United States, the NSABP B-06 trial did not specify the margins on the lumpectomy specimen, providing they were grossly free of tumor.

In all trials, the authors noted comparable disease-free survival in both arms. The only difference noted was in local recurrence. In addition to the randomized trials, there are many nonrandomized reports published with similar results in survival between breast conservation and mastectomy.

Radiation therapy is an important component of breast conservation. Adequate surgical margins are required to be negative on pathologic inspection. After healing, the radiation therapy is planned. Treatment to the entire breast should be at a dose of 1.8 to 2.0 Gy per day for a total of 45 to 50 Gy. A 10- to 15-Gy electron-therapy boost is often given to the lumpectomy bed.

Breast conservation depends on the use of radiation. The question of whether lumpectomy alone would yield similar results has been addressed through randomized trials. Local recurrence rates of 18% to 40% with lumpectomy alone have been reported compared with 2% to 14% with lumpectomy and radiation. In these studies, a significant reduction in relapse was noted in the lumpectomy-and-radiation arm.

The NSABP B-17 trial is the only randomized trial of lumpectomy alone versus lumpectomy and radiation in patients with DCIS. Ipsilateral relapse was 7% in the radiation arm versus 16.4% in the lumpectomy-alone arm. Actuarial 5-year survival showed an ipsilateral recurrence rate of 7.5% for noninvasive and 2.9% for invasive recurrence in the lumpectomy-plus-radiation arm. By comparison, the rates were 10.4% and 10.5%, respectively, in the lumpectomy-alone arm. The overall survival was excellent and comparable to that seen with mastectomy. In cases of invasive recurrence, patients in the lumpectomy-plus-radiation arm can be salvaged with mastectomy.

Patient Selection

Possible contraindications can interfere with offering a patient breast-conservation therapy. Cosmetic result should be considered when deciding whether to offer breast-conserving surgery; tumor size in relation to breast size is an important consideration. In addition, other factors that may affect the ability to receive irradiation must be considered (i.e., history of prior breast or chest irradiation, concurrent pregnancy, autoimmune connective-tissue disease). Particularly with a history of systemic lupus erythematosis, radiation may not be a possibility. Women with multiple cancers in the breast are not candidates for this approach and require a mastectomy. In addition, in patients with extensive calcifications on a mammogram suggesting a diffuse process may be better treated with mastectomy.

An area of controversy remains over the status of negative margins at the time of lumpectomy. Generally a reexcision should be performed. Extensive intraductal component (EIC) is a condition that exists when greater than 25% of the tumor is associated with DCIS. In these cases, the invasive component may be outside the area of the intraductal carcinoma. This has been reported to have a higher relapse rate with breast conservation; however, it is thought to be secondary to margin status, since margin involvement may be an indication of residual intraductal carcinoma. In DCIS, Silverstein and associates developed the Van Nuys prognostic index (VNPI). The system combines the scores for histologic grade, tumor size, and margin status of a lesion in order to obtain an overall score. It considers margins of 1 cm to indicate a decreased rate of local relapse, even with no radiation.

Management of the Axilla

The axilla is a pyramidal space between the arm and thoracic wall. It contains the axillary vessels and their branches, the brachial plexus and its branches, and lymph nodes embedded in fatty tissue. The primary route of lymphatic drainage of the breast is through the axillary lymph nodes. The lymph nodes are also divided into levels based on location relative to the pectoralis minor. Level 1 lymph nodes lie lateral to the lateral border of the pectoralis minor muscle. Level 2 nodes lie behind the pectoralis minor muscle, and level 3 nodes are medial to the medial border of this muscle.

In an axillary dissection, nerve branches of the brachial plexus are encountered. The lateral and medial pectoral nerves supply the pectoralis muscles. The thoracodorsal nerve runs downward, and innervates the latissimus dorsi. The long thoracic nerve is located on the medial wall of the axilla on the serratus anterior. It arises from the C5 to C7 roots, and injury to these nerves results in paralysis to part or all of the serratus anterior. The functional deficit is inability to raise the arm above the level of the shoulder.

At the time of Halsted's radical mastectomy procedure, a complete axillary dissection was performed. The status of the axilla is the most important prognostic factor for breast cancer. The use of axillary dissection has, in the past, been demonstrated to significantly decrease local recurrence, which may ultimately translate to a survival advantage.

Clinical examination of the axilla is inaccurate, since even in patients with a T1 lesion, there is a 10% risk of lymph node metastasis. Prior to the use of sentinel lymph node biopsy, there was no accurate method to adequately stage the axilla without an axillary dissection. Axillary lymph node sampling (i.e., removal of only a few lymph nodes) was inadequate.

Metastatic involvement of lymph nodes usually occurs in a stepwise manner. Rosen and co-workers demonstrated the incidence of ?skip metastasis? to be less than 2%. A complete level 1 and 2 lymph node dissection provides excellent local control, and local recurrence after this procedure has been shown to be less than 1%. The NSABP B-04 trial randomized patients with clinically negative nodes to one of three groups: radical mastectomy, total mastectomy with nodal irradiation, or total mastectomy alone. The patients who had no axillary nodal therapy had an overall worse survival if recurrence occurred.

The morbidity associated with axillary lymphadenectomy is not inconsequential. About 10% to 15% of patients will develop lymphedema. In addition, numbness, pain, or weakness contribute to a significant decrease in the quality of life in these patients.

Sentinel Lymph Node Biopsy Sentinel lymph node (SLN) biopsy in breast cancer evolved out of efforts to minimize the morbidity associated with axillary lymph node dissection while still providing important staging information. Initial studies in melanoma, by Morton and colleagues in 1992, demonstrated the feasibility of the concept. Methods employed include use of blue dye or radioisotope (Fig. 50.5).

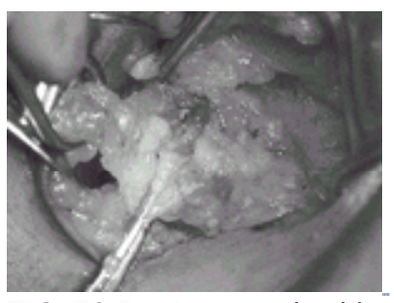

FIG. 50.5. Intraoperative identification of the sentinel lymph node.

Several studies have confirmed the accuracy of SLN biopsy. In the majority of the studies, successful identification of the SLN occurs between 92% and 98% of the time. The combination of blue dye and isotope has been reported to be better for identification of the SLN; when used in combination, the positive predictive value of the technique approaches 100%, with a negative predictive value close to 95%. The false-negative rate is about 5% to 10% in most studies. The validity of the SLN concept lies in the ability of the SLN to predict the status of the regional lymphatic basin. Turner and colleagues performed IHC staining of all lymph nodes, sentinel and nonsentinel, in a series of patients undergoing standard axillary dissection with negative nodes. Of 157 SLNs, 10 (6%) demonstrated IHC positivity compared with 1 of 1,087 (0.09%) of the non-SLNs. This provided validity of the SLN concept. Overall, greater scrutiny is paid to SLNs through serial sectioning and IHC stains. This is

possible because only a few SLNs are obtained at the time of the procedure, and would not be cost-effective in a standard axillary dissection that yields an average of 20 nodes. The use of the SLN biopsy procedure is widely employed in invasive breast cancer. In certain situations, however, a standard axillary dissection should still be considered. These include:

- in cases of palpable suspicious nodes
- in cases of large lesions (the majority of reports indicate that the procedure is reliable if there are no suspicious nodes in the axilla)
- in cases of prior radiation, of a large excisional cavity close to the axilla, or any condition in which disruption of the lymphatics is suspected.

Systemic Treatment

Adjuvant treatment in breast cancer was first used over 100 years ago. In 1894, Beatson reported on the results of oophorectomy and response rate in the metastatic breast cancer setting. Initially, the use of systemic therapy involved the use of single-agent chemotherapy; later, multi-agent chemotherapy was employed. As in most breast cancer trials, the initial reports were of patients with metastatic disease.

Multiple randomized studies have demonstrated that the addition of chemotherapy improves overall survival in patients with breast cancer. The decision to use adjuvant chemotherapy or hormonal therapy depends on certain factors such as the size of the primary tumor, lymph node status, and the presence or absence of metastatic disease. In addition, the expression or lack of expression of ER or PR (ER/PR status) is also an important factor.

Adjuvant chemotherapy is standard treatment for patients with positive nodes or large tumors. The combination of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil [5-FU]) has been used for many years in the treatment of patients with breast cancer. An anthracycline-based regimen such as FAC (5-FU, adriamycin, and cyclophosphamide) has been used in patients with high risk factors for recurrence. The use of paclitaxel is also considered in this setting. For patients with intermediate risk factors, such as ER-negative tumors (>1 cm in size) and negative nodes, chemotherapy is considered.

The Early Breast Cancer Trialists' Collaborative Group was formed in 1985 to analyze all available, properly conducted, randomized trials. A second overview was done in 1990, and a third in 1995. In women under the age of 50, administration of multi-agent chemotherapy decreased the annual risk of relapse by 35% and mortality by 27%. With 10 years of follow-up, this translates into absolute gains of 7% in patients with node-negative tumors and 11% in those with node-positive tumors. For women over the age of 50 years, the benefits of chemotherapy were smaller but still significant. Annual risk reduction was 20% for recurrence and 11% for mortality. At 10 years of follow-up, this risk reduction translated into absolute gains of 2% in patients with node-negative tumors and 3% in patients with node-positive tumors. It is important to note that in the overview, different regimens of CMF were used; but the greatest benefit was seen in those using CMF for 6 months or longer.

The question of whether to use CMF or FAC in high-risk patients (tumors = 2 cm in size or ER/PR-negative with negative nodes) has been addressed. While the anthracycline regimen is more toxic than CMF, trials have shown superiority with this regimen. Presently, other factors are used to determine which regimen to recommend in this subgroup. The most promising candidate factor is HER2/ *neu* overexpression because increased response rates with an anthracycline-based therapy have been reported in cases where there is overexpression of HER2/ *neu*.

The use of taxanes such as docetaxel and paclitaxel as adjuvant treatment in combination with anthracycline-based chemotherapy is being investigated. Postmenopausal women with negative nodes and ER-negative tumors greater than 1 cm in size are also considered for chemotherapy. In these patients, CMF is usually the treatment of choice.

Metastatic Disease

The goal of therapy in metastatic disease is palliation of symptoms, as cure is unlikely. The majority of patients with metastatic disease receive antihormonal therapy. First-line agents include tamoxifen, or aromatase inhibitors such as letrozole or anastrozole. These agents offer a 20% response with in ER/PR-positive tumors. Disease stabilization is the goal of therapy, and because these therapies are less toxic than chemotherapy, most patients will remain on them for prolonged periods of time. Upon failure of these agents, however, chemotherapy is the next step.

High-Dose Chemotherapy

Five large randomized trials have been conducted addressing the use of high-dose chemotherapy with bone-marrow or stem-cell rescue in metastatic breast cancer. Only one trial, conducted in South Africa, showed a lower rate of relapse. The other four trials showed no increase in overall survival. The investigators of the trial conducted in South Africa subsequently admitted to fraud. Thus, it is felt that high-dose chemotherapy offers no survival advantage over conventional treatment approaches.

Neoadjuvant Chemotherapy

Preoperative or neoadjuvant chemotherapy is attractive, as it may reduce the amount of disease present and thereby facilitate in obtaining clean surgical margins when the disease is still confined to the breast. This is often the case in inflammatory breast cancer, or in N2 disease, in which neoadjuvant chemotherapy may improve surgical resectability. A significant response of 50% to 90% has been seen with this approach.

Down-staging of the tumor, as well as the axillary lymph nodes, has been reported.

The NSABP B-18 trial randomized patients with operable breast cancer to receive adjuvant chemotherapy preoperatively for four cycles followed by reevaluation for surgical treatment. Results for this group were compared with those for patients who received surgery followed by adjuvant chemotherapy. Preoperative chemotherapy was associated with a higher incidence of breast conservation. Also, a significant reduction in the number of positive axillary nodes was noted in the preoperative chemotherapy group. There was, however, no difference in overall survival between those patients who received preoperative chemotherapy and those who received postoperative chemotherapy. Several subsequent trials have reported a higher local recurrence rate for patients treated with neoadjuvant chemotherapy and breast-conservation therapy.

Radiation Therapy

Radiation therapy is used in conjunction with lumpectomy for patients opting for breast conservation. The dose used is 1.8 to 2.0 Gy per day for a total of 45 to 50 Gy to the entire breast. A 10- to 15-Gy electron-therapy boost is often given to the lumpectomy bed.

Postmastectomy chest-wall irradiation is used with increasing frequency. Patients with large tumors (T3 lesions) and more than four positive nodes are offered chest-wall radiation because they are at risk for local–regional failure. Chest-wall radiation is 50 Gy over 5 weeks, with a 10-Gy boost to the mastectomy scar. For patients with a chest-wall recurrence, the option of surgical debulking followed by chest-wall irradiation is employed.

Radiation therapy can also be used in the palliative setting. It can be used for metastatic lesions to the bone or brain and can help to alleviate the patient's symptoms.

Stage-Directed Therapy

Patients with intraductal carcinoma and stage I and stage II breast cancer have the options of breast-conservation therapy and mastectomy.

For patients with invasive breast cancer, the axillary nodes can be addressed with an SLN biopsy and, possibly, an axillary dissection.

In intraductal carcinoma, an SLN biopsy or axillary dissection is generally not indicated. There are special circumstances of intraductal carcinoma such as high-grade DCIS or extensive DCIS in which a microinvasive component may be associated with the intraductal carcinoma. In these circumstances, particularly if a mastectomy is being performed, an SLN biopsy may be considered.

For patients with more extensive disease, a mastectomy may be necessary. The use of postmastectomy chest-wall irradiation in these patients may also be considered.

Breast Reconstruction

Breast reconstruction represents a major advance in cancer rehabilitation for patients undergoing a mastectomy. Previously, a 2-year surveillance period was recommended prior to reconstruction for detection of local disease recurrence. Immediate reconstruction has not interfered with disease detection, however, and it has the advantage of combining the two procedures into one. In addition, a greater amount of skin can be saved with planned immediate reconstruction, and the scar tissue that would be encountered with delayed procedure can be avoided.

A delayed reconstruction can be performed if the patient is ambiguous about the reconstruction, or if operative risk is increased with prolonged anesthesia. It is also considered in those patients with locally advanced disease if a delay in adjuvant irradiation or chemotherapy is anticipated because of the reconstruction.

Reconstruction options include expandable breast prosthesis (implant) and autologous tissue transfer. Tissue-transfer operations may yield the greatest symmetry between breasts, especially with larger breasts; however, they take longer, require greater surgical expertise, involve a longer recovery, and result in another scar at the donor site. The donor site may be the latissimus dorsi, transverse rectus abdominus, or gluteal muscle.

SPECIAL ISSUES

Hereditary Breast Cancer

One of the most characteristic features of hereditary breast cancer is its tendency to manifest at a young age. In the Breast Cancer Consortium's study of *BRCA1*-linked families that transmit *BRCA1* mutations, more than 80% of breast cancers occurred in women under 50 years of age.

Pathologic Features Most *BRCA1*-associated breast cancers have been reported to be of an infiltrating ductal type with an over-representation of poorly differentiated high-grade types. The tumors tend to be ER/PR-negative. Less than 20% of these cancers are ER/PR-positive, even when age matched with non– *BRCA1*-associated controls. In *BRCA2* there is less of this over-representation of aggressive histology. Overall, *BRCA2*-associated breast cancers tend to be ER/PR-positive.
Stage Most studies demonstrate that *BRCA*-associated breast cancers are seen at a stage comparable to non– *BRCA*-associated breast cancers. The incidence of axillary metastasis does not appear to be significantly different in patients with *BRCA*-associated breast cancers. In the literature, conflicting study data exist regarding the prognosis of patients with *BRCA*-associated breast cancer. Some studies have conferred a worse prognosis in patients with certain mutations in *BRCA1*. Some of these reports have been of highly selected groups of women, and thus further study is necessary in larger series of women with *BRCA1* and *BRCA2* mutations.
Treatment Although some researchers have questioned the role of breast-conservation therapy in women with hereditary predisposition, there is no reason to suspect a unique survival advantage for mastectomy in these women. Studies that have examined the outcomes of breast-conservation therapy in women with *BRCA* mutations are small with variable follow-up. Local ipsilateral recurrence appears to be about 15% at 5 years. Although this is higher than would be expected for patients treated with breast-conservation therapy, it is within the range observed for treatment of young women with breast cancer. It is likely to be an influence of the age at diagnosis and not because of radiation resistance. After breast-conservation therapy, however, the breast tissue remains at risk for developing a second primary. Women with *BRCA* mutations may be at risk for a late ipsilateral recurrence because of the development of a second primary breast cancer. The degree of contralateral risk needs to also be addressed with patients. Some studies have reported an estimated average risk of 2.5% to 5% per year in *BRCA1* mutation carriers, and this risk may be higher with younger age at diagnosis. In patients with *BRCA2*, the risk appears lower, estimated at 1.8% per year. Unlike the *BRCA1*-associated risk, in *BRCA2* the age dependence is unknown.

Chemoprevention

Chemoprevention is the principle that cancer prevention can be achieved through pharmacologic intervention. It refers to the use of a medication in a healthy patient to reduce the risk of a particular cancer. It is an option for all women with significant risk for future breast cancer development. Currently, the only FDA-approved medication for prevention of breast cancer is tamoxifen. Tamoxifen is a selective estrogen-receptor modulator that acts as an antiestrogen in breast tissue. It has been used in the adjuvant setting in breast cancer since 1972 for both metastatic and early breast cancers. A reduction of 40% to 50% in contralateral breast cancer was seen in the adjuvant setting; thus, it was thought to be an ideal agent to use in a chemopreventive setting.

The trial to determine the role of tamoxifen in chemoprevention was performed by the NSABP. In this randomized, double-blinded trial, women with a projected risk of breast cancer of greater than 1.66% over a 5-year period received either tamoxifen or a placebo for a period of 5 years. The Gail model was used to assess the risk. When an independent reviewing agency verified a 50% reduction in both invasive and noninvasive breast cancer cases in the population taking tamoxifen, the trial results were unblinded earlier than expected. Shortly thereafter, the use of tamoxifen was approved for chemoprevention.

Two other chemoprevention trials using tamoxifen have been reported: the Italian tamoxifen-prevention study and the Royal Marsden Hospital tamoxifen trial in the United Kingdom. These two trials did not reveal a statistically significant reduction in breast cancer risk in women randomized to tamoxifen. However, the studies differed in respect to subject numbers, median age, eligibility criteria, risk, and use of HRT.

Raloxifene is also a selective estrogen-receptor modulator (SERM) and is FDA-approved for use in osteoporosis. In studies in which raloxifene was used for treatment of osteoporosis, a secondary finding was a noted reduction of breast cancer risk of 50% to 70% in the population taking the medication. The women in those trials were at fairly low risk of breast cancer development. A randomized, double-blinded trial to compare raloxifene with tamoxifen in a population of postmenopausal women at increased risk for breast cancer development is currently open, the Study of Tamoxifen and Raloxifene (STAR) trial/P-2 study. In the NASBP P-1 study there was an increased risk of developing endometrial cancer with tamoxifen use (annual risk 2.3/1,000 women vs. 0.9/1,000 women in the placebo group). All cases of endometrial cancer in the patients taking tamoxifen were early stage. Another important side effect noted was a higher incidence of thromboembolic phenomena. Raloxifene does not increase the risk of endometrial cancer and thus may prove to be an alternative to tamoxifen in a chemopreventive role. An ideal SERM would have an antiestrogenic activity on breast and uterine tissues, but estrogenic effects on bone and the cardiovascular system among others. Current investigations into other SERMs are being conducted.

CONCLUSIONS

Screening for breast cancer is clearly indicated for all women at the appropriate age. Determining a woman's unique risk factors will help to determine both the age at which that screening should begin and also the intensity of that screening. It will also help to identify those women who need to be counseled regarding options for prevention of breast cancer. The hope is that, by correctly identifying high-risk populations and then applying appropriate screening schedules and chemopreventive agents, many cases of breast cancers will be averted completely and that those that still occur will be found at the earliest stages. The role of the obstetrician and gynecologist in providing information on breast cancer diagnosis and screening is very important.

In addition, the understanding of breast disease, benign and malignant, is crucial not only in the diagnosis of disease, but also in helping to guide women in their treatment and follow-up.

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Chapter 51

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Vulvar and Vaginal Cancer

VULVAR CARCINOMA IN SITU
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VAGINAL CARCINOMA
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Vaginal Cancer

Vulvar and vaginal cancer represent uncommon gynecologic cancers that occur most often in older women. Squamous lesions are the most frequent histology and risk factors are similar for both disease sites. This chapter describes the epidemiology, clinical presentation, patterns of spread, and treatment of squamous cell carcinomas of the vulva and vagina. Less common histologic subtypes including Paget disease, melanoma, adenocarcinomas, and sarcomas are also reviewed.

VULVAR CARCINOMA IN SITU

Vulvar carcinoma theoretically results from malignant transformation of a vulvar carcinoma in situ as is seen with cervical squamous lesions. Unlike squamous lesions of the cervix, the natural history of vulvar intraepithelial neoplasia (VIN) is less well understood. The incidence of vulvar dysplasia has increased over the last 20 years, particularly among younger women. A report from Austria demonstrated a 307% increase in the overall incidence of high-grade VIN and a 394% increase among women under 50 years of age between 1985 and 1998. In a review of Surveillance, Epidemiology, and End Results (SEER) data, Sturgeon found that the incidence of VIN III nearly doubled between 1973 and 1976 and 1985 and 1987, from 1.1 to 2.1 per 100,000 woman years. Factors implicated in this increase include increased human papillomavirus (HPV) infection, increased surveillance, tobacco use, and immunosuppression, either with human immunodeficiency virus (HIV), organ transplant, or diabetes.

Patients with VIN most commonly present with pruritis and vulvar lesions. These lesions may appear scaly, white, red, or hyperpigmented (Fig. 51.1, Fig. 51.2, Fig. 51.3 and Fig. 51.4). Careful inspection with 5% acetic acid and liberal use of punch biopsy are the cornerstones of diagnosis. An underlying malignancy may be present in 7% to 22% of patients who undergo surgical excision for vulvar carcinoma in situ. Wide local excision with at least a 5-mm margin is the preferred management option as it allows pathologic confirmation and is associated with less morbidity than skinning vulvectomy. Skinning vulvectomy with split thickness skin graft may be an option in patients with widespread disease. Laser ablation is also an effective nonmutilating option in patients with multifocal or clitoral disease. Recurrences are frequent (10%–50%) despite negative surgical margins and therapy should be tailored to symptom control and ruling out underlying malignancy. Patients should be followed every few months with careful visual inspection of the vulva and taught self-exam skills as well.

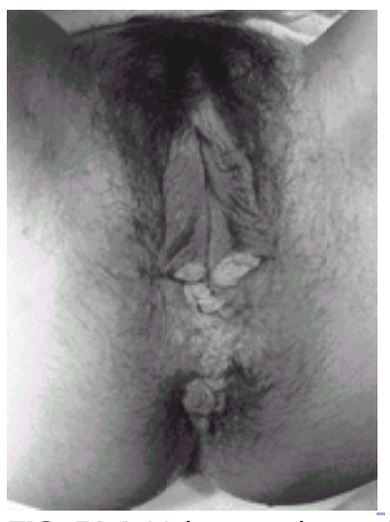

FIG. 51.1. Vulvar carcinoma in situ presenting as white or hyperpigmented lesion. See color figure 51.1.

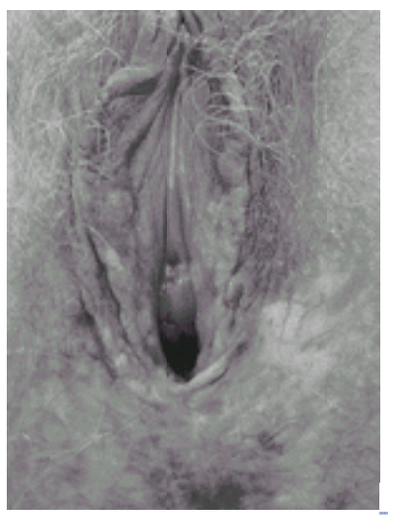

FIG. 51.2. Vulvar carcinoma in situ before application of 5% acetic acid. See color figure 51.2.

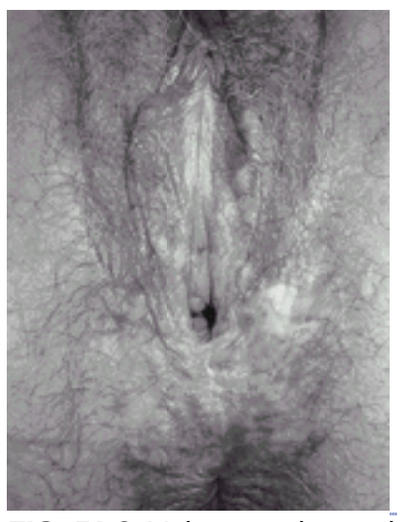

FIG. 51.3. Vulvar carcinoma in situ after application of 5% acetic acid. See color figure 51.3.

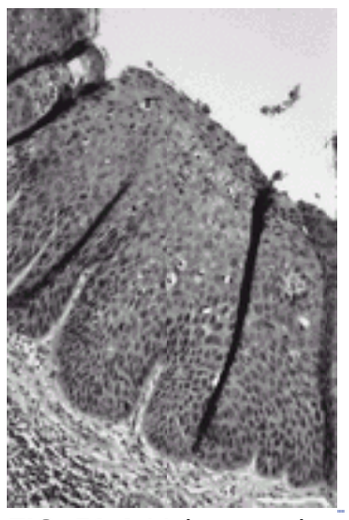

FIG. 51.4. Vulvar carcinoma in situ with full thickness involvement of dysplastic cells.

Epidemiology

Vulvar carcinoma is the fourth most common genital tract malignancy in women, representing 3% to 5% of gynecologic malignancies and affecting an estimated 3,600 women in the United States in 2001. The majority of cancers are squamous in origin with occasional cases of basal cell carcinoma, melanoma, adenocarcinoma, and Paget disease.

Vulvar cancer tends to be a disease of older women with a mean age at diagnosis of approximately 65 years. As the population ages, more older women will be at risk for vulvar carcinoma. Evidence exists that there are two distinct types of vulvar carcinoma with different etiologies. Tumors in older women are often unifocal and may be associated with chronic vulvar inflammation of long-standing duration such as lichen sclerosus or hyperplastic dystrophy. These keratinizing squamous cell carcinomas have associated HPV changes in only 6% of cases. While retrospective studies indicate that up to 50% of vulvar carcinomas are related to hyperplastic dystrophies and lichen sclerosus, prospective studies have demonstrated only 5% of women with vulvar dystrophies develop invasive carcinoma. Cancers found in younger women tend to be multifocal with adjacent VIN and have a basaloid or warty histology. Nearly 90% are associated with HPV infection, particularly HPV 16. Thirty-eight percent of women with HPV-associated lesions in a series by Trimble and colleagues were under age 55, compared with only 17% of those with classic keratinizing squamous cancers. Other associated risk factors include immunosuppression from chronic steroid use, diabetes or HIV, smoking, and a history of other lower genital tract dysplasia or neoplasia.

Presentation

Most women present with pruritis and an identifiable lesion (Fig. 51.5, Fig. 51.6). Less common symptoms include pain and bleeding. Unfortunately, there is often a delay of many years between onset of symptoms and diagnosis. This is in part because patients self-medicate with a variety of over-the-counter preparations rather than seeking care and also because physicians may not biopsy liberally. The cornerstone for diagnosis of vulvar malignancy is a low threshold for a punch biopsy as it may be extremely difficult to distinguish between dysplasia, chronic vulvar dystrophy, and carcinoma. Any patient with symptoms lasting for longer than 2 weeks deserves a thorough exam and a biopsy. In order to adequately evaluate a patient with a vulvar lesion, 5% acetic acid is applied to the vulva for 5 minutes and then the area is examined either with the naked eye or a handheld magnifying glass. The entire vulva including the hair-bearing, perianal, and periclitoral regions should be examined for suspicious ulcerations and hyperpigmented, acetowhite, or gross warty lesions. Up to 5% of patients will have multifocal disease and may require multiple punch biopsies.

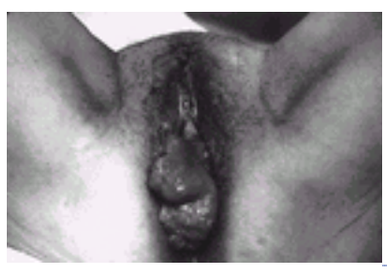

FIG. 51.5. Exophytic vulvar carcinoma involving posterior fourchette.

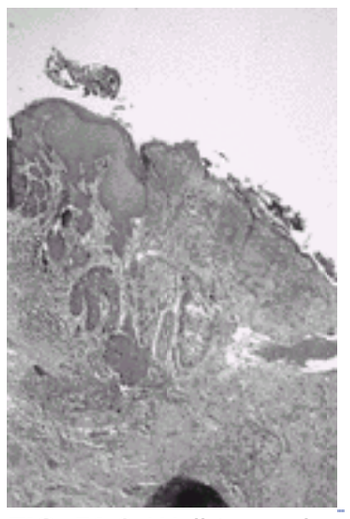

FIG. 51.6. Well-to-moderately differentiated invasive squamous cell carcinoma of the vulva.

Staging/Spread Patterns

An International Federation of Gynecologists and Obstetricians (FIGO) surgical classification system replaced clinical staging for vulvar cancer in 1989 (Table 51.1). By relying on histopathologic classification of the lymph nodes, the new system more accurately reflects prognosis since the previous system provided an inaccurate assessment of groin node involvement in one-fourth of cases.

Stage 0	Carcinoma in situ, intraepithelial neoplasia grade III
Stage I	Lesions ≤ 2 cm in size (T1), confined to the vulva or perineum, no nodal metastasis
Ia	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis
Ib	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion >1.0 mm, no nodal metastasis
Stage II	Tumor confined to the vulva or perineum; >2 cm in greatest dimension (T2); no nodal metastasis
Stage III	Tumor of any size with adjacent spread to the lower urethra or vagina, the anus, or unilateral regional lymph node metastasis
Stage IVa	Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone, or bilateral regional node metastases
Stage IVb	Any distant metastasis including pelvic lymph nodes

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 51.1. *Vulvar carcinoma: FIGO staging 1994*

Local spread occurs to contiguous structures such as the vagina, urethra, and rectum. Metastatic spread via lymphatics is common and has been well characterized by anatomic studies. Ipsilateral lesions tend to be characterized by spread to the ipsilateral groin nodes first, followed by contralateral groin, and then pelvic nodes. Lesions that cross the midline may have lymphatic drainage to both groins. Metastasis to the contralateral groin or pelvic nodes is highly unusual in the absence of ipsilateral groin node involvement. The superficial inguinal nodes above the cribriform fascia are believed to be involved prior to the deep femoral nodes below the cribriform fascia. Risk of lymphatic spread is related to tumor size, tumor thickness, older patient age, tumor grade, presence of lymphovascular space invasion, and clinically suspicious groin nodes. Groin node metastasis was found in 19% of patients with lesions =2 cm and in 42% of patients with lesions greater than 2 cm. The Gynecologic Oncology Group (GOG) surgicopathologic staging analysis demonstrated that lymph node dissection could be safely omitted in patients with less than 1 mm of stromal invasion. Hematogenous metastasis to distant organs such as bone, liver, and lungs is rare as a primary event but may be seen in patients with recurrent disease.

Treatment

Historically vulvar cancer has been treated with en-bloc radical vulvectomy and bilateral inguinofemoral lymphadenectomy or “longhorn incision” (Fig. 51.7, Fig. 51.8 and Fig. 51.9). This technique resulted in a median hospitalization of 30 days, 70% to 90% wound breakdown, and chronic debilitating lymphedema in nearly 9% of women. Significant disruption in self-image and sexual function also occurred. Attempts to decrease morbidity first led to the use of separate incisions for groin node dissection while continuing to use radical vulvectomy. In 1981, Hacker and colleagues reported a series of 100 patients who underwent radical vulvectomy and lymphadenectomy through three separate incisions. The incidence of major wound breakdown was only 14% with a mean hospitalization shortened to 19 days. This procedure lead to the shortest length of hospitalization reported at that time and produced a dramatic decrease in complications. The majority of local recurrences were salvaged with repeat excision. Overall survival was not compromised by deviating from en-bloc dissection and the authors concluded that this technique is appropriate for patients with stage I and II vulvar carcinoma.

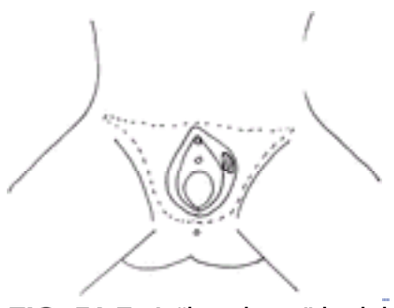

FIG. 51.7. A “longhorn” incision. Radical excision of the vulva from genitocrural fold to genitocrural fold, deep to the inferior fascia of the urogenital diaphragm along with en-bloc lymphadenectomy.

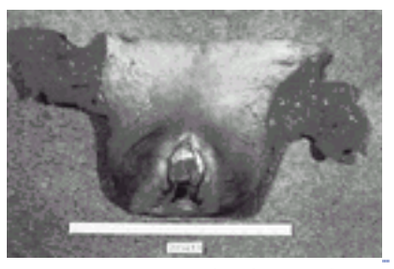

FIG. 51.8. Surgical specimen after en-bloc radical vulvectomy and inguinofemoral lymphadenectomy via longhorn incision.

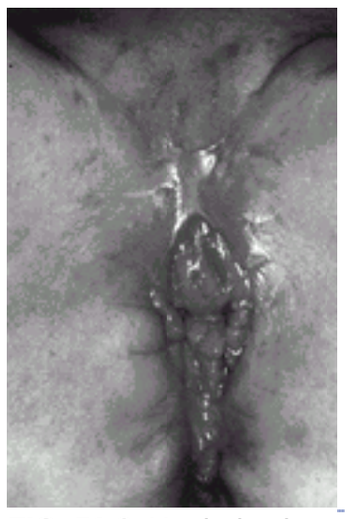

FIG. 51.9. Healed vulva after en-bloc resection via longhorn incision.

DiSaia and associates first proposed conservative vulvar surgery in 1979 as a way of preserving sexual function in young patients. Requirements for conservative surgery were an invasive cancer 1 cm or less in diameter confined to the vulva with less than a 5-mm depth of invasion. Patients were treated with radical wide excision ensuring a 3-cm margin and lymphadenectomy was performed through separate groin incisions. There were no recurrences at a mean follow-up of 32 months and sexual function was deemed preserved. The authors concluded that there existed a subset of patients with vulvar cancer who could be treated with less radical vulvar procedures.

Berman and co-workers expanded the experience with conservative surgery in 1989 with a report of 50 patients with T1 lesions treated with radical local excision, again providing a 3-cm margin and superficial lymphadenectomy. No patient had a resection margin positive for carcinoma. Median hospital stay was shortened to 7 days and only 12% required wound debridement compared to 50% or more with historical controls. There were five recurrences (10%), four of them local. All local recurrences were salvaged with a second local resection.

In 1990, Burke and colleagues provided the first report of a conservative vulvar surgery in patients with both T1 and T2 lesions. Thirty-two patients (15 with T2 lesions) underwent radical wide excision removing a 1- to 2-cm margin of normal tissue in addition to selective inguinal dissection. The mean lesion diameter was 23 mm with a mean depth of invasion of 4.1 mm. No patients had invasive cancer at the surgical margins but 19% were positive for VIN. The authors reported only 15.5% wound separation with a mean hospital stay of 10 days. Three patients (10%) developed local recurrence and two were salvaged with repeat excision. The authors concluded that radical wide excision appears to be an acceptable surgical option for patients with resectable vulvar carcinomas.

As these retrospective trials used differing criteria to identify patients suitable for less radical approaches, the GOG conducted a prospective trial beginning in 1983 which evaluated modified radical hemivulvectomy and ipsilateral superficial inguinal lymphadenectomy in 155 patients with clinical stage I vulva carcinoma limited to a depth of invasion of less than 5 mm. A 2-cm margin of normal skin around the lesion was excised. There were 19 recurrences and 7 deaths among 122 patients available for evaluation. Recurrences were evenly distributed between local and distant failures. Acute and long-term morbidity was decreased significantly compared to historical controls, but at the cost of increased risk of local recurrence. The authors concluded that although there was no consensus regarding the characteristics that would make a patient with early vulvar carcinoma a candidate for a limited surgical approach, this approach appeared to be an alternative to traditional radical surgery for a highly selected group of patients with stage I vulvar carcinoma (Fig. 51.10, Fig. 51.11).

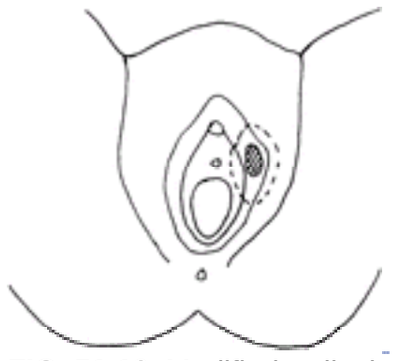

FIG. 51.10. Modified radical vulvectomy. Radical excision of the vulva deep to the inferior fascia of the urogenital diaphragm with a 2-cm margin around the lesion.

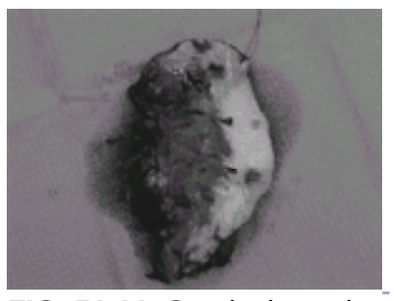

FIG. 51.11. Surgical specimen after modified radical vulvectomy. Lymphadenectomy is performed through separate incisions.

A need for establishing a clear margin for treatment of patients with vulvar cancer may be more important than the particular treatments. Heaps and colleagues reviewed surgicopathologic factors predictive of local recurrence in 135 patients treated with radical vulvectomy or radical local excision. Twenty-one developed local recurrence after radical resection. No patient with a surgical tumor-free margin = 8 mm suffered from local recurrence but 48% with less than an 8-mm margin recurred locally. As an 8-mm margin on fixed tissue corresponds to 10-mm margin with fresh tissue, the authors concluded that use of a 1-cm margin should successfully prevent local recurrence and reduce the currently used standard margin by over 50%. This would allow further modification of the procedure in order to decrease morbidity and avoid disfigurement and loss of organ function without sacrificing survival.

Other modifications in the surgical management of vulvar carcinoma over the last 30 years include the elimination of routine pelvic lymphadenectomy and elimination of contralateral groin node dissection in patients with lateral T1 lesions and negative ipsilateral nodes.

Overall survival in vulvar carcinoma is related to groin node status and lesion diameter with nodal status being the most important factor. Five-year survival is 98% for patients with negative nodes and a T1 lesion. Patients with one to two positive ipsilateral nodes have over 70% to 80% 5-year survival while those with three or more positive nodes or bilaterally positive nodes have survival in the range of 12% to 36% (Table 51.2). Postoperative adjuvant groin radiotherapy is indicated in patients with more than one positive node or clinically evident groin nodes.

Node status	Lesion size	Relative 5-y survival (%)
Negative	≤ 2 cm	98
Negative	2.1–8.0 cm	87
One positive	≤ 2 cm	87
Negative	>8 cm	75
One positive	>2 cm	75
Two unilaterally positive	≤ 8 cm	75
Two unilaterally positive	>8 cm	29
Three or more positive	Any	29
Bilaterally positive	Any	29

TABLE 51.2. *Survival by groin node status and lesion size in vulvar carcinoma*

Radiotherapy for vulvar carcinomas is indicated in patients with unresectable vulvar tumors or unresectable groin nodes. Boronow popularized treatment of locally advanced tumors with radiotherapy followed by resection of the primary tumor in order to preserve urethral, bladder, or rectal function and to avoid the morbidity of pelvic exenteration. In recent years, concurrent radiotherapy and chemotherapy has been shown to improve both local control and overall survival. The GOG has demonstrated high rates of resectability and local control of the lymph nodes in patients with clinically suspicious, fixed, or ulcerated nodes treated preoperatively with radiotherapy, concurrent cisplatin/5-fluorouracil (5-FU) chemotherapy, and followed by tailored surgery.

New approaches to decrease morbidity of groin node dissection include the use of lymphatic mapping and sentinel lymph node biopsy. Intraoperative mapping with vital dye with or without lymphoscintigraphy may identify 56% to 100% of sentinel nodes. While this technique is widely used for breast cancer and melanoma, it is being prospectively evaluated by the GOG and other investigators. If the sentinel node can predict lymph node involvement with sufficiently high negative predictive value, then more extensive lymphadenectomy may be avoided. This may decrease one of the major morbidities of vulvar cancer surgery.

Recurrence after definitive therapy for vulvar carcinoma may occur locally in the vulva or in the groin. The risk of local recurrence depends on prior surgical technique with higher rates of recurrence seen with less aggressive vulvar approaches. Vulvar recurrences may be characterized as new primaries due to field effect or recurrence at the prior site of excision. They are usually salvageable with radical excision though patients who have had prior radiotherapy to the groin will require some type of reconstructive flap to ensure adequate vascular supply and healing. Groin recurrences are much more difficult to treat. If the patient has not been irradiated, surgical excision of the nodes with postoperative radiotherapy is the treatment of choice. If radiotherapy has already been administered, no satisfactory therapy exists and survival is dismal.

Other Histologic Subtypes

Rare histologic types of vulvar carcinoma exist, representing about 10% of vulvar malignancies. These include melanoma, invasive Paget disease, basal cell carcinoma, verrucous carcinoma, Merkel cell carcinoma, adenocarcinoma, adenosquamous carcinoma, transitional cell carcinoma, sarcomas, and metastatic disease from other sites.

Melanoma Melanoma is the second most common vulvar malignancy, accounting for about 6% of vulvar lesions and 1.3% of all melanomas among women. It is highly aggressive and characterized by both local recurrence and distant metastasis through hematogenous spread. The median age at presentation is 66 years, several decades older than for cutaneous melanomas. It is more common in white women with a relative risk of 2.6 compared to other races. Overall 5-year survival ranges from 35% to 50%. Patients frequently present with pruritis and visible lesions but many may be asymptomatic. The differential diagnosis of a pigmented lesion includes melanoma, lentigo, vulvar melanosis, squamous dysplasia, hemangioma, Paget disease, various nevi, and acanthosis nigricans. Biopsy should be considered of any pigmented lesion, particularly if the borders are indistinct r spreading or the lesion is raised. Excisional biopsy is preferred to better delineate depth of invasion. A punch biopsy of the most nodular area is the next best option. Three histologic subtypes of vulvar melanoma have been described. The most common is superficial spreading melanoma followed by nodular and acral lentiginous melanoma. Immunohistochemical testing may be necessary to distinguish between melanoma and Paget disease. Paget disease is typically positive for carcinoembryonic antigen (CEA) and melanoma is positive for S-100. Unlike squamous lesions, vulvar melanoma is staged using classification systems for cutaneous melanomas. The Clark system is based on level of invasion, while the Breslow system is based on vertical thickness of the lesion from the surface of intact epithelium to the deepest point of invasion. Other staging systems include Chung's modification of the Clark's system and the American Joint Committee on Cancer (AJCC) staging system (Table 51.3). While the Breslow and Chung microstaging systems are more accurate than the Clark system, prospective evaluation by the GOG found that the AJCC staging system is most predictive of survival (Table 51.4).

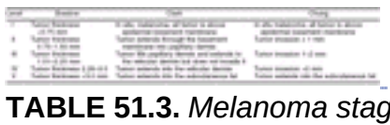

TABLE 51.3. *Melanoma staging: Breslow, Clark, and Chung microstaging levels*

Stage	Description
IA	Primary melanoma <0.75 mm thick or Clark's level II
IB	Primary melanoma 0.75–1.50 mm thick or Clark's level III
IIA	Primary melanoma 1.51–4.0 mm thick or Clark's level IV
IIB	Primary melanoma >4.0 mm thick or Clark's level V
III	Regional lymph node or in-transit metastases
IV	Systemic metastases

TABLE 51.4. *American Joint Committee on Cancer staging for vulvar melanoma*

As with squamous lesions, more conservative vulvar surgery is now being advocated for melanoma. Excision should include a 1- to 2-cm lateral margin and at least a one centimeter deep margin. The presence of capillary lymphatic space involvement and central tumor location has been correlated with positive groin node status. The role of lymphadenectomy in vulvar melanoma remains unresolved. Prospective evaluations have failed to show a survival benefit with lymphadenectomy. Adjuvant therapy for advanced disease includes the use of chemotherapy, immune modulators, and tumor vaccines. Given the small number of patients, no trials specific to vulvar melanoma have evaluated the role of adjuvant therapy.

Paget Disease Paget disease accounts for 1% to 2% of vulvar malignancies. It occurs most frequently in postmenopausal white women and is characterized by red eczematous lesions with a superficial white coating and intense pruritis. As with other vulvar malignancies, there may be a long delay between initial symptoms and diagnosis. Histologic disease may spread well beyond the visible lesion. Biopsy reveals characteristic large eosinophilic cells in the basal layer of the epithelium (Fig. 51.12). Paget disease of the vulva may exist as four clinical entities, the first of which is noninvasive or intraepithelial Paget disease. This represents 60% of cases and is cured with local excision. In invasive Paget disease, the Paget cells penetrate the basement membrane and invade the dermis. Intraepithelial Paget disease may also be associated with an underlying adenocarcinoma of sweat gland origin or a coexistent cancer. Underlying malignancy is seen in approximately 20% to 30% of patients, a rate lower than that seen with mammary Paget disease. Parker and co-workers reported poor survival in patients with invasive Paget disease and in patients with underlying malignancy. Patients with clitoral disease also had a poorer prognosis. Therapy for Paget disease involves wide excision. A skinning vulvectomy with split thickness skin graft is often needed to remove large areas of involved skin. Recurrences tend to be local and range from 7% to 58% with an average of about 30%. Some authors recommend sending margins for frozen section to ensure complete resection while others have not demonstrated a benefit to this approach with respect to recurrence. Radical surgery is reserved for patients with underlying malignancy.

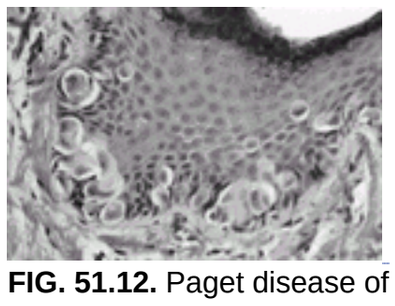

FIG. 51.12. Paget disease of the vulva. Large eosinophilic cells with large nuclei and prominent cytoplasm in basal cells represent Paget cells.

Basal Cell Carcinoma Basal cell carcinoma accounts for 2% to 4% of vulvar malignancies. It is typically seen in older women and tends to be well circumscribed, firm, and typically less than 2 cm in diameter. Metastasis is extremely rare and wide local excision is the preferred therapy.

Verrucous Carcinoma Verrucous carcinoma is a variant of squamous cell carcinoma with distinctive pathologic and clinical characteristics. It is characterized by a large condylomatous or cauliflower-like lesion with minimal cellular atypia, a pushing border, and rare metastasis. Unless biopsies are deep enough, it may be confused with benign condyloma or papilloma. Wide local excision is the preferred therapy. Radiotherapy is contraindicated given the potential for anaplastic transformation.

Merkel Cell Carcinoma Merkel cell tumors are neuroendocrine tumors of the skin and resemble small cell carcinomas. They are associated with lymphatic and distant metastases and have a very poor prognosis.

Adenocarcinoma Adenocarcinoma of the vulva tends to arise in the Bartholin gland, although it may also arise from the sweat glands or Skene glands of the vulva (Fig. 51.13). Adenoid cystic carcinoma also arises from the Bartholin gland and is characterized by slow growth and a tendency for local and perineural invasion (Fig. 51.14). Distant metastasis is most commonly seen in the lung. Therapy involves radical excision, ipsilateral lymphadenectomy, and postoperative radiotherapy.

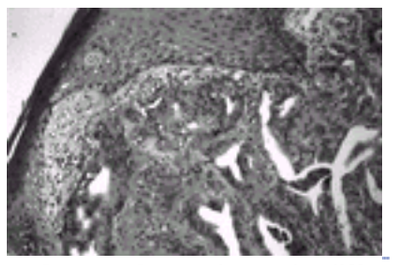

FIG. 51.13. Moderately differentiated adenocarcinoma arising from vulva.

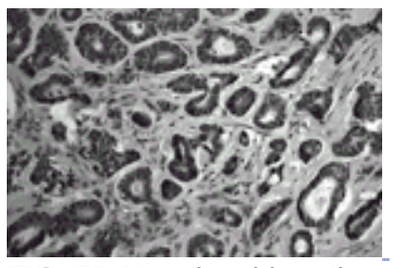

FIG. 51.14. Adenoid cystic carcinoma arising from Bartholin gland.

Adenosquamous Carcinoma Adenosquamous carcinoma is a rare cause of Bartholin gland carcinoma and is composed of both malignant squamous and glandular components.
Transitional Cell Carcinoma Transitional cell carcinoma may arise within the Bartholin gland but is more commonly seen as metastatic spread from a urethral or bladder carcinoma.

Sarcoma

Sarcomas of the vulva are extremely rare, representing only 1% to 3% of vulvar malignancies. While leiomyosarcoma is the most common histologic subtype, malignant fibrous histiocytoma, and various other sarcomas have been reported. Radical surgery is the primary therapy, although the behavior of these neoplasms is not well understood.

Metastatic Disease Metastatic disease to the vulva usually occurs from other lower genital tract malignancies, most commonly cervix. Rare causes include malignancies arising from the vagina, endometrium, ovary, breast, kidney, stomach, or lung.

VAGINAL CARCINOMA

Primary vaginal cancer is the fifth most common gynecologic malignancy, with an expected 2,000 new cases in the United States in 2001. Only fallopian tube carcinomas are a less common gynecologic malignancy than vaginal carcinoma. The vast majority of vaginal neoplasms are metastatic from other sites, particularly direct extension from the cervix or endometrium. Lymphatic or hematogenous spread to the vagina is also possible. Primary vaginal neoplasms are typically squamous in origin and occur in postmenopausal women. Risk factors for vaginal dysplasia or carcinoma include a history of prior lower genital tract dysplasia or carcinoma, tobacco use, low socioeconomic status, history of genital warts or HPV infection, prior abnormal Pap smear, prior radiotherapy of the genital tract, immunosuppression, vaginal discharge or irritation, and early hysterectomy. History of diethylstilbestrol (DES) exposure is associated with development of clear cell adenocarcinoma of the vagina.

Vaginal Intraepithelial Neoplasia

The vagina is the least common site for lower genital tract dysplasia, occurring 100 times less frequently than cervical dysplasia. A review by Dodge and associates of 121 patients with biopsy-proven vaginal intraepithelial neoplasia (VAIN) showed that 65% of women with a uterus in place had associated cervical intraepithelial neoplasia and 10% had associated VIN. The upper third of the vagina is the most common site of involvement and over 60% of these women will have multifocal disease. The mean age for patients with VAIN III is approximately 40 years.

Diagnosis is through careful colposcopic inspection after application of 5% acetic acid and directed biopsy (Fig. 51.15, Fig. 51.16). Due to the rugated nature of the vagina, colposcopic evaluation may be a challenge. It is important to remember to colposcopically evaluate the vagina in patients with cytologic abnormalities, particularly those with normal appearing cervices. Acetowhite epithelium is the most common colposcopic feature. Application of half-strength Lugol solution allows for identification of nonstaining areas, which may represent dysplasia. Most patients with vaginal dysplasia are completely asymptomatic, fewer than 5% will present with bleeding or abnormal vaginal discharge. Postmenopausal patients with atrophy may benefit from a course of vaginal estrogen prior to undergoing colposcopy and directed biopsies.

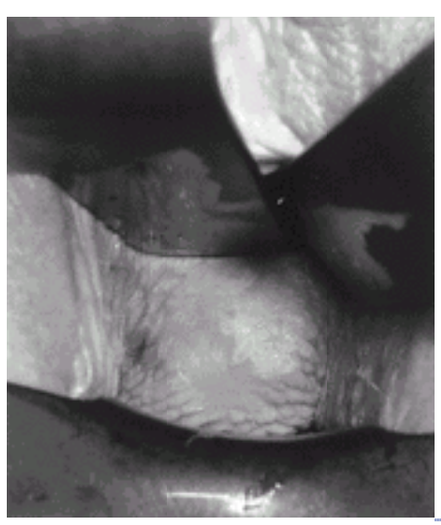

FIG. 51.15. Vaginal intraepithelial neoplasia III after application of acetic acid. Note acetowhite lesions. See color figure 51.15.

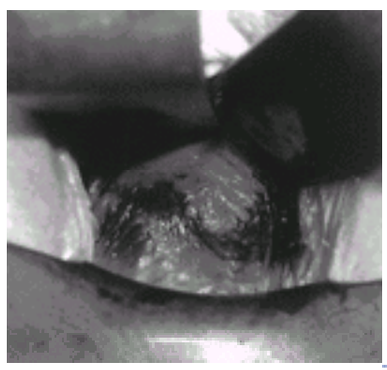

FIG. 51.16. Vaginal intraepithelial neoplasia III after application of Lugol solution. Note nonstaining lesions.

Various treatment options have been employed for therapy of VAIN. These include laser ablation, partial or total vaginectomy, topical 5% 5-FU cream, cavitron ultrasonic aspiration, and loop electrosurgical excision procedure (LEEP). Choice of therapy for VAIN depends on the number and severity of lesions and their location, whether the patient is sexually active, and prior radiotherapy, as well as physician and patient preference. Hoffman and associates found invasive carcinoma in 28% of patients undergoing upper vaginectomy for VAIN III. Overall recurrence rates after therapy range from 10% to 42%. While partial vaginectomy is well suited to unifocal lesions and those involving the upper aspect of the vagina, it may lead to vaginal shortening and sexual dysfunction. Total vaginectomy with split thickness skin graft is reserved for patients who have failed more conservative approaches. Laser ablation to a depth of 2 to 3 mm is associated with minimal blood loss and is well suited for multifocal lesions. The challenge with laser therapy is ensuring that no lesions have been missed among the vaginal rugae. While 5-FU allows patients to treat themselves medically, it may be associated with significant skin desquamation, chronic ulceration, and be poorly tolerated. Dodge and colleagues found that recurrence is highest after laser ablation (38%) and 5-FU (59%) as well among those patients with multifocal disease (45%). Recurrence is lowest after partial vaginectomy (0%). Overall 2% to 12% of patients progress to vaginal cancer after therapy for vaginal dysplasia so careful cytologic and colposcopic surveillance is critical.

Squamous Carcinoma

Squamous carcinoma accounts for 80% to 90% of vaginal carcinomas with a mean age at presentation of 60 to 65 years. As with vaginal dysplasia, the most common location will be the posterior upper third of the vagina but the entire vaginal cylinder is at risk for malignant transformation. Abnormal vaginal bleeding occurs in over half of patients. Less common symptoms include abnormal vaginal discharge, pain, and dysuria (Fig. 51.17).

FIG. 51.17. Vaginal carcinoma located in upper third of the vagina.

Vaginal carcinoma may spread by local extension, lymphatic spread to pelvic or inguinal nodes, and hematogenously. Lesions involving the upper two-thirds of the vagina tend to spread to pelvic nodes while lesions involving the lower third of the vagina tend to spread to inguinal nodes as would be seen with vulvar malignancies. To be considered primary vaginal carcinoma, a patient must have no evidence of disease in either the vulva or cervix. Staging of vaginal cancers is clinical and based on either the FIGO or AJCC systems (Table 51.5).

TABLE 51.5. *Vaginal carcinoma: FIGO and AJCC clinical staging*

Therapy for vaginal carcinoma typically involves both external irradiation and brachytherapy. Surgical resection is typically reserved for small stage I tumors confined to the posterior aspect of the vaginal apex. Complications from therapy include fistula formation and stenosis. Overall prognosis is poorer than for cancer of the cervix. Recurrent disease tends to occur locally within 2 years of primary therapy. Extenterative procedures are required to adequately treat locally recurrent or persistent disease but are associated with considerable morbidity. Chemotherapy does not yet have a significant role in treatment of vaginal carcinoma.

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma of the vagina is a rare malignancy most commonly seen in young women whose mothers received DES during pregnancy for prevention of miscarriage (Fig. 51.18). This association was first noted in 1970, leading to removal of the drug from the U.S. market in 1971. Approximately 60% of patients with clear cell carcinoma are known to have been exposed to DES or other synthetic estrogens. The risk of developing clear cell adenocarcinoma of the cervix or vagina has been estimated at 1 per 1,000 to 1 per 1,500, with DES exposure in the first trimester conveying the greatest risk. The median age at diagnosis for DES-exposed patients is 19 years. DES-exposed daughters do not appear to have an increased risk of developing any other malignancies but do have an increased risk of cervical dysplasia. This may be due to increased surveillance or congenital abnormalities in the lower genital tract. No increased risk in squamous cancers of the cervix or vagina has been reported in DES-exposed women.

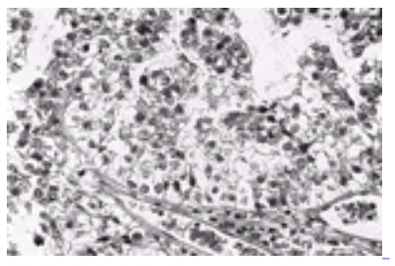

FIG. 51.18. Clear cell adenocarcinoma of the vagina associated with diethylstilbestrol exposure.

Most patients present with early stage disease, located in the exocervix or upper third of the vagina. Therapy is typically surgical and involves radical hysterectomy with removal of the upper vagina and pelvic lymphadenectomy. While this results in sterility, it may allow ovarian preservation and improved vaginal function over treatment with radiotherapy. Overall 5-year survival for stage I disease is more than 90% and approximately 80% for patients with stage II disease. Favorable factors in survival include early stage disease, older age, a tubulocystic histology, superficial invasion, small tumor diameter, and negative nodal status. Adenocarcinoma unrelated to DES exposure is a rare entity seen in postmenopausal women.

Melanoma

Melanoma is the second most common cancer of the vagina, accounting for less than 5% of vaginal malignancies and 0.3% of all melanomas among women. Nodular lesions are the most frequent histologic subtype. While vulvar melanoma is more common among white women, no association with race is seen for vaginal melanoma. It is a disease of older women and overall 5-year survival is poor at only 19%.

Sarcoma Botryoides

Sarcoma botryoides, or embryonal rhabdomyosarcoma, is a rare sarcoma found in young girls. It presents with vaginal bleeding and a polypoid “grapelike” mass. Historically this was treated with radical surgery, but now multimodality chemotherapy with VAC (vincristine, dactinomycin, and cyclophosphamide) and limited surgery can allow for a cure while preserving reproductive function. Radiotherapy may also be used in conjunction with multi-agent chemotherapy.

Endodermal Sinus Tumor

This is an extremely rare germ cell tumor arising in the vagina. It is seen in infants and is treated with combination chemotherapy as is used for germ cell tumors of the

ovary.

Lymphoma

Vaginal involvement with lymphoma may be secondary to systemic disease or may be localized to the vagina. This rare entity presents with bleeding and a vaginal mass. Primary vaginal lymphomas are typically diffuse, large, B-cell type.

Metastatic Disease

Although primary vaginal malignancy is quite rare, metastatic spread to the vagina is common and occurs through direct extension of vulvar, cervical, endometrial, and rectal malignancies. A thorough search for another primary site should be undertaken before concluding that a patient has a primary vaginal malignancy.

SUMMARY POINTS

- The incidence of vulvar intraepithelial neoplasia (VIN) is increasing with younger patients more likely to have human papillomavirus (HPV)-related lesions. The underlying risk for cancer in a field of VINIII is 7% to 22%.
- Vulvar carcinoma in older women tends to be unifocal and is associated with chronic vulvar irritation rather than HPV changes. Carcinomas in younger women tend to be multifocal and HPV changes are seen in 90% of cases (HPV 16 is most common).
- The risk of groin node metastasis with vulvar carcinoma increases with increasing tumor size, depth of invasion, and presence of lymphovascular space involvement.
- Modifications in surgery to reduce the radical nature of vulvar and groin surgery are possible in select patients. Vulvar resection margins should be at least 1 cm. The use of sentinel node biopsy to modify groin node dissections remains investigational.
- Squamous cell carcinoma of the vagina is a rare entity best treated with combined external beam radiation therapy and brachytherapy.

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Chapter 52

Robert E. Bristow

Cervical Cancer

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In the United States, cancer of the uterine cervix is the sixth most common solid cancer in women after carcinoma of the breast, lung, colorectum, endometrium, and ovary. The American Cancer Society has estimated that in 2002 there will be 13,000 new cases of invasive carcinoma of the cervix in the United States, over 50,000 cases of carcinoma in situ, and 4,100 deaths from the disease. The average age of diagnosis for cervical cancer is 52 years, and the distribution of cases is bimodal with peaks at 35 to 39 years and 60 to 64 years. Worldwide, cervical cancer continues to be a leading cause of death due to cancer among women, with approximately 500,000 cases occurring annually. Lifetime risks for cervical cancer show significant geographic variation, ranging from 0.4% in Israel to 5.3% in Cali, Colombia, where cervical cancer is the most common malignancy in women.

RISK FACTORS

Screening

Cytologic evaluation of cells obtained from the cervix and vagina was first proposed by Papanicolaou and Traut in the 1940s as a method for detecting cervical cancer and its precursors. Since that time, cervical cytology has proved to be the most efficacious and cost-effective method for cancer screening. By increasing detection of preinvasive and early invasive disease, cervical cancer screening with the Pap smear has decreased both the incidence and mortality from cervical cancer in communities with active screening programs. A single negative Pap smear may decrease the risk for cervical cancer by 45%, and nine negative smears during a lifetime decreases the risk by as much as 99%. Eddy, using a mathematical model, indicated that in women 35 to 64 years of age, screening intervals of 10, 5, and 3 years would reduce the incidence of invasive cervical cancer by 64%, 84%, and 91%, respectively. Despite the recognized benefits of cytologic screening, substantial subgroups of women in the United States have not been screened or are not screened at regular intervals. One-half of women with newly diagnosed invasive cervical carcinoma have never had a Pap smear, and another 10% have not had a Pap smear in the 5 years preceding diagnosis. The absence of prior regular Pap smear screening is associated with a two- to six-fold increase in the risk of developing cervical cancer. Unscreened populations include older women, the uninsured, ethnic minorities, and women of lower socioeconomic status, particularly those in rural areas. Women over age 65 years should continue to be screened, as 25% of all cases of cervical cancer and 41% of deaths from the disease occur in women in this age group.

Race

Although the incidence of cervical cancer in the United States has declined significantly over the past 50 years, the rates among African Americans remain about twice as high as those among whites. The incidence is also approximately two times higher for Hispanic Americans and even higher for Native Americans, while most Asian-American groups experience rates similar to whites. These differences are at least partially accounted for by the strong inverse association between cervical cancer incidence and socioeconomic factors. When socioeconomic differences are controlled for, the excess risk of cervical cancer among African Americans is substantially reduced, from over 70% to less than 30%. Racial differences are also apparent in survival, with 59% of African Americans with cervical cancer surviving 5 years, compared to 67% of whites with the disease.

Sexual and Reproductive Factors

First intercourse before 16 years of age is associated with a two-fold increased risk of cervical cancer compared with that for women whose first intercourse occurred after age 20 years. Cervical cancer risk is also directly proportional to the number of lifetime sexual partners. Although difficult to separate epidemiologically, there is evidence to indicate that both early age at first coitus and the number of lifetime sexual partners have independent effects on cervical cancer risk. Increasing parity also appears to be a separate risk factor for cervical cancer, even after controlling for socioeconomic and reproductive characteristics. There is little evidence to support an association between age of menarche, age at menopause, or character of menses with carcinoma of the cervix.

Smoking

Cigarette smoking has emerged as an important etiologic factor in squamous cell carcinoma (SCC) of the cervix. The increased risk for smokers is approximately two-fold, with the highest risk observed for long-term or high-intensity smokers. Proposed mechanisms include genotoxic or immunosuppressive effects of smoke-derived nicotine and cotinine, which can be detected in high levels in the cervical mucus of smokers.

Contraceptive Use

Numerous confounding factors—time interval since last cervical smear, sexual behavior, and role of the male partner, among others—complicate the interpretation of the data on oral contraceptive use and cervical cancer. After controlling for these and other variables, it appears that long-term oral contraceptive users (5 years or more) have about a two-fold increased risk of cervical cancer, compared to nonusers. Use of barrier methods of contraception, especially those that combine both mechanical and chemical protection, have been shown to lower the risk of cervical cancer, presumably because of reduced exposure to infectious agents.

Immunosuppression

Cell-mediated immunity appears to be a factor in the development of cervical cancer. Immunocompromised women (e.g., from renal transplantation or human immunodeficiency virus [HIV] infection) may not only be at higher risk for the disease but also demonstrate more rapid progression from preinvasive to invasive lesions and an accelerated course once invasive disease has been diagnosed. Maiman and colleagues report that HIV-positive women with cervical cancer may have a higher recurrence risk and cancer-related death rate compared to HIV-negative control subjects.

Human Papillomavirus Infection

During the past decade, epidemiologic evidence has accumulated, implicating infection with human papillomavirus (HPV) as a likely etiologic agent in cervical SCC. All known types of HPV have a similar structural and genomic organization. They are non-enveloped virions with a double-stranded circular DNA genome of 7,800 to 7,900 base pairs and an icosahedral capsid. HPV DNA is present in virtually all cases (93%) of cervical cancer and its precursor lesions. While HPV infection is thought to be a component of neoplastic transformation, it is unlikely to be entirely sufficient in and of itself.

HPV colonizes mucosal or cutaneous epithelium and may induce hyperproliferation, resulting in the formation of warts at the site of infection. Based on differences in DNA sequencing, over 70 different types of HPV have been identified, 23 of which are known to infect the anogenital tract. Low oncogenic risk–type viruses include types 6, 11, 42, 43, and 44 and are associated with condyloma acuminatum and some cases of low-grade squamous intraepithelial lesions, but rarely with invasive cancer. High oncogenic risk–type viruses include types 16, 18, 31, 45, and 56 and are commonly detected in women with high-grade squamous intraepithelial lesions (HGSIL) and invasive cancer. HPV types 33, 35, 39, 51, and 52 can be considered as being of intermediate oncogenic risk, as they are associated with HGSIL but are uncommonly detected in invasive carcinomas.

Following acute HPV infection, three clinical sequelae are possible:

1. Latent viral infection occurs when the HPV genome becomes stabilized as a nonintegrated episome and remains in the host cell without clinical or morphologic changes in the squamous epithelium. Clinically, patients may display no gross or morphologic evidence of infection but still harbor virus as demonstrated by DNA detection techniques.
2. Active infection, manifested by proliferation of squamous epithelium into benign tumors (warts), is present when HPV undergoes vegetative replication.
3. Highly oncogenic HPV viruses associated with high-grade lesions can become integrated into the host genome, interrupting control of proliferation by certain oncoproteins.

Initiation of cervical dysplasia and carcinoma may involve interactions between HPV and specific genes that regulate cell growth. The E6 and E7 open reading frames of the HPV genome are particularly important in the immortalization and transformation of infected cells. In HPV types 16 and 18, the protein products synthesized from the E6 and E7 open reading frames can bind to the gene products of the *p53* and retinoblastoma (*Rb*) tumor suppressor genes, respectively. Viral integration results in the overexpression of the E6 and E7 viral protein products with increased binding and inactivation of their respective tumor suppressor proteins. Removal of these two inhibitory influences on cellular proliferation is thought to provide HPV-infected cells with a growth advantage, ultimately leading to neoplastic transformation.

CLINICAL FEATURES

Presenting Symptoms

The most common symptom of cervical cancer is abnormal vaginal bleeding or discharge. Abnormal bleeding may take the form of postcoital spotting, intermenstrual bleeding, menorrhagia, or postmenopausal spotting. If bleeding has been chronic, a patient may complain of fatigue or other symptoms related to anemia. Serosanguineous or yellowish vaginal discharge, frequently associated with a foul odor, may accompany an advanced or necrotic carcinoma. Pelvic pain may result from locally advanced disease or tumor necrosis. Tumor extension to the pelvic side wall may cause sciatic pain or back pain associated with urinary tract obstruction and hydronephrosis. Metastatic tumor to the iliac and paraaortic lymph nodes can extend into the lumbosacral nerve roots and present as lumbosacral back pain. Urinary or rectal symptoms (e.g., hematuria, hematochezia, fistulae) can be associated with bladder or rectal invasion by advanced-stage cervical carcinoma.

Physical Findings

Invasive carcinoma of the cervix displays a wide range of gross appearances. Early lesions may be focally indurated or ulcerated, or present as a slightly elevated and granular area that bleeds readily on contact (Fig. 52.1). More advanced tumors have several types of gross appearance: exophytic, endophytic, or infiltrative. Exophytic tumors characteristically have a polypoid or papillary appearance and will often demonstrate contact bleeding. Endophytic tumors are usually ulcerated or nodular but may be clinically inapparent if located high within the endocervical canal. Such tumors frequently invade deep into the cervical stroma to produce an enlarged, hard, barrel-shaped cervix that may only be appreciated on rectovaginal pelvic examination. The infiltrative pattern of tumor growth may produce surrounding tissue necrosis and erosion of normal anatomic landmarks.

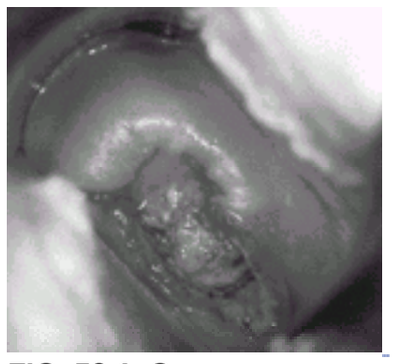

FIG. 52.1. Gross appearance of squamous cell carcinoma of the cervix. This is an ulcerative type of lesion.

Spread of Disease

Parametrial Extension Cervical cancer generally follows an orderly pattern of disease progression. Initially, tumor cells usually spread through parametrial lymphatic vessels, expanding and replacing parametrial lymph nodes (Fig. 52.2). These individual tumor masses enlarge and become confluent, eventually replacing the normal parametrial tissue. Less commonly, the central tumor mass reaches the pelvic sidewall by direct contiguous extension through the cardinal (Mackenrodt) ligament. Significant involvement of the medial portion of this ligament may result in ureteral obstruction and hydronephrosis.

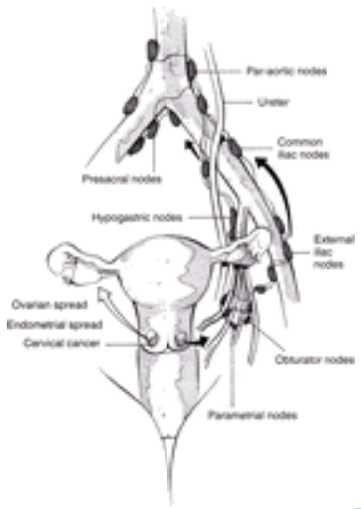

FIG. 52.2. Anatomic pathways of spread in invasive cervical carcinoma.

Lymph Node Involvement The pelvic lymph nodes will usually be the first site of embolic lymphatic spread of cervical cancer. The lymph node groups most commonly involved are the obturator, external iliac, and hypogastric (Fig. 52.2). The inferior gluteal and presacral lymph nodes are less frequently involved. Secondary nodal involvement (i.e., common iliac, paraaortic) rarely occurs in the absence of pelvic nodal disease. The percentage of involved lymph nodes increases directly with primary tumor volume. Rarely, retrograde lymphatic embolization may occur to the inguinal lymph nodes. Patients with locally advanced pelvic disease may have detectable metastatic spread to the scalene nodes. Consequently, careful clinical assessment of the groin and supraclavicular fossa areas should be included as part of the physical examination.
Vaginal Extension When the primary tumor has extended beyond the confines of the cervix, the upper vagina is frequently involved (50% of cases). Anterior extension through the vesicovaginal septum is most common, often obliterating the dissection plane between the bladder and underlying cervical tumor, making surgical therapy difficult or impossible. Posteriorly, a deep peritoneal cul-de-sac (pouch of Douglas) can represent an anatomic barrier to direct tumor spread from the cervix and vagina to the rectum.
Bladder and Rectal Involvement In the absence of lateral parametrial disease, anterior and posterior spread of cervical cancer to the bladder and rectum is uncommon. Approximately 20% of patients with tumor extending to the pelvic sidewall will have biopsy-proven bladder invasion.
Endometrial Involvement The endometrium is involved in 2% to 10% of cervical cancer cases treated with surgery, although the overall incidence (including nonsurgical cases) is unknown. Although endometrial extension does not alter a patient's stage of disease, it has been associated with decreased survival and a higher incidence of distant metastases.
Ovarian Metastasis Ovarian involvement with cervical cancer is rare but, when present, most likely occurs through the lymphatic connections between the uterus and adnexal structures. In patients undergoing surgical treatment for early-stage disease, ovarian metastasis is present in less than 1% of SCCs and slightly more than 1% of adenocarcinomas. The true incidence of ovarian involvement with advanced-stage tumors is unknown, as pathologic evaluation of the adnexae is not commonly performed in such cases.
Hematogenous Spread Hematogenous spread of cervical cancer is uncommon, particularly at the time of initial diagnosis. However, when blood-borne metastases do occur, the lung, liver, and bone are the sites most frequently involved. Metastasis to the bowel, adrenal gland, spleen, and brain are extremely rare.

DIAGNOSIS AND STAGING

Diagnosis and Evaluation of Disease Extent

Pathologic documentation of invasive disease should always be obtained prior to initiating therapy for cervical cancer. The International Federation of Gynecology and Obstetrics (FIGO) staging system used for the diagnosis and evaluation of cervical carcinoma is based on clinical evaluation (visual inspection, palpation, colposcopy, endocervical curettage, cervical biopsy, or conization), radiographic examination of the chest, kidneys, and skeleton, and ECC and biopsies. Cervical cancer is one of the few gynecologic malignancies (vaginal cancer being the other) that still uses a clinically based staging system by international convention, which facilitates comparison of results between institutions irrespective of the availability of diagnostic technological resources. Staging procedures allowed by FIGO convention are shown in Table 52.1. Lymphangiograms, arteriograms, computed tomographic (CT) scans, magnetic resonance imaging (MRI), and laparoscopy or laparotomy should not be used for clinical staging. However, information from such additional studies and procedures may be used to modify the treatment approach.

Physical examination	Examination under anesthesia recommended
Radiologic studies	Chest x-ray
	Intravenous pyelogram
	Barium enema
	Skeletal x-ray
Procedures	Colposcopy
	Cervical biopsy
	Conization
	Endocervical curettage
	Cystoscopy
	Proctoscopy
Optional studies*	Computed tomography
	Lymphangiography
	Ultrasonography
	Magnetic resonance imaging
	Radionucleotide scanning
	Laparoscopy/laparotomy

*Not allowed for staging purposes by the International Federation of Gynecology and Obstetrics (FIGO).

TABLE 52.1. *Staging procedures for cervical cancer*

In 1995, FIGO revised the clinical staging system of cervical carcinoma (Table 52.2). Stage I disease includes those neoplasms that are clinically confined to the cervix. In the current staging classification, stage IA tumors are those that are diagnosed by microscopic evaluation of a conization specimen (microinvasive carcinoma). Stage IA1 is defined as a tumor with stromal invasion no greater than 3 mm in depth beneath the basement membrane and no wider than 7 mm. This definition reflects data indicating that patients with less than 3 mm of invasion are at very low risk of metastatic disease and may be treated more conservatively. All grossly visible lesions should technically be classified as stage IB. The 1995 staging system divides stage IB lesions into stage IB1 (no greater than 4 cm in maximal diameter) and stage IB2 (greater than 4 cm in maximal diameter), reflecting the prognostic importance of tumor volume for macroscopic lesions limited to the cervix.

Stage	Clinical features
0	Carcinoma in situ, intraepithelial carcinoma
I	Carcinoma is strictly confined to the cervix
IA	Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are stage IB cancers. Invasion is limited to measured stromal invasion ≤ 5 mm deep and <7 mm wide
IA1	Measured invasion of stroma ≤ 3-mm deep and <7-mm wide
IA2	measured invasion of stroma >3-mm deep but ≤ 5-mm deep and <7-mm wide
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA
IB1	Clinical lesions ≤ 4 cm in size
IB2	Clinical lesions >4 cm in size
II	Carcinoma extends beyond the cervix but has not extended to the pelvic wall. Carcinoma involves the vagina but not as far as the lower third.
IIA	No obvious parametrial involvement
IIB	Obvious parametrial involvement
III	Carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or nonfunctioning kidney are included, unless known to be due to another cause.
IIIA	No extension to the pelvic wall
IIIB	Extension to the pelvic wall, hydronephrosis, or nonfunctioning kidney
IV	Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. Bullous edema does permit a case to be allocated to stage IV.
IVA	Spread of growth to adjacent organs
IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 52.2. *FIGO staging of cervical carcinoma*

Determination of clinical stage depends on careful inspection and palpation of the cervix, vagina, and pelvis. Examination under anesthesia is recommended. It is important to palpate the entire vagina to determine whether disease is limited to the cervix (IB), extends to the upper two-thirds of the vagina (IIA), or also involves the

lower third of the vagina (IIIA) (Fig. 52.3). Tumor extension into the parametrial tissue (IIB) or to the pelvic sidewall (IIIB) is best appreciated on rectovaginal examination. It is impossible at clinical examination to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory, and the case should be considered stage III only if the parametrium is nodular on the pelvic wall or if the growth itself extends to the pelvic wall. Biopsy-proven invasion of bladder or rectal mucosa by cystoscopy or proctoscopy is required for a diagnosis of stage IVA disease. In the United States, the distribution of patients by clinical stage is stage I, 38%; stage II, 32%; stage III, 26%; and stage IV, 4%.

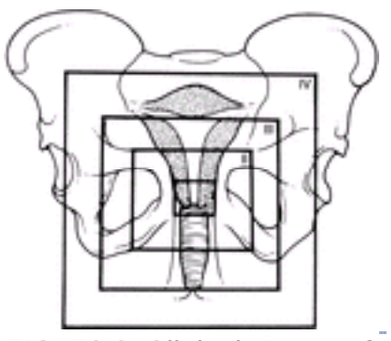

FIG. 52.3. Clinical stages of carcinoma of the cervix. In stage I, only the cervix is involved. In stage II, the parametrium or upper two-thirds of the vagina is involved. In stage III, the malignancy extends to the pelvic sidewall or involves the lower third of the vagina. Stage IV reflects involvement of the bladder or rectal mucosa (stage IVA) or distant metastasis (stage IVB).

When there is doubt concerning which stage a tumor should be assigned, the earlier stage is mandatory. Once a clinical stage has been determined and treatment initiated, subsequent findings on either extended clinical staging (CT, etc.) or surgical exploration should not alter the assigned stage. Assignment of a more advanced stage during treatment will result in an apparent but deceptive improvement in the results of treatment for earlier stage disease.

Surgical Staging

The current FIGO staging classification for cervical cancer is based on pretreatment clinical findings. Only the subclassification of stage I (IA1, IA2) requires pathologic assessment. Discrepancies between clinical staging and surgicopathologic findings range from 17.3% to 38.5% in patients with clinical stage I disease, to 42.9% to 89.5% in patients with stage III disease. This has led some authors to emphasize surgical staging of cervical carcinoma to identify occult tumor spread and determine the presence of extrapelvic disease so that adjunctive or extended-field radiation therapy may be offered. Transperitoneal surgical staging procedures (e.g. laparotomy), when followed by abdominopelvic irradiation, are associated with appreciable complications, particularly enteric morbidity. The extraperitoneal surgical approach can be performed through a paraumbilical or paramedian incision and allows accurate assessment of pelvic and paraaortic nodal status. Using this approach, an incision in the peritoneum is avoided and adhesion formation is minimized. It is associated with few complications and does not delay institution of radiation therapy. Laparoscopic surgical staging for cervical cancer has also been advocated; however, the safety and efficacy of this approach has yet to be determined.

PROGNOSTIC VARIABLES

Tumor Characteristics

Clinical stage of disease at the time of presentation is the most important determinant of subsequent survival, regardless of treatment modality. Five-year survival declines as FIGO stage at diagnosis increases: stage IA, 97%; stage IB, 70% to 85%; stage II, 60% to 70%; stage III, 30% to 45%; stage IV, 12% to 18%. Prognostic variables directly related to surgicopathologic tumor characteristics and their effect on survival were compiled by Kosary for the National Cancer Institutes Surveillance, Epidemiology, and End Results (SEER) program for the period of 1973 through 1987. This study included 17,119 cases of invasive cervical cancer and found that FIGO stage, tumor histology, histologic grade, and lymph node status are all independent prognostic variables relating to survival.

SCCs accounted for 74.9% of cases in the SEER database and can be categorized according to the degree of histologic tumor differentiation. Well-differentiated tumors account for about 5% of cervical SCCs and are composed of sheets and cords of cells with abundant acidophilic cytoplasm, clearly visible intercellular bridges, and often production of variable amounts of keratin. Moderately differentiated tumors are the most common variety, with 85% of SCCs falling in this category (Fig. 52.4). These tumors are characterized microscopically by masses and cords of spindle-shaped squamous cells with elongated nuclei and scant cytoplasm and more frequent mitoses. Poorly differentiated tumors have a rapid growth rate, with numerous mitoses and cells with closely crowded nuclei and scant cytoplasm. These tumors are difficult to recognize as having originated in squamous cells and constitute approximately 10% of cervical SCCs. The degree of histologic tumor differentiation does correlate with overall survival. In the SEER database, 5-year survival for patients with well-differentiated tumors was 74.5%; for those with moderately differentiated tumors it was 63.7%, and it fell to 51.4% for those patients with poorly differentiated carcinomas. Approximately 15% to 20% of cervical cancer cases are adenocarcinomas. After controlling for known prognostic variables, the SEER study found no difference in overall survival between patients with cervical SCC and adenocarcinoma. However, adenosquamous histology was associated with decreased survival. Survival is also orrelated with depth of tumor invasion into the cervical stroma and overall tumor volume.

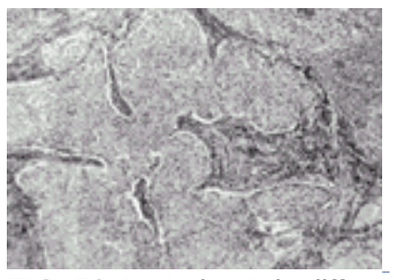

FIG. 52.4. Moderately differentiated squamous cell carcinoma of the cervix.

Among surgically treated patients, survival is directly related to the number and location of lymph node metastasis. The frequency of positive lymph nodes increases with the stage of disease (Table 52.3). For all stages of disease, when both pelvic and paraaortic lymph nodes are negative, the 5-year survival rate is 75.2%. Survival decreases to 45.6% with positive pelvic nodes, and the risk of recurrence is related to the number of nodes involved. The recurrence rate is 35% with one positive pelvic lymph node, 59% with two or three positive nodes, and 69% with metastases to more than three pelvic lymph nodes. When paraaortic nodes are involved, the 5-year survival rate ranges from 15% to 45%.

Stage	n	Positive pelvic nodes (%)	Positive paraaortic nodes(%)
IA1	179	0.5	0
IA2	178	6.2	<1
IB	1,926	15.9	2.2
IIA	110	24.5	11
IIB	324	31.4	19
III	125	44.8	30
IVA	23	55	40

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 52.3. *Incidence of pelvic and paraaortic lymph node metastasis by FIGO stage of cervicalcarcinoma*

Host Factors

Whether or not patient age at diagnosis of cervical cancer is a significant and independent predictor of clinical outcome remains controversial. Some investigators have observed decreased survival in women younger than 35 to 40 years, who have a greater frequency of poorly differentiated tumors. Others have found no significant

difference in survival between younger and older patients.

Several hematologic parameters have been associated with cervical cancer survival outcome. The incidence of pretreatment anemia (hemoglobin of 12 g/dL or less) increases with advancing stage of disease, occurring in 25%, 33%, and 45% of patients with stages I, II, and III disease, respectively. Anemia is associated with a higher incidence of pelvic recurrences and decreased survival, primarily due to more frequent radiation therapy failures. Tumor hypoxia is the proposed mechanism of radio resistance in the presence of anemia. Another prognostic hematologic parameter is thrombocytosis (>400,000/mm ^{3}), which has been associated with decreased survival after controlling for cell type, stage, and age.

Coexistent medical conditions may also affect the success of treatment. Diabetes and hypertension are frequently associated with significant vascular disease and potentially contribute to both tumor hypoxia and decreased blood supply to normal pelvic tissues. Patients with these conditions are subject to a higher incidence of treatment complications and pelvic tumor recurrence, as well as decreased survival.

TREATMENT MODALITIES

Surgery and radiation therapy are the two primary therapeutic modalities most commonly used to treat invasive cervical carcinoma. In general, primary surgical management is limited to patients with stage I and IIA disease, while radiation therapy can be applied to patients with all stages of disease. For patients with early-stage disease, multiple factors should be considered in selecting the most appropriate treatment program. Age is not a contraindication to surgical management, provided the patient does not have significant medical comorbidity. Young patients desiring ovarian preservation and sexually active patients are preferentially managed surgically. Other reasons for the selection of radical surgery over radiation include concomitant inflammatory bowel disease, previous radiation for other disease, and the presence of a coexistent adnexal neoplasm.

Primary Surgery

Surgery provides the opportunity to perform a thorough pelvic and abdominal exploration, which can identify patients with a disparity between the clinical and surgicopathologic stages. Such patients can then be offered an individualized treatment plan based on their precise disease status. The primary surgical management of cervical cancer generally consists of hysterectomy. For patients with stage IA1 lesions who desire fertility preservation, cervical conization with clear surgical margins is acceptable treatment. The safety and efficacy of surgery to preserve fertility (e.g., radical trachelectomy) for patients with larger stage I lesions however has yet to be fully evaluated. There are five distinct variations or types of hysterectomy used in the treatment of cervical cancer.

Types of Hysterectomy

Type I A type I hysterectomy refers to the standard extrafascial total abdominal hysterectomy. This procedure ensures complete removal of the cervix with minimal disruption to surrounding structures and is appropriate treatment for stage IA1 disease.
Type II A type II hysterectomy is also referred to as a modified radical hysterectomy (Fig. 52.5, Fig. 52.6 and Fig. 52.7). This procedure involves dissection of the ureters from the parametrial and paracervical tissues down to the ureterovesical junction. This permits removal of all parametrial tissue medial to the ureters, as well as the medial half of the uterosacral ligament and proximal 1 to 2 cm of vagina. This operation is usually performed in conjunction with pelvic lymphadenectomy.

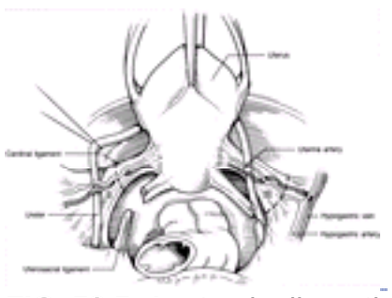

FIG. 52.5. Anatomic dissection of radical hysterectomy. The cardinal ligaments are transected (*dashed line*) at the level of the ureter (type II) or at the pelvic side wall (type III).

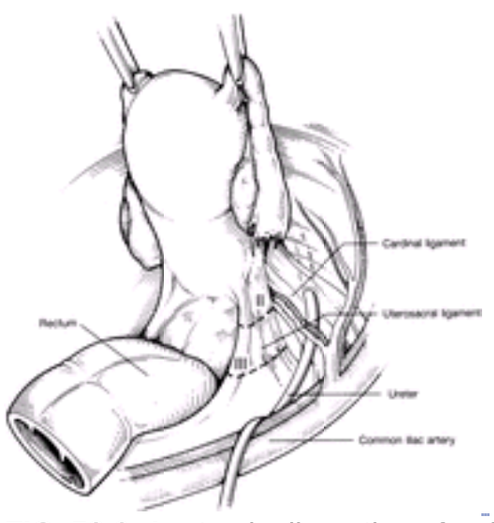

FIG. 52.6. Anatomic dissection of radical hysterectomy. The uterosacral ligaments are divided at the sacrum (type III) or midway between the sacrum and the uterus (type II).

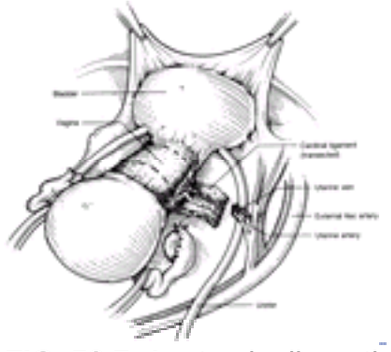

FIG. 52.7. Anatomic dissection of radical hysterectomy. In a type II radical hysterectomy, the upper 1 to 2 cm of vagina is excised. In type III radical hysterectomy, the proximal one-third to one-half of the vagina is removed.

Type III In a type III or radical abdominal hysterectomy, the ureters are completely dissected from within the paracervical tunnel, and the bladder and rectum are extensively mobilized (Fig. 52.5, Fig. 52.6 and Fig. 52.7). Establishing the paravesical and pararectal spaces facilitates removal of all the parametrial tissue out to the pelvic sidewall, complete resection of the uterosacral ligaments, and excision of the upper one-third to one-half of the vagina. Bilateral pelvic lymphadenectomy is performed with this procedure, removing all lymph-bearing tissue between the mid-common iliac vessels distally to the circumflex iliac vessels and from within the obturator fossa ventral to the obturator nerve.
Type IV/Type V A type IV or extended radical hysterectomy includes removal of the superior vesical artery, periureteral tissue, and up to three fourths of the vagina. In a type V or partial exenteration operation, the distal ureters and a portion of the bladder are resected. Type IV and type V procedures are rarely performed today because most patients with disease extensive enough to require these operations can be more adequately treated with primary radiation therapy.
Complications of Radical Abdominal Hysterectomy Modern surgical techniques and anesthesia have reduced the operative mortality associated with radical hysterectomy to 0.6%. Potentially fatal pulmonary embolism occurs in 1% to 2% of patients. Urinary and bowel fistula formation and incisional complications related to surgical treatment tend to occur early in the postoperative period and are usually amenable to surgical repair. Ureterovaginal and vesicovaginal fistulae occur in 2%

and 0.9% of patients, respectively. The most commonly observed complication after radical hysterectomy is urinary dysfunction resulting from partial denervation of the detrusor muscle during excision of the paracervical and paravaginal tissue. Radical hysterectomy results in vaginal shortening; however, with sexual activity gradual lengthening will occur. Pelvic lymphocyst formation occurs in 2% to 6.7% of patients following radical hysterectomy and pelvic lymphadenectomy. The incidence is somewhat lower when the retroperitoneal spaces are left open. Most lymphocysts are asymptomatic and do not require intervention; however, lymphocysts may occasionally produce pelvic pain, ureteral obstruction, or partial venous obstruction with thrombosis.

Primary Radiation Therapy

Radiation therapy can be used for all stages of disease and for most patients regardless of age, body habitus, or coexistent medical conditions. The recommended nomenclature for measurement of absorbed radiation dose is the gray (Gy); 1 Gy is equal to one joule (J) of energy absorbed per kilogram of substance. Radiation dose is also commonly expressed as centi-gray (cGy), with 100 cGy equal to 1Gy. By convention, the irradiation dose used in the treatment of cervical cancer is described relative to two anatomic landmarks within the pelvis. Point A is defined as a point 2 cm above the lateral vaginal fornix and 2 cm lateral to the uterine canal corresponding to the paracervical triangle. Point B reflects the dose delivered to the pelvic sidewall and is located 3 cm lateral to point A.

The technical treatment modalities used in modern radiation therapy for cervical cancer consist of a combination of external irradiation and local irradiation. External irradiation is delivered from a source remote from the body (e.g., linear accelerator, cobalt-60) and is used to treat the regional lymph nodes, decrease tumor volume, and reduce the anatomic distortion produced by larger tumor masses. External beam irradiation treatment for cervical cancer is usually delivered using a four-field technique (anterior, posterior, and lateral fields). The precise treatment volume is determined according to individual patient anatomy, but usually measures 15 cm × 15 cm to 18 cm × 18 cm. The pelvic radiation field extends 1 to 2 cm beyond the lateral borders of the bony pelvis and inferiorly beyond the border of the obturator foramen. The cephalad margin may be extended to 18 cm in length to treat the common iliac lymph nodes or even higher if paraaortic lymph node coverage is necessary. A typical external beam radiation treatment portal for cervical cancer is shown in Fig. 52.8.

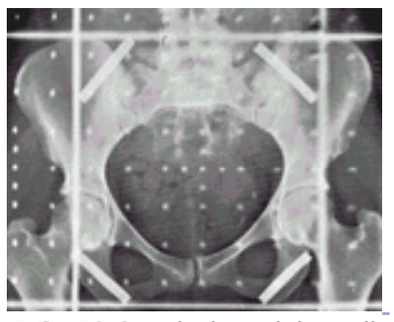

FIG. 52.8. Whole pelvis radiation treatment field for cervical cancer. In this case, the lower margin of the treatment field extends below the pubic symphysis to provide coverage of the proximal vagina. Lead tapes (white stripes) are used for excluding the corners of a square field, reducing the total irradiated volume by approximately 10%.

Brachytherapy, refers to a radiation source in direct proximity to the target tissue and may be delivered using a variety of intracavitary applicator devices, but the intrauterine tandem and vaginal colpostats are used most frequently for primary treatment (Fig. 52.9). Once adequate placement is assured, the device is after-loaded with radioactive isotope (e.g., radium-226, cesium-137, iridium-192). Alternatively, vaginal cylinders or interstitial needle implants may be used to deliver local radiation therapy, depending on patient anatomy and tumor distribution.

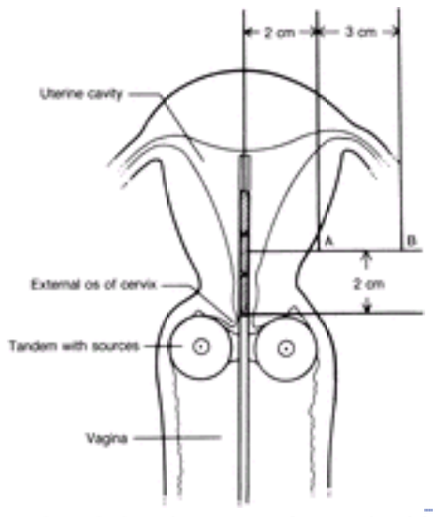

FIG. 52.9. Diagram of a typical intrauterine tandem and vaginal colpostat brachytherapy placement for cervical cancer showing the anatomic landmarks point A and point B.

The total dose delivered to point A is determined by the volume of disease to be treated and ranges from 6,500 to 7,000 cGy for small stage IB lesions to 8,500 to 9,000 cGy for bulky stage IIB and stage III lesions. For patients with documented paraaortic node metastasis, or those at high risk, 4,500 cGy of extended field irradiation is delivered to the paraaortic region. Cure rates with irradiation therapy are stage-dependent, with 5-year survival rates averaging 70% to 85% for stage I, 60% for stage II, 45% for stage III, and 18% to 20% for stage IV disease.

Concurrent Chemotherapy and Radiation Therapy In 1999, five multi-institutional, randomized controlled trials reported a survival advantage associated with the concurrent administration of chemotherapy and radiation therapy in the management of cervical cancer. Although these trials differed in their inclusion criteria, chemotherapy schedules, and prescribed radiation treatment, all demonstrated a similar improvement in progression-free survival (10%–27%) and overall survival (10%–17%). Many centers now administer concurrent treatment with chemotherapy and radiation therapy as standard practice for patients with locally advanced cervical cancer. Cisplatin (Platinol), 5-fluorouracil (Adrucil), and hydroxyurea (Hydrea) have been the chemotherapeutic agents most extensively studied as part of a combined modality treatment program. A commonly used contemporary regimen is cisplatin 40 mg per m^2 administered intravenously on a weekly basis during the radiation treatment interval.

Complications of Radiation Therapy Radiation therapy is associated with both acute and chronic complications. Perforation of the uterus may occur at the time of intracavitary insertion and, if unrecognized, may result in significant blood loss, radiation damage, and peritonitis. Appropriate management consists of removal of the implant and broad-spectrum antibiotic coverage if signs of infection are present. Vaginal fibrosis and stenosis is the most common chronic complication of radiation therapy for cervical cancer and is seen in up to 70% of cases. Ovarian function is lost in virtually all patients undergoing radiation therapy to the pelvis. Proctosigmoiditis occurs in up to 8% of patients undergoing radiation therapy for cervical cancer. Symptoms include abdominal pain, diarrhea, and nausea. An antispasmodic agent, a low-gluten and low-lactose diet, and steroid enemas may be useful; however, severe cases may require hyperalimentation and a diverting colostomy. Hemorrhagic cystitis is seen in approximately 3% of patients undergoing radiation therapy for cervical cancer. In contrast to surgical therapy, fistulous complications associated with radiation therapy tend to occur late and are more difficult to repair secondary to poorly vascularized tissues from radiation fibrosis and vasculitis. Rectovaginal and vesicovaginal fistulae each occur in approximately 1% of cervical cancer patients treated with irradiation. In such cases, biopsy specimens should be obtained from the edge of the fistula to rule out recurrent cancer. Diversion of the fecal (colostomy) or urinary (percutaneous nephrostomy) stream is usually required to allow adequate healing (3–6 months) prior to surgical repair. Two percent of patients experience small bowel obstruction as a consequence of radiation therapy; it is more common in those patients with vascular disease or a history of previous abdominal surgery. The most common site of small bowel obstruction is the terminal ileum, which is relatively fixed within the radiation field by the cecum. Complete small bowel obstruction or cases recalcitrant to conservative management require surgical intervention.

Chemotherapy

Chemotherapy as the sole mode of treating cervical cancer is indicated for patients with extrapelvic metastases (stage IVB) or those with recurrent disease who are not candidates for radiation therapy or exenterative surgery. Cisplatin has been the most extensively studied agent and has demonstrated the most consistent clinical

response rates. Complete clinical responses have been observed in 24% of patients, with an additional 16% demonstrating a partial response. Unfortunately, in most series, responses to cisplatin are short-lived (3–6 months). Other agents demonstrating at least partial activity against cervical cancer include carboplatin (Paraplatin), ifosfamide (Ifex), doxorubicin hydrochloride (Adriamycin), vinblastine sulfate (Velban), vincristine sulfate (Oncovin), 5-fluorouracil, methotrexate, and altretamine (Hexalen). There is little objective evidence to suggest that combination chemotherapy is superior to single-agent cisplatin treatment in improving the overall survival of patients with advanced or recurrent cervical cancer.

GENERAL MANAGEMENT BY STAGE

Stage IA1

The 5-year survival rate of these patients approaches 100% with primary surgical therapy. Extrafascial hysterectomy is adequate treatment for this group of patients. Conization may be used selectively if preservation of fertility is desired, provided the surgical margins are free of disease. In the absence of lymph–vascular invasion, the incidence of pelvic lymph node metastasis is 0.3%, and lymphadenectomy is not indicated. In the presence of lymph–vascular involvement, the risk of pelvic node metastasis increases to 2.6%. Pelvic lymphadenectomy and extrafascial hysterectomy should be performed in these cases. In patients who are medically inoperable, stage IA1 carcinoma can be effectively treated with intracavitary radiation.

Stage IA2

Microinvasive carcinoma with stromal invasion of 3.1 to 5.0 mm is associated with positive pelvic lymph nodes in 6.2% of patients. The preferred treatment for these lesions is modified radical (type II) hysterectomy with pelvic lymphadenectomy. Radiation therapy is equally effective from a survival standpoint but may carry a greater risk of post-treatment morbidity compared to modified radical hysterectomy.

Stages IB1, IB2, IIA

Both radical surgery and radiation therapy are equally effective in treating stages IB and IIA carcinoma of the cervix. Numerous uncontrolled studies support the merits of each modality, with no significant differences in pelvic tumor control or overall survival. Zander and colleagues reported on 1,092 patients with stages IB and II cervical cancer treated with radical (type III) hysterectomy and pelvic lymphadenectomy. Five-year survival rates were 84.5% for stage IB and 71.1% for stage II disease. Similar survival rates are obtained with primary radiation therapy. In one series, Perez and associates reported 5-year survival rates of 85% for 312 patients with stage IB disease and 70% for 98 patients with stage IIA disease treated with primary radiation therapy.

Treatment should be individualized for patients with bulky stage I (IB2) tumors. Tumor expansion of the upper endocervix and lower uterine segment can distort cervical anatomy and lead to suboptimal placement of intracavitary radiation sources. Consequently, the central failure rate has been reported as high as 17.5% in patients with cervical lesions greater than 6 cm treated with radiation alone. In such situations, a “completion” extrafascial hysterectomy is usually performed following radiation therapy. While many clinicians limit the use of radical hysterectomy to patients with small stage IB (<3–4 cm) or stage IIA lesions, there is evidence that acceptable survival rates can be obtained with primary surgical treatment in patients with bulky disease confined to the cervix. Five-year survival rates range from 73.6% to 82% after radical hysterectomy and pelvic lymphadenectomy for cervical lesions greater than 4 cm. Survival decreases to 66% at 5 years for lesions greater than 6 cm.

An alternative management plan for patients with bulky local disease is to administer chemotherapy in order to reduce the primary tumor volume prior to attempting radical hysterectomy. This approach has been termed *neoadjuvant chemotherapy.* Cisplatin, bleomycin sulfate (Blenoxane), and vinblastine has been the most extensively used drug combination. When chemotherapy is administered prior to surgery, complete clinical response rates range from 17% to 44%, with overall response rates of 80% to 90%. In addition to increasing surgical resectability, preoperative chemotherapy also decreases the number of positive pelvic lymph nodes and, in some studies, has seemingly improved 2- and 3-year survival rates.

Adjuvant Therapy Following Surgery Data are limited concerning the efficacy of postoperative pelvic irradiation in patients at high risk of recurrence after radical hysterectomy and pelvic lymphadenectomy. High-risk prognostic factors include positive pelvic lymph nodes, microscopic parametrial invasion, pelvic lymph node metastases, deep cervical invasion, and positive or close surgical margins. Sedlis and co-workers report results of a randomized, prospective trial of the Gynecologic Oncology Group comparing postoperative pelvic radiation therapy versus no further therapy for patients with high-risk stage IB cervical cancer following radical hysterectomy and pelvic lymphadenectomy. High- risk factors included large tumor diameter, deep stromal invasion, and the presence of tumor in capillary lymphatic spaces. For patients with these risk factors and negative pelvic lymph nodes, adjuvant pelvic radiation was associated with a statistically significant 47% reduction in the risk of disease recurrence. Survival analysis for this study however awaits additional data maturation.
Grossly Positive Lymph Nodes Encountered at Radical Hysterectomy The management of patients with grossly positive lymph nodes encountered at the time of radical hysterectomy has been controversial. Although there are no controlled studies, radiation therapy is commonly administered in such circumstances. In order to minimize postoperative radiation-related complications and preserve cervical anatomy for brachytherapy radiation placement, some clinicians advocate abandoning the surgical procedure once metastatic disease is confirmed by intraoperative histologic frozen section. Conversely, retrospective data suggest that postoperative irradiation after resection of all gross nodal disease and radical hysterectomy is associated with a lower rate of local recurrence and may provide a modest gain in survival, particularly for patients with three or more positive pelvic lymph nodes. Hacker and colleagues report their experience with patients undergoing complete resection of grossly positive lymph nodes in conjunction with radical hysterectomy and postoperative radiation therapy. The 5-year survival rates were 80% for patients with positive pelvic nodes and 48% for patients with positive paraaortic nodes; however, serious morbidity occurred in 18% of patients in this series. In addition, lower-extremity lymphedema has been reported in up to 23.4% of patients receiving combined modality therapy.

Stages IIB, III, IVA, and IVB

Radiation therapy is the treatment of choice for patients with stage IIB and more advanced disease. Radiation therapy for invasive cervical cancer is given as a combination of external and intracavitary treatments as described earlier. Long-term survival rates are approximately 60% for stage II, 45% for stage III, and 18% for stage IV disease. Patients with stage IVB disease are usually treated with chemotherapy alone or chemotherapy in combination with local irradiation for palliation of symptoms. These patients have a uniformly poor prognosis regardless of treatment modality.

Post-treatment Surveillance

Among patients with recurrent cervical cancer, recurrence is detected within 1 year in 50% of patients and within 2 years in more than 80%. Pelvic examination and lymph node evaluation, including supraclavicular nodes, should be performed every 3 months for 2 years and then every 6 months for an additional 3 years. As many as 70% of patients with recurrent cervical cancer in the pelvis will have abnormal cervical or vaginal cytology; therefore, appropriate cytologic smears should be obtained at the time of each routine examination. Any palpable pelvic mass should be evaluated by CT with fine-needle aspiration cytology if possible. A chest x-ray should be obtained annually to detect pulmonary metastases.

TREATMENT OF RECURRENT CERVICAL CANCER

General Considerations

Cervical cancer detected within the first 6 months after primary therapy is often termed *persistent* cancer, while that diagnosed later is referred to as *recurrent* disease. Appropriate treatment of recurrent cervical cancer is dictated by both the site of recurrence and the modality of primary therapy. In general, patients in whom locally recurrent disease develops following primary surgery should be considered for salvage radiation therapy. Conversely, surgical treatment should be considered for those patients with recurrent central disease who initially received irradiation. Distantly metastatic recurrent tumor is not amenable to either modality alone and is an indication for palliative chemotherapy and possibly radiation therapy for local control.

Surgical Treatment of Recurrent Cervical Cancer

Only patients with recurrent tumor confined to the central pelvis are candidates for surgical intervention. Total hysterectomy is inadequate treatment for centrally recurrent cervical cancer. Additionally, when radical hysterectomy is performed following maximum-dose radiation therapy, 20% to 50% of patients will experience ureteral strictures, urinary fistulae, or other serious complications. Therefore, pelvic exenteration is usually the procedure of choice for centrally recurrent cervical cancer.

Prior to exenterative surgery, a thorough investigation should be undertaken to rule out extrapelvic metastases. The clinical triad of unilateral leg edema, sciatic pain, and ureteral obstruction heralds tumor extension to the pelvic sidewall and is a contraindication to surgery. In most series, approximately 25% of patients with recurrent

cervical cancer are deemed satisfactory candidates for exenterative surgery.

Anterior exenteration is indicated for treatment of recurrent cervical cancer limited to the cervix, anterior vagina, or bladder. The procedure combines radical cystectomy with radical hysterectomy and vaginectomy. *Posterior exenteration* combines abdominal perineal resection of the rectum with radical hysterectomy and vaginectomy and is indicated for lesions confined to the posterior fornix and rectovaginal septum. *Total pelvic exenteration* is most often required for recurrent cervical cancer. The procedure involves the *en-bloc* excision of the bladder, uterus, rectum, and vagina (Fig. 52.10).

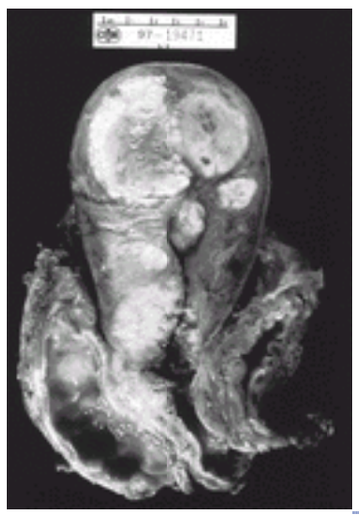

FIG. 52.10. Total pelvic exenteration performed for recurrent cervical cancer involves en-bloc resection of the bladder, vagina, uterus, and rectum. In this specimen, recurrent cervical cancer has replaced the cervix (uterine leiomyomata occupy the uterine fundus).

Using current surgical stapling devices, low-rectal reanastomosis can be performed in approximately 70% of cases. Reconstruction of the urinary system is accomplished using either an intestinal urinary conduit or one of the many techniques of continent urinary diversion (Miami pouch, Indiana pouch). A neovagina can be created by a variety of techniques using myocutaneous flaps (e.g., bulbocavernosus, gracilis, transverse rectus abdominus) or an omental flap with split-thickness skin graft. Modern surgical techniques and intensive care unit support have reduced the perioperative mortality to less than 7% in recent series. With proper patient selection and sound surgical judgment, 5-year survival rates after pelvic exenteration range from 45% to 61%.

GLANDULAR LESIONS OF THE CERVIX

Adenocarcinoma In Situ

Adenocarcinoma in situ (AIS) is characterized by replacement of the endocervical glandular cells by tall columnar cells with nuclear stratification, hyperchromatism, irregularity, and increased mitotic activity (Fig. 52.11). About 50% of women with AIS also have coexistent squamous cervical intraepithelial neoplasia (CIN). A diagnosis of AIS may be detected incidentally at the time of conization performed for CIN. Historically, a point of major concern regarding AIS is that these lesions were multifocal, so that conization margins were thought to be unreliable in predicting the presence of residual disease. In one study, Poyner and associates report on 28 patients with AIS in which 4 of 10 patients with negative conization margins had residual AIS in hysterectomy or repeat conization specimens. In contrast, studies using careful histologic sectioning indicate that cervical AIS lesions are usually located within the transformation zone and that true multifocality occurs in fewer than 15% of cases. A retrospective study from Shin and co-workers found only one case of residual or recurrent AIS among 98 patients undergoing conization with negative surgical margins and followed with conservative surveillance. As additional data accumulate, it appears that negative conization margins may be a more reliable indicator of disease clearance than previously thought. For young patients desiring to maintain reproductive capacity, AIS appears to be safely managed by cold knife conization and diligent surveillance. Clear surgical margins however are an absolute prerequisite to conservative management. For patients who have completed their childbearing, a simple hysterectomy should be performed because of the risk of recurrence, even in the presence of negative margins. Patients with unreliable follow-up and those with persistently positive conization margins should be offered simple hysterectomy as definitive therapy.

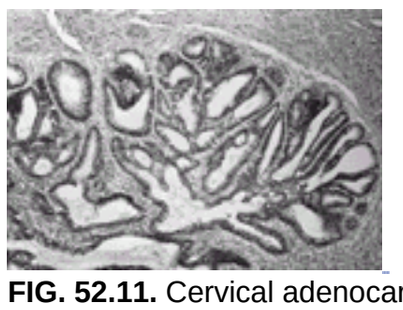

FIG. 52.11. Cervical adenocarcinoma in situ showing tall columnar cells with nuclear stratification, hyperchromatism, and irregularity.

Cervical Adenocarcinoma

Adenocarcinoma of the cervix accounts for approximately 10% to 15% of all invasive cervical neoplasms. As with SCC of the cervix, tumor size, depth of invasion, and histologic tumor grade have been identified as predictors of pelvic lymph node metastasis and overall survival. Although cervical adenocarcinoma has been reported to have a worse prognosis than similar stage SCC, this difference is due, at least in part, to the tendency of adenocarcinoma to grow endophytically and establish a large tumor volume prior to clinical detection. When cervical adenocarcinoma and SCC are comparatively matched by patient age, clinical stage, tumor volume, and treatment method, survival outcomes are not significantly different. In general, the same treatment algorithms can be applied to patients with adenocarcinoma of the cervix as to those with cervical SCC. Some authors have advocated performing a “completion” simple hysterectomy for patients with bulky, barrel-shaped adenocarcinomas of the cervix following primary radiation therapy. While this approach may decrease the risk of local recurrence, an associated survival benefit has yet to be conclusively demonstrated.

SMALL CELL CARCINOMA

Small cell carcinoma of the uterine cervix is similar to small cell “neuroendocrine” tumor of the lung and other anatomic locations. These tumors are clinically aggressive, demonstrating a marked propensity to metastasize to local and distant sites. At the time of presentation, disease is often widely disseminated, with bone, brain, and liver being the most common sites. Because of the high metastatic potential of small cell carcinoma, local therapy alone (surgery or radiation) rarely results in long-term survival. Multi-agent chemotherapy, in combination with external-beam and intracavitary radiation therapy, is a therapeutic approach currently under study. The two most commonly used chemotherapeutic regimens are vincristine, doxorubicin, and cyclophosphamide (VAC) and etoposide and platinum (i.e., cisplatin) (EP).

CARCINOMA OF THE CERVICAL STUMP

The natural history and patterns of spread of carcinoma of the cervical stump are similar to those of carcinoma of the intact uterus. The diagnostic evaluation, clinical staging, and principles of staging are also unchanged. In appropriate surgical candidates, early-stage disease can be treated with simple or radical trachelectomy with or without lymphadenectomy, depending on the volume of disease. Advanced-stage disease is treated with radiation therapy. However, the lack of a uterine cavity can make placement of intracavitary radiation sources difficult or impossible. In this case, vaginal colpostats alone or an interstitial needle implant technique can be used in combination with external-beam therapy.

INCIDENTAL CERVICAL CANCER FOUND AT SIMPLE HYSTERECTOMY

Invasive cervical cancer may be incidentally discovered in the surgical specimen after hysterectomy has been performed. For disease more advanced than stage IA1 (without lymph-vascular involvement), simple hysterectomy is inadequate treatment, as the parametria, vaginal cuff, and pelvic lymph nodes may harbor residual tumor. Additional treatment is dictated by the volume of disease and the status of the surgical margins of resection.

Radical surgery following simple hysterectomy for invasive cervical cancer generally includes radical parametrectomy, resection of the cardinal ligaments, excision of the vaginal stump, and pelvic lymphadenectomy. Although it may be technically difficult to perform an adequate radical resection, reoperation should be considered in selected clinical situations, particularly for young patients in whom ovarian preservation is desired. Use of postoperative adjuvant radiation therapy is dictated by surgical and pathologic findings.

Cervical carcinoma at the margins of resection after simple hysterectomy or the presence of gross residual tumor are both absolute indications for radiation therapy. Patients with such findings have a much less favorable prognosis than those without residual tumor and those with comparable disease who have been appropriately staged and treated with radiation alone. Radiation therapy is also well suited for older patients or those who are poor surgical candidates. Five-year survival is 95% to 100% for patients with microscopic disease, while 82% to 84% of those with macroscopic disease and negative surgical margins survive 5 years. If the surgical margins of resection are microscopically involved with carcinoma, 5-year survival ranges from 38% to 87%; survival drops to 20% to 47% for patients with gross residual tumor.

CERVICAL CANCER IN PREGNANCY

Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence ranging from 1 in 1,200 to 1 in 2,200 pregnancies (1.6–10.6 cases per 10,000 pregnancies). Conversely, 1 of every 34 women diagnosed with cervical cancer is pregnant at the time of diagnosis. The most common complaint of pregnant patients with cervical cancer is abnormal bleeding. However, confusion between the symptoms of early cervical cancer and those of normal pregnancy frequently leads to a delay in diagnosis. Pathologic confirmation of the presence of invasive cervical cancer should be obtained by directed biopsy in the presence of a grossly visible lesion. Conization is only indicated for those patients with apparent microinvasive disease on directed biopsy or for patients with persistent cytologic evidence of invasive cancer in the absence of a colposcopically visible lesion. Diagnostic conization should only be considered when a diagnosis of invasive cancer will result in a modification of treatment recommendations, timing, or mode of delivery. From an obstetric standpoint, the optimal time to perform conization is between 14 and 20 weeks gestational age or after the time of fetal viability has been reached.

The same clinical staging system of cervical cancer is employed for both nonpregnant and pregnant patients alike (see Table 52.2). For pregnant patients with cervical cancer, the use of MRI may be an appropriate substitute for intravenous pyelogram (IVP) or CT if minimizing fetal exposure to ionizing radiation is desirable. Once the diagnosis of cervical cancer has been established, treatment recommendations are individualized and are dependent on the stage of disease, gestational age at the time of diagnosis, and the desires of the patient regarding continuation of the pregnancy. Patients with well-documented stage IA1 disease (conization with negative surgical margins) may be managed with vaginal delivery and reevaluation postpartum. If the patient has completed childbearing, a simple extrafascial hysterectomy would be appropriate, otherwise close clinical follow-up is required. For patients with stage IA2 disease, a modified radical cesarean hysterectomy with pelvic lymph node dissection is the preferred treatment. Patients with stage IB or IIA disease may be treated with surgery in the form of radical hysterectomy and pelvic lymph node dissection, either in conjunction with cesarean section or with the fetus in situ, depending on the gestational age. Radiation therapy is the treatment of choice for patients with stage IIB to IVA disease or those with stage IB and IIA disease who are not favorable candidates for radical hysterectomy. Radiation therapy may be initiated with the fetus in situ for nonviable pregnancies, with spontaneous abortion occurring 4 to 5 weeks after starting treatment. For more advanced gestations, classic cesarean delivery is performed initially, with radiation therapy commencing 2 to 3 weeks following delivery. The issue of delaying treatment in order to reach a gestational age consistent with fetal viability has been controversial. Although the data are limited and retrospective in nature, it appears that a treatment delay of 6 to 12 weeks is not detrimental for patients with localized (stage I) disease. Treatment delays are not recommended for patients with more advanced disease.

SUMMARY POINTS

- Regular cervical cytologic screening with the Pap smear is the single most effective means of reducing the incidence and mortality of invasive cervical cancer.
- By convention, cervical cancer is a clinically staged disease; however, ancillary tests and surgical staging may provide useful information and facilitate a treatment approach tailored to the true extent of disease.
- Surgery (radical hysterectomy with pelvic lymphadenectomy) and radiation therapy are associated with equivalent survival outcomes for patients with early-stage (I–IIA) cervical cancer.
- Patients with advanced-stage disease (IIB–IVA) should receive radiation therapy with curative intent, preferably in combination with concurrent chemotherapy.

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Chapter 53

Ellen E. Sheets

Management of the Abnormal Pap Smear

EVOLUTION OF SCREENING CERVICAL CYTOLOGY AND THE BETHESDA SYSTEM
EPIDEMIOLOGY AND MOLECULAR BIOLOGY OF HUMAN PAPILLOMAVIRUS INFECTION
HUMAN PAPILLOMAVIRUS TESTING METHODS
ASCUS/LSIL TRIAGE STUDY
AMERICAN SOCIETY OF COLPOSCOPY AND CERVICAL PATHOLOGY CONSENSUS GUIDELINES FOR THE MANAGEMENT OF THE ABNORMAL PAP SMEAR
TREATMENT
TECHNIQUES FOR TREATMENT OF SQUAMOUS INTRAEPITHELIAL LESIONS
- Cryosurgery
- Laser Vaporization
- Laser Excisional Conization
- Loop Electrical Excisional Procedure
- Cold Knife Cervical Conization
- Hysterectomy
- Immunotherapy

POSTTREATMENT SURVEILLANCE
SUMMARY POINTS

RECOMMENDED READINGS
- Screening Cervical Cytology and the Bethesda System
- Epidemiology and Molecular Biology of Human Papillomavirus Infection
- Human Papillomavirus Testing Methods
- ASCUS/LSIL Triage Study (ALTS)
- Guidelines for the Management of the Abnormal Pap Smear
- Treatment

Since the advent of widespread Papanicolaou (Pap) smear screening in the United States during the 1950s, the incidence of invasive cervical cancer and mortality from this disease has fallen approximately 70%. The Pap smear collects exfoliated cells from the surface of the cervix. Exfoliation occurs from normal, precancerous, and cancerous cervical epithelium. It is the detection of precancerous cells, which predate invasive disease by years, that leads to treatment of the cervical epithelium and prevention of invasive disease.

The management of the abnormal Pap test has undergone numerous updates, which are reflected in the consensus guidelines from the American Society of Colposcopy and Cervical Pathology (ASCCP). Full guideline disclosure can be reviewed at http://www.asccp.org/. These guidelines were the result of a widely inclusive consensus conference convened in 2001 and reflect the new terminology for Pap test classification, known as the Bethesda System, which also underwent consensus review in 2001. A full classification can be reviewed at http://bethesda2001.cancer.gov/.

Treatment should be based on a diagnosis that results from evaluation of the tissue's abnormal cervical cytology. Screening and subsequent treatment are aimed at the detection and elimination of preinvasive cervical disease, thus eliminating subsequent invasive disease. Management guidelines have been developed for preinvasive cervical disease.

EVOLUTION OF SCREENING CERVICAL CYTOLOGY AND THE BETHESDA SYSTEM

The evolution of the Pap smear is instructive in many aspects. First devised as a simple method to determine the reproductive cycle of laboratory animals by George Papanicolaou, it has evolved into a source of cellular material for sophisticated molecular and diagnostic techniques. Although apparently ever changing, the one consistent aspect of its past and future is the success Pap screening has had in the prevention of invasive cervical cancer.

Papanicolaou introduced collection of cervical cells from the posterior vaginal fornix as a method of finding early invasive cervical cancer. Ayers introduced direct sampling of the cervix with the spatula that still bears his name. Such direct sampling significantly increased the cellular yield.

The next major advance was the support that the beginnings of the American Cancer Society provided for increasing the visibility of the Pap smear. Such exposure led to increasing adoption of the technique, and this coincided with the realization that Pap smears could detect preinvasive disease, as well. Richart and colleagues identified the preinvasive component to squamous cell cancer of the cervix. This was achieved, in part, by use of the colposcope in defining the cervical transformation zone.

Terminology was developed for squamous preinvasive disease and reflected its origin in the cervical epithelium. The term *cervical intraepithelial neoplasia*, or *CIN*, was developed, and increasing involvement in the epithelial layer was reflected by CIN grades. CIN grade 1 (CIN 1) was used when fewer than one half of cells of the squamous cervical epithelium were abnormal. CIN 2 represented approximately two thirds involvement and CIN 3 a full-thickness epithelial abnormality. Until the early 1990s, some iteration of these categories was used to describe cervical cytology results. These terms still are used to describe the histology of squamous cervical lesions.

Technology also has led to changes in the way that we obtain cervical cytologic specimens. The first advance was the Ayers spatula, as noted above. Next, cotton swabs, often moistened with saline, were used to obtain cells directly from the cervical transformation zone. Although an improvement, a major advance in obtaining endocervical cells occurred when the endocervical brush was introduced in the 1980s. Although earlier thinking was that squamous metaplastic cells or endocervical cells were important in determining the adequacy of cervical screening, this concept has not been supported by the data. It has since become evident that a certain amount of squamous cellularity is more reflective of adequate sampling.

In the late 1980s, increased attention was paid to the potential false-negative result rate of the Pap smear, widely quoted to be as high as 50%. A false-negative Pap smear result does not reflect the current condition of the cervical epithelium and can arise from errors in screening, interpretation, or sampling. Several studies have shown that the inability of a Pap smear to render the true cervical diagnosis is more likely due to the smeared cellular sample not representing the state of the epithelium rather than the technical interpretation being misleading. Given these data, several efforts were made to reduce the false-negative rate and resulted in technology that allows for the cervical cellular sample to be rinsed into a preservative solution. Data have shown that up to 80% of the cells collected are thrown away after a conventional smear is made. Less than 10% are left on the collection device when the device is rinsed rather than smeared onto glass. From the concept of improving the cellular sample came the basis for liquid-based Pap tests, thus attempting to decrease the false-negative rate.

The Food and Drug Administration (FDA) has approved two liquid-based Pap tests. Both allow for the cellular material to be deposited in a liquid preservative that rinses the collection device and fixes the cells. The liquid-based Pap tests are the ThinPrep Pap Test (TPPT, Cytyc Corporation, Boxborough, MA, 1996 approval) and the AutoCyte PREP (TriPath Imaging, Burlington, NC, 1999 approval).

FDA labeling for the TPPT allows the makers of this system to claim that it is more sensitive than the conventional Pap smear for the detection of low-grade squamous intraepithelial lesion (LSIL) or greater disease. In 2001, they were allowed a claim that it was more sensitive for the detection of high-grade squamous intraepithelial lesion (HSIL) or greater disease. Further data had been required by the FDA to substantiate the LSIL or greater claim, and the data from a six-site clinical trial resulted in a greater than 53% increase in detection of HSIL or greater disease.

FDA labeling allows the makers of AutoCyte PREP to state that it is a replacement for the conventional Pap smear and leads to fewer unsatisfactory specimens. There is less published literature on this system than on the TPPT. Although there have been editorials indicating that the two systems are probably equivalent, the data sets as yet do not support equivalency, and there has been no head-to-head trial comparing the two systems.

Given the significant concern regarding the quality of Pap smears, the U.S. Government developed the Clinical Laboratories Improvement Amendment released in 1988. This guideline addressed the number of Pap smears that could be screened by cytotechnicians and the need for quality assurance review. Additionally, this amendment directed the National Institutes of Health to establish guidelines on Pap smear terminology in order for the cytology results to be more consistent. As a

result of this direction, the first Bethesda conference was held in 1990, leading to the development of the Bethesda System for Pap cytology reports.

The Bethesda System used the categories of:

1. No evidence of malignant cells
2. Atypical squamous cells of undetermined significance (ASCUS) for cells felt to represent some of the spectrum of changes found in precancerous cells but not diagnostic of such
3. LSIL for cells with findings consistent with either human papillomavirus (HPV) effects or consistent with CIN 1–type changes. The thinking was that there was little ability to discern cytologically koilocytic effect from CIN 1 changes.
4. HSIL for cells with findings consistent with CIN 2, 3, or carcinoma in situ. The ability to discern among these categories was limited, but these cytologic changes were distinct from CIN 1–HPV effect.

In 2001, the third Bethesda conference was held and resulted in some more subtle, yet very important, changes. At major issue was the category of ASCUS. This category is difficult to interpret clinically, and it was felt that more recent data regarding this category supported a change. The change was to remove from the ASCUS category those Pap tests that contained cells suspicious for HSIL but not diagnostic. Therefore, the category of atypical squamous cells suspicious for HSIL (ASC-H) was developed. Further, the remaining atypical Pap test results would be designated atypical squamous cells of undetermined significance (ASC-US).

The 2001 Bethesda System update did not alter the categories of LSIL and HSIL. It did designate a specific cytology category for adenocarcinoma in situ. In the glandular preinvasive categories, atypical glandular cells (AGC) also have an undetermined significance (AGC-US) and suggest neoplasia. Within the glandular neoplasia section, the cytopathologist is asked to designate further whether the cells are from the endocervix or endometrium, if possible.

Further, those in compliance with the 2001 Bethesda System will now report benign endometrial cells, when seen in the cytology specimen, for women age 40 and older. As a women nears and goes beyond the menopausal years, the presence of benign endometrial cells can be indicative of more significant endometrial cavity pathology, such as polyps, hyperplasia (both simple and atypical), and endometrial cancer.

Educational notes are recommended at the end of the Bethesda System report and now will reflect the recommendations of the ASCCP consensus conference guidelines. A further discussion of these consensus conference guidelines is presented later in this chapter.

Interestingly, the 2001 Bethesda conference also took into account data from the Atypical/Low-grade Triage Study (ALTS), which looked at the overall best way to find histologic high-grade precancer within the cytology categories of ASCUS and LSIL. The expectation of the 2001 Bethesda conference was to triage ASC-US cytology by testing for HPV high-risk (HR)-type DNA and sending to colposcopy those whose ASC-US Pap tests were positive. The full results and recommendation of the ALTS and the ASCCP consensus conference will be discussed later in this chapter.

EPIDEMIOLOGY AND MOLECULAR BIOLOGY OF HUMAN PAPILLOMAVIRUS INFECTION

Since the early 1990s, HPV has been accepted as a necessary but not sufficient cause in the development of invasive cervical cancer, both squamous cell cancer and adenocarcinoma. It is the natural history of an HPV infection that has given rise to the not-sufficient portion. Excellent data support the concept that the majority of HPV infections, particularly the initial exposure in a woman's teens and early 20s, regress spontaneously.

Although HPV-related diseases have been noted in the medical literature since the Roman-Hellenic era, it was not until researchers using electron microscopy identified mature viral particles in condylomata during the 1950s that a viral cause for these diseases was entertained strongly. The next breakthrough came with the isolation of HPV type 6 DNA from condylomata by zur Hausen and colleagues during the early 1980s. Since that time, more than 100 HPV types have been identified. A new type is designated when there are sufficient differences in the DNA sequences but still enough homology such that it is consistent with the overall family of papovaviruses.

Interestingly, HPV types have specific preferences for the type of epithelium that they infect. Our interest is in those HPV types that exclusively infect lower genital tract epithelium. These HPV types have been categorized further according to their ability to cause cervical neoplasia. Those HPV types that rarely, if ever, are found in preinvasive or invasive cervical cancer are put in the category of low-risk viruses. Conversely, those types found at least occasionally in high-grade cervical intraepithelial neoplasia or cancer are categorized as high-risk viruses (Table 53.1). The prototypes of HR HPV are HPV 16 and 18. Combined, these viral types are present in more than 90% of high-grade precancers and over 80% of invasive disease.

Low-risk HPV types	6, 11
High-risk HPV types	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

TABLE 53.1. *Human papillomavirus types*

The genetic areas of interest in HPV are the E6 and E7 (E, early) reading frames. The protein products of these areas bind tumor suppressor genes *p53* and *pRB*, respectively. Simply, these genetic regions can cause transformation but not immortalization in cell culture when derived from the HR HPV types. Low-risk types do not give rise to such changes. Disruption of these tumor suppressor genes causes a cascade of events including alteration of the cell cycle. The viral capsule is quite uniform within the types and is formed from the L1 and L2 (L, late) reading frames. These capsule proteins are utilized in prophylactic vaccine therapy, whereas various manipulations of either the protein or HPV DNA from E6 and E7 are used in therapeutic immunologic approaches. An in-depth discussion of these events can be found in reviews of HPV molecular biology.

Exposure to HPV appears to occur primarily by intimate sexual contact but does not require intercourse. Other avenues of exposure have been discussed but not verified, such as common pools, hot tubs, and bathrooms. How HPV infects the skin has not been proven definitively but most likely requires breaks in the epithelial surface. Once exposed, the recipient's options are to kill the virus or become infected. When infection occurs, replication of the viral particle requires mature squamous keratinocytes for capsule assembly. This is the underlying reason why HPV cannot yet be cultured successfully in routine microbiology laboratories as a method of HPV detection.

Prolonged HPV infection allows the virus to produce its proteins and, in the case of high-risk viral types, that means E6 and E7 proteins. It is this process that is tied intimately to the morphologic changes that we perceive as CIN and invasive disease. For low-risk types, expression of the viral proteins leads to a proliferative epithelial response and the formation of condylomata or, in some cases, low-grade CIN.

Epidemiologic case studies, often using HPV DNA detection techniques, indicate that widespread exposure of the female and male sexually active population has occurred, yet the majority of these HPV-related infections appear to regress spontaneously. Koutsky and colleagues followed young women manifesting evidence of their first exposure to HPV and found that all evidence of HPV appears to regress spontaneously within 9 to 18 months from first exposure. The reason for eradication of this viral infection is not known, but immune response to the infection is a leading theory.

Reasons for suspecting that an immune response to HPV infection is the source of regression of disease are well founded but have not yet been proven definitively. Those whose immune systems are compromised, such as organ transplant recipients and human immunodeficiency virus–infected individuals, have virtually no ability to clear their HPV infections, even with repetitive treatment. Even when patients who are seropositive for human immunodeficiency virus or who have acquired immunodeficiency syndrome are treated aggressively with antiretroviral therapy, their HPV infections remain.

Interestingly, young women first exposed to HPV will be most likely to manifest their infections by developing CIN 1, which is detected by Pap test and can be confirmed by biopsy. However, the HPV types involved in these lesions are predominately in the high-risk category. Although this finding has not led to a change in the definition of low-risk versus high-risk types, it indicates that clinically detectable cervical cytologic abnormalities most likely represent HR HPV no matter what the degree of morphologic abnormality.

More significant precancerous changes, such as CIN 2 or 3, tend to occur in the mid to late 30s and into the 40s. These morphologic changes are indicative of risk for progression to invasive disease and, again, are caused by HR HPV types. How these women, often in apparent monogamous relationships, became exposed to HPV remains an area of strong research. Some believe that this represents reexposure, while others feel that perhaps a form of viral latency is at play. Obviously, HPV does not exhibit the classic manifestations of a latent virus, and perhaps the best way to describe this situation is a lack of clinical symptoms of the HPV infection after

apparent spontaneous regression during the woman's 20s.

Underlying the information regarding HPV discussed to this point is that studies increasingly are showing that cytologically normal women who harbor HR HPV types in the cervix over a period of years are at increased risk for the development of high-grade preinvasive disease. Although not yet completely accepted clinically, certainly these women represent the at-risk pool among those who have had sequentially normal cytology findings on Pap testing. These data become increasingly significant as the woman's age advances to 30 years or older.

Many clinicians are not aware that women who practice a homosexual life style are also at risk for HPV exposure. They, like their heterosexual counterparts, require Pap test screening and develop evidence of HPV exposure with positive cervical cytology findings. An abnormal Pap test result in a homosexual women is no different in its etiology than in those with other sexual orientations.

HUMAN PAPILLOMAVIRUS TESTING METHODS

Because HPV cannot be cultured, its detection depends on the identification of its DNA. Since the advent of polymerase chain reaction (PCR) and similar DNA amplification methods, very minute amounts of viral DNA can be detected from infected cells. Generally, these methods require the extraction of the cell's DNA, and then the aggregate DNA is probed specifically for the presence of viral DNA. Using such techniques, although very sensitive, does not allow for identification of what cell in the sample carried the viral DNA. Therefore, contamination from sperm, white cells, or mucus of male origin may lead to false-positive HPV DNA test results. The most common methods for HPV DNA detection are PCR based and RNA-DNA hybrid detection, which is the method used in Hybrid Capture (HC; Digene, Gaithersburg, MD).

HC II is a relatively simple and inexpensive method of detecting and amplifying a specific DNA signal and is clinically relevant as the only FDA-approved test for HPV. Cells are disrupted with a base solution that liberates the aggregate sample's DNA. RNA probes specific for HPV types are then added to the solution and allowed to adhere to target DNA to form DNA-RNA hybrids. This sample is then exposed to antibodies to DNA-RNA hybrids. These antibodies are already adherent to the walls of a well and, thus, the DNA-RNA hybrids are fixed to the walls. Multiple antibodies that have alkaline phosphatase attached to them, thus amplifying the signal, then further detect these hybrids. The signal amplification can be up to 3,000-fold. A chemiluminescent dioxetane substrate is then added to the sample and it is cleaved by the alkaline phosphatase. The subsequent substrate produces a type of light that can be measured in a luminometer. Such light is reported as relative light units (RLUs). The RLU of an unknown is compared with that produced from a control sample containing 10 pg/mL of relevant HPV DNA. Final data is reported as a RLU-to-PC ratio, and a positive sample must have a value of 1.0 or greater.

The beauty of HC is that little additional equipment is necessary for the assay. Also, multiple HPV DNA probe types can be placed into the sample at one time, allowing for detection of multiple different HPV DNA sequences. The assay is separated into high-risk and low-risk groups. In the high-risk group, the assay contains RNA probes for types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.

Problems noted in the literature with HC II surround its reproducibility and potential for cross-reactivity in the high-risk assay with low-risk types, which may be present in overwhelming amounts. Other issues surround whether or not the RLUs are directly proportional to the amount of HPV DNA present in the sample and, therefore, can be used as a method of viral load determination. No final consensus has been reached on that issue. Additionally, it is hard to discern from recent reports whether the relative changes noted in viral load are a byproduct of the size and grade of the cervical lesion or predictive of a larger lesion as Sun and others propose.

The general consensus is that HC II is as sensitive and specific as PCR-based HPV detection methods. PCR techniques have not yet been perfected that will multiplex for the presence of HPV DNA and discern high-risk HPV DNA from low-risk. However, in contrast to HC II, PCR does not appear to suffer from cross-contamination of its results from other HPVs that are not clinically relevant for that given patient or sample. Additionally, some researchers feel that sensitivity of PCR is slightly better than that of HC II and advocate that HPV-negative cytology be retested with PCR using the MY09-MY11 primers. Another potential advantage of PCR is the ability to determine specifically which HPV is present, whereas HC II will be able to determine only if the DNA lies within the high-grade or the low-grade category.

ASCUS/LSIL TRIAGE STUDY

Although only a small percentage, typically 10% to 14%, of ASCUS or of LSIL neoplasia actually represents a histologic high-grade lesion, such Pap test results are common enough to give rise to the majority, greater than 60%, of high-grade histology or CIN 2 or 3. Many clinicians would prefer not to perform colposcopy for the first ASCUS Pap test due to the frequency of this cytologic diagnosis.

More than 5% of all Pap tests per year in the United States reveal ASCUS. This would mean approximately 2 million colposcopies per year solely to evaluate ASCUS if all of these results were immediately triaged to colposcopy. LSIL represents approximately 2% of annual Pap test diagnoses. Given that the vast majority of histologic low-grade lesions or CIN 1 will regress spontaneously, one would prefer to follow patients with ASCUS/LSIL Pap test results, if possible.

The ALTS trial was developed to determine if CIN 3 lesions could be identified within these cytologic categories using either repetitive Pap tests, immediate colposcopy, or ancillary testing for the presence of HR HPV types. The colposcopy arm was considered the gold standard. Patients with a Pap test showing LSIL or ASCUS were randomized into either immediate colposcopy, interval Pap test follow-up, or HPV DNA testing using the HC II test to detect high-risk oncogenic viral types, with referral for colposcopy for positive test results. The main end point of the trial was a histologic diagnosis of CIN 3.

Approximately 640 patients were randomized into the LSIL arm when it was closed. Accrual was terminated due to the high percentage of patients found to have HR HPV by HC II results. Given that more than 80% of HC II results were HR positive, HPV DNA testing could not be utilized in this cytologically defined group for colposcopy triage.

In the ASCUS group, however, the results indicated that HC II HR-positive result was an effective parameter for triage for colposcopy and resulted in the greatest detection rate of CIN 3 from the three ASCUS study arms. HC II detection of HR types resulted in approximately 56% of this arm of the ASCUS study being referred for colposcopy. The repetitive Pap test arm reached equivalency over a year of follow-up when colposcopy was done for a repeat ASCUS result or greater. It is from this large pivotal trial and several smaller antecedent trials that the ASCCP based its recommendations for ASCUS and LSIL evaluation.

Since publication of the ALTS trial data, there has been some dissent regarding HPV testing of ASCUS Pap tests. Herbst and others have cited the difficulties in reproducing the ASCUS Pap test results as a potential pitfall of the trial results. Other obvious concerns for clinicians with the ASCUS triage to HPV testing are as follows: (a) discussing the HPV test results with patients and their families, (b) potential cross-over reactivity when high viral loads of low-risk HPV 6 and 11 are present, (c) potential increase in the ASCUS category because reflexive testing for this category will occur, (d) how to manage the ASCUS-positive, HC II HR-positive patient with a colposcopy that reveals no evidence of disease. The challenge will be to educate the consumer and medical personnel on how to handle these situations.

AMERICAN SOCIETY OF COLPOSCOPY AND CERVICAL PATHOLOGY CONSENSUS GUIDELINES FOR THE MANAGEMENT OF THE ABNORMAL PAP SMEAR

Following the 2001 Bethesda conference, the ASCCP held a consensus conference to discuss the changes in the Bethesda System and to utilize data from the ALTS and other clinical trial data to develop guidelines for the clinician in the management of abnormal Pap test results. These guidelines can be viewed in their entirety at http://www.asccp.org/.

For the Pap test that does not reveal any evidence of cytologic abnormalities, the ASCCP has indicated that routine screening should allow for physician-patient decision making. There was considerable discussion regarding how to determine if a woman is in a high-risk category and, therefore, should be screened more frequently compared with those women felt to be at low risk for the development of CIN. No true consensus was reached. The concept of HPV DNA testing for high-risk viral types by HC II in women with normal cytology as a means of determining risk was discussed, but it was felt that the data were insufficient to allow them to reach a conclusion.

In the category of ASCs, the ALTS data were utilized for ASC-US. Interestingly, little mention is made of ALTS use of the ASCUS category without further subcategories, and the ASCCP guidelines will use the 2001 Bethesda System category of ASC-US. Essentially, ASCCP guidelines indicate that the preferred method of evaluation of the ASC-US Pap test is two-fold. If it comes from a liquid-based sample, reflex testing for HR HPV DNA is done using HC II, and if it comes from a conventional Pap smear, secondary HPV testing is performed using a second co-collected sample. If no co-collection was performed, then for the ASC-US category, Pap smears are repeated at 6-month intervals and the patient is referred for colposcopy if results are repetitively ASC-US or greater. When HC II is done, those patients with ASC-US samples positive for HR HPV should have immediate colposcopy, whereas those negative for HR HPV can revert to yearly screening.

For those patients with ASC-US with HR HPV on HC II who do not have documented CIN at the time of colposcopy, repeat cytology testing at 6-month intervals is

recommended, with repeat colposcopy for any positive results. An alternative is to repeat the HPV DNA testing after 12 months and, if positive for high-risk types, repeat the colposcopy. Little is known as to the rates of CIN for the initial ASC-US and less for those who require follow-up of negative colposcopy findings. Postapproval studies will be extremely useful in guiding clinicians and patients.

Patients with ASC-H Pap test results should be referred for immediate colposcopy. Although there are no specific data for this category regarding the possibility of CIN 2 or 3 being found, it is inferred from previous reports that the possibility will be high enough to warrant colposcopic intervention. Postimplementation studies will be of interest. Additionally, the guidelines lead one to assume that HPV DNA testing would not be a useful triage tool for this category.

When negative colposcopy results are noted for ASC-H, the recommendation is to review the cytology and histology for correlation and confirmation. If again supportive of the respective diagnoses, then repeat cytology at 6-month intervals or retesting for HR HPV DNA after 12 months is acceptable, with repeat colposcopy for positive findings.

For LSIL, the ASCCP guidelines note that HPV DNA triage is not useful. This is based primarily on the ALTS data that revealed 83% of LSILs positive for HR types. Given these data, colposcopy is the preferred method of evaluation for LSIL. If colposcopically directed biopsies are consistent with CIN 1 or less, then continued screening with cervical cytology at 6-month intervals is acceptable. Another follow-up method postcolposcopy would be for patients with documented CIN 1 to undergo an HC II assay after 1 year and, if positive, move on to treatment. In any scenario, the guidelines recommend a follow-up period after histologically documented CIN 1 to allow for spontaneous regression. Those patients with cytologically demonstrated LSIL who have CIN 2 or 3 shown by biopsy should follow the guidelines for treatment.

The general guidelines for LSIL are for complete visualization of the transformation zone. When the colposcopy is unsatisfactory, an endocervical curettage is preferred, because it may reveal a diagnosis confirmed by this histology. If all histologic findings are negative, repeat cytologic studies at 6-month intervals or testing for HPV DNA after 1 year is appropriate.

When postmenopausal women have a Pap test consistent with LSIL, one should evaluate the Pap test for evidence of atrophy. If present, treatment with topical estrogen cream should be performed and the Pap test repeated after several weeks. Should the Pap test result then revert to normal, routine screening can be instituted. If still abnormal, colposcopy should be performed.

Pregnant women with LSIL should have colposcopy and biopsy performed when deemed appropriate by examination. Continual follow-up with either cytology or HPV DNA testing is warranted. Adolescents can be followed prospectively without colposcopy for the LSIL category. Either cytologic examination at 6-month intervals or follow-up HPV DNA testing after 1 year is acceptable.

There is no question that an HSIL detected with cytology most likely will reveal CIN 2 or 3 on colposcopically directed biopsies and, therefore, colposcopy is the preferred method. With HSIL cytology results, one would still recommend colposcopy, even if the HC II screen were negative for HR HPV DNA.

Pregnant women should receive colposcopy and directed biopsy of any identified lesion. Vascular changes are more marked during pregnancy, thus making simple interpretation of the lesion colposcopically without biopsy confirmation more difficult. Therefore, even though bleeding may occur, it is recommended that biopsy be performed to rule out invasive disease.

Many clinicians are concerned when HSIL cytology is followed by negative colposcopy and biopsy findings. The guidelines indicate that for a satisfactory colposcopy, follow-up at 4- to 6-month intervals is acceptable for up to 1 year. If cytology results are still positive without lesions noted at that time, then a loop electrical excisional procedure (LEEP) should be performed.

In glandular lesions, the ASCCP guidelines are explicit that the Pap test that shows AGC, whether further qualified or not, must be evaluated with colposcopy and endocervical sampling. For those Pap tests showing AGC that are further qualified as suggestive of neoplasia, a negative colposcopy with negative histologic assessment does not end the evaluation. In that setting, further tissue sampling is required, and the preferred method is by cold knife conization. The same intervention applies for repetitive Pap tests showing AGC that are not explained by colposcopic assessment.

When the glandular cytology is felt to be endometrial in origin, then endometrial sampling is indicated. Also, when the glandular cytology is not further qualified and the woman is perimenopausal or postmenopausal, again endometrial sampling is recommended.

The finding of benign endometrial cells on a Pap test in a woman over age 40 should trigger the consideration of endometrial sampling. A careful history of the woman's menstrual pattern or evidence of any recent changes should be sought in addition to questioning, when appropriate, about postmenopausal bleeding.

Cytologic findings consistent with squamous cell cancer always should trigger a further examination, either visual if the lesion is obvious or by colposcopy if not clinically apparent. There is no consensus as to how tissue sampling of possible occult squamous cell cancer should be performed, and many advocate a LEEP be done rather than cold knife conization.

For those whose cytology is consistent with adenocarcinoma in situ, colposcopy should be performed to identify any obvious areas of malignancy, but unless a diagnosis of adenocarcinoma in situ is found on biopsy, a diagnostic procedure is indicated, preferably a cold knife conization. Such a tissue excision should be evaluated for the presence of adenocarcinoma in situ and the possibility of early invasive adenocarcinoma.

TREATMENT

The criteria for treating preinvasive cervical disease depend on the histologic diagnosis, the location and size of the lesion, and the distance from the endocervical canal to the lesion. For CIN 2 or 3, treatment without delay is advised. In the case of CIN 1, persistence of the lesion for longer than 12 months is a reason for treatment. When the histology indicates a glandular lesion, cold knife conization (CKC) is indicated.

Treatment can be either ablative or excisional. Ablative techniques do not generate any further tissue specimens and include laser vaporization and cryosurgery. Such treatment requires a satisfactory colposcopic examination that identifies the entire transformation zone and the full extent of the lesion area. Excisional techniques will generate further tissue for histologic review and include conization by cold knife, LEEP, or laser excisional technique. Generally, when LEEP is used in the office, the same criteria used for ablation apply in order to minimize the potential for bleeding.

Mitchell and colleagues randomly compared cryosurgery, laser vaporization, and LEEP for patients with cervical squamous intraepithelial lesions. No essential difference was noted in success rates or complications among these techniques. As noted above, glandular lesions, either suspected by cytology or documented by histology, require surgical intervention. Because controversy still exists regarding the status of the type of conization for glandular disease, the ASCCP guidelines do recommend CKC for depth of excision and clarity of margins.

TECHNIQUES FOR TREATMENT OF SQUAMOUS INTRAEPITHELIAL LESIONS

Treatment techniques are listed in Table 53.2. It is important to remember that the final pathology after these excisional techniques occasionally will reveal apparently normal epithelium. The most likely reason for this is that the area of morphologic change was removed by a prior colposcopically directed biopsy.

Ablative
Cryosurgery
Laser vaporization
Excisional
Laser excisional conization
LEEP (loop electrical excisional procedure)
Cold knife (scalpel) conization
Hysterectomy

TABLE 53.2. *Techniques for treatment of squamous intraepithelial lesions*

Cryosurgery

The technique of cryosurgery initially was reported for treatment of CIN in the early 1970s. Using either carbon dioxide or nitrous oxide under pressure as the coolant, the cervical epithelium is frozen to a depth of 6 to 10 mm. The length of time for the freeze and the absolute temperature of the probe will determine the depth of penetration and subsequent tissue loss. Tissue is sloughed off slowly, over a period of 10 to 14 days, as a watery discharge. The most widely accepted technique for cryosurgery is to freeze the cervix for 3 minutes after formation of an ice ball on the cervix, followed by a 5-minute thaw and a repeated 3-minute freeze.

Although not as widely used as it was prior to LEEP, cryosurgery is less expensive and therapeutically will have results similar to LEEP when adequate caution is used with its application. In general, cryosurgical lesions need to be close to but not extend far into the cervical canal. They ideally need to be within a 2-cm radius from the canal, not occupy more than 50% of the cervical surface, and not involve the endocervical glands. Generally, cryosurgery is performed after childbearing has been completed.

Laser Vaporization

Initially discussed in the gynecology literature in the late 1970s, laser (light amplification by stimulated emission of radiation) became the mainstay of therapy throughout the 1980s and into the 1990s. Its use does require a learning curve, and the length of time for vaporization of cervical lesions should not exceed that taken by cryosurgery. Laser is light generated in the infrared spectrum by running electricity through a gas. For lower genital tract use, the gas used is carbon dioxide. The wavelength of such a laser is absorbed primarily by water. Thus, individual cells are heated instantaneously when the light contacts them, leading to their immediate vaporization by boiling the cellular water content. One can control the depth of laser penetration into the cervical epithelium quite closely by altering the spot size, the power, and the dwell time. Settings used lead to a lower power density that creates a larger area of vaporization and is achieved by a beam spot size of 2.0 to 2.5 mm. Generally, laser vaporization is done to a depth of 7 to 10 mm.

The procedure can be done safely in the office under local anesthesia, using nonsteroidal antiinflammatory drugs to reduce postprocedure discomfort. It is not uncommon to perform laser procedures in the operating room when the area to be treated is extensive.

Laser was widely replaced by LEEP. Tissue generation and ease of use have made LEEP attractive. However, treatment of extensive, preinvasive disease involving multiple lower genital tract structures, such as the cervix and vagina, often are performed in one sitting using laser.

Laser Excisional Conization

Rather than using laser for vaporization leading to ablation, one can use it to excise a conization specimen. The settings for the latter create a significantly greater power density, allowing the laser beam to act in an excisional rather than ablative manner. This is achieved by decreasing the spot size of the beam. Difficulty interpreting cone margins due to “char” artifact caused by laser excision and the ease of LEEP conization have reduced significantly the indications of laser conization.

Loop Electrical Excisional Procedure

LEEP, variably known as simply loop or LLETZ (large loop excision of the transformation zone), was made possible after modifications were developed in the wire loop and the electrosurgical current running through it. Now the current, a blend of coagulative and cutting electrosurgical currents, allows for excision with minimal bleeding and minimal coagulative artifact of the excisional margin.

Most practitioners who perform LEEP will do so in the office on patients with satisfactory colposcopy findings, with the extent of the lesion visible. Vasoconstrictive agents, such as epinephrine or pitressin, are combined with local anesthetics given in an intrastromal technique, circumferentially over the cervical face and avoiding the lesion area. Such treatment maximizes vasoconstriction and provides local anesthesia. Many practitioners will identify the transformation zone and lesion tissue by staining the cervix with modified Schiller iodine solution prior to excision. The procedure is best performed as a single pass encompassing the transformation zone and lesion. Coagulation of the surgical bed is then done with a roller ball cautery using a spark technique. Monsel solution commonly is placed in the surgical bed for hemostasis, thus avoiding sutures.

Cold Knife Cervical Conization

The role of CKC has become increasingly limited due to the widespread use of LEEP. Most clinicians feel that CKC should be performed when the margins of resection are important, because LEEP can leave a cautery effect difficult to interpret at the margin. The uses of CKC have been focused on evaluation of microscopic invasive disease, both squamous cell cancer and adenocarcinoma. Certainly there is support for CKC in adenocarcinoma in situ for evaluation of margins and depth of the conization sample. The incidence of adenocarcinoma in situ is increasing in women of childbearing age, and sparing of fertility is an important concern. Given this rise in incidence, much has been made regarding conservative management. Shin and others point out that deep conization of greater than 1½ to 2 cm with negative margins can assess the extent of adenocarcinoma in situ involvement and margin status. With negative margins, the patient can be highly reassured that no residual disease exists in the residual cervix.

CKC generally is performed under general anesthetic with the patient in the dorsal lithotomy position. The cervical transformation zone is identified by use of iodine solution, and the areas that are iodine negative are not part of the transformation zone.

Hysterectomy

Although not commonly used at this time, there still is a role for hysterectomy in the treatment of the abnormal Pap test. Such a need does arise in the scenario of repetitive high-grade CIN that recurs despite less invasive treatments. It is not uncommon in this situation to end up with cervical scarring that makes Pap test and colposcopy virtually impossible to perform. The patient, particularly postchildbearing, may opt for more definitive management with hysterectomy. However, she should be counseled that her abnormal cytology result rate posthysterectomy will not be zero. Preinvasive disease can occur in the upper vaginal vault at the hysterectomy cuff area.

Immunotherapy

Because HPV is necessary for the development of CIN and invasive cancer, one would assume that a prolonged infection is required for transformation. HPV-related cell surface proteins have been identified and certainly should induce an immune response. This immune response potentially could be supplemented by inducing a further immune response by the administration of similar HPV-related proteins. The concept is to enhance a T-lymphocyte response that will lead to eradication of the cervical lesion.

Several methodologies have been evaluated in phase 1 and 2 clinical trials looking to treat CIN 2 and 3 or invasive squamous cell carcinoma. The results have shown some responses but are not yet definitive.

Vaccines have been developed that employ the use of the HPV viral capsule. The capsule is produced by the L1 and L2 regions of the HPV genome and have very little variation from one type of HPV to another. Therefore, capsules generated in vivo from the proteins of these regions are being given as viruslike particles, or VLP, as vaccines against initial infection. The concept is to develop an antibody response to the VLP and thus create an antibody barrier to HPV infection transvaginally. It will be several more years before the preliminary clinical results are known, but initial antibody data from the cervix appear to support the induction of an immune response.

POSTTREATMENT SURVEILLANCE

Although the excisional and ablative methods are extremely effective for the treatment of CIN, there are instances of persistence and failure posttreatment. In general, these are found at the time of follow-up Pap testing. However, there is a growing interest in using HPV DNA after LEEP to predict which woman with positive margins after LEEP are at greatest risk of recurrence. At this point, there is no specific recommendation for HPV DNA testing post-LEEP, but it is certain to be evaluated further.

Most clinicians follow patients posttreatment with Pap tests every 6 months for a year and, if normal, yearly. Some have advocated the additional use of an endocervical curettage in the follow-up of women with glandular lesions, particularly adenocarcinoma in situ. If the Pap test result is abnormal, colposcopy should be performed to define the extent of disease and allow for directed biopsies.

SUMMARY POINTS

- The Pap test has a proven track record for success. Since its widespread inception in the 1950s, the incidence of invasive cervical cancer and related death has dropped significantly. Since then, the technique surrounding how cervical cytology is obtained and processed has changed, with increases in transformation zone sampling and decreases in apparent false-negative test result rates.
- In the 1960s, the categories of cervical intraepithelial neoplasia were used to describe preinvasive cervical cytology. CIN ranged from minor or grade 1 changes to the most severe cytologic atypia, designated CIN 3. In the 1990s, the Bethesda System created the categories of ASC-US, HSIL, AGC, and adenocarcinoma in situ to complement the invasive squamous cell cancer and adenocarcinoma categories.
- HPV is a necessary but not sufficient cause for the development of cervical precancerous and cancerous lesions. Testing for the presence of HPV DNA can improve the triage pattern of women whose Pap tests fall within the category of ASC-US. Data from the ALTS have shown that screening such Pap tests for the presence of HR HPV will better identify those women within the ASC-US cytology screening category who harbor high-grade CIN.
- Treatment advances stem from understanding that preinvasive and invasive cervical disease arises at the transformation zone. Treating this zone of change will completely eliminate preinvasive disease approximately 90% of the time or more. Therapies range from simple excisions of the abnormal cervical epithelium to laser or cryosurgical ablations, to surgical excisional biopsies of the cervix, to hysterectomy.

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Chapter 54

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Uterine Cancer

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The uterus and endometrium are unique organs. Almost any type of tissue histology can and does arise from these pluripotent tissues. This chapter will present premalignant and malignant conditions of the uterus. This includes the premalignant condition endometrial hyperplasia, as well as the frankly malignant conditions of the uterus that comprise the following two broad categories: (a) epithelial cancer and (b) mesenchymal tumors. Both of these types of malignancies develop within the lining or the body of the uterus, and this chapter will describe the epidemiology, staging, and treatment of these cancers. The epithelial cancers are primarily comprised of endometrioid, clear cell, and papillary serous type tumors. The mesenchymal tumors are less common and are comprised of three broad categories, (a) mixed müllerian tumors, (b) stromal tumors, and (c) leiomyosarcomas.

ENDOMETRIAL HYPERPLASIA

Classification

Endometrial hyperplasia is an abnormal condition that usually represents an overgrowth of the endometrium. This terminology encompasses a wide variety of conditions. Some of these are clearly benign and some potentially malignant. Unfortunately, there have been so many different classifications over the years that there is significant confusion about the meaning of the term *endometrial hyperplasia.* For many years, it has been suggested that endometrial hyperplasia reflects the histologic representation of the continuum between normal proliferating endometrium and adenocarcinoma in situ. This theory was based on studies first reported by Gusberg and Kaplan in 1963. In that study, the authors reported that 20% of patients who had a hysterectomy were found to have a coexisting adenocarcinoma and that endometrial cancer developed in almost 12% of the remaining patients, with an average follow-up of 5.3 years. They concluded that the risk of cancer was significantly higher in women with endometrial hyperplasia than those without and that 10 years later the cumulative risk for cancer was approximately 30%.

During the ensuing years, several different classification schemes were developed, which resulted in increased confusion regarding both diagnostic criteria and prognosis of the various subtypes of hyperplasia. In the early 1990s the International Society of Gynecological Pathologists endorsed a classification that used both architectural features (the degree of glandular crowding and complexity) and cytologic features, especially cellular atypia. Simple hyperplasia is defined as abnormally thickened endometrium with histologic evidence of an increased ratio of glands to stroma; the glands are cystically dilated and somewhat irregular with some infolding and budding. Complex hyperplasia represents glandular crowding with even less intervening stroma, and the glands show significant infolding and budding (Fig. 54.1). Atypical hyperplasia refers to either simple or complex architectural patterns, in which the cells lining the glands show loss of polarity, nuclear enlargement with increased nucleus-to-cytoplasm ratio and prominent nucleoli, and irregularly condensed chromatin (Fig. 54.2). Cystic hyperplasia is a benign condition arising from inactive endometrium and is not premalignant.

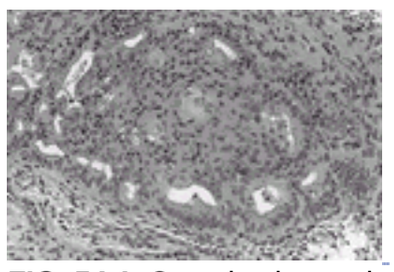

FIG. 54.1. Complex hyperplasia without atypia. Closely packed glands are connected by morular squamous metaplasia. No cytologic atypia is present.

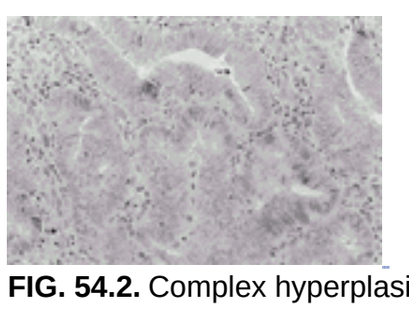

FIG. 54.2. Complex hyperplasia with atypia. Closely packed, irregular glands demonstrate cytologic atypia in the form of loss of polarity and rounding up of the nuclei

and nucleoli.

Since the study by Gusberg and Kaplan, additional studies have clarified some of the questions regarding this disorder. Using the new criteria, Kurman and colleagues reported that the risk of progression of endometrial hyperplasia to cancer varied according to the subtype. In this study of 170 patients, untreated endometrial hyperplasia regressed spontaneously in 74% and remained stable for more than 10 years in 18%. The risk of progression to cancer was 1% for patients with simple hyperplasia without atypia, 3% for those with complex hyperplasia without atypia, 8% for those with atypical simple hyperplasia, and 29% for patients with complex atypical adenomatous hyperplasia (Table 54.1).

TABLE 54.1. *Natural history of premalignant endometrial conditions*

Clinical Picture and Diagnosis

Endometrial hyperplasia usually becomes apparent with irregular vaginal bleeding. For this reason, this symptom should be evaluated with liberal use of the endometrial biopsy. Endometrial hyperplasia often is associated with a history of unopposed estrogen exposure, either exogenous or endogenous. In premenopausal women it is associated with obesity and anovulation. Therefore, women with known polycystic ovary syndrome or known anovulation are at increased risk for developing this disease, as are obese women. Any abnormal bleeding should be investigated in the postmenopausal woman, but features that would increase the suspicion of an abnormal endometrium are unopposed estrogen exposure from obesity or oral intake.

Cervical cytologic screening techniques are not a reliable means to diagnose endometrial abnormalities and should not be used to screen for endometrial abnormalities. Nonetheless the Pap smear can reveal endometrial abnormalities. Atypical glandular cells of undetermined significance (AGUS) should be evaluated aggressively, because the risk of having underlying endometrial pathology is high. Endometrial biopsy clearly should be included in the evaluation of this abnormal cytology. An endometrial biopsy is reported to be 97% as sensitive as a formal dilation and curettage (D&C). Therefore a D&C to evaluate these abnormalities is usually not necessary and should be used only when an endometrial biopsy cannot be performed, when persistent bleeding is unexplained by the biopsy, or when there is some uterine structural abnormality suspected, such as a polyp.

Management

Therapy for endometrial hyperplasia must be individualized and depends on histologic criteria, predisposing factors, patient age, and desire to maintain fertility. In addition to differences in overall prognosis, the various subtypes of endometrial hyperplasia also respond differently to progestin therapy. Ferenczy and Gelfand reported on the results of progestin therapy in 85 postmenopausal women with endometrial hyperplasia. Patients who had hyperplasia without atypia enjoyed complete reversal of the abnormality following treatment with medroxyprogesterone acetate, 10 to 20 mg daily. Patients with cellular atypia noted only a 50% response rate to the same treatment regimen. In patients with atypical hyperplasia, there was also an increased risk of recurrent hyperplasia or cancer after completion of the progestin therapy when compared with those who had hyperplasia without atypia (50% vs. 6%).

Premenopausal women can be treated with oral contraceptives for 3 months if they have no significant contraindications to their use. Most studies suggest that cancer will develop eventually in about 20% to 30% of patients with complex atypical adenomatous hyperplasia, but some have suggested a risk as high as 82% for those with untreated atypical hyperplasia. The risk of progression appears to be higher for postmenopausal than premenopausal women. The mean duration of progression from endometrial hyperplasia to carcinoma is about 10 years for lesions without atypia and 4 years for atypical lesions. In patients with atypical hyperplasia diagnosed by an endometrial biopsy specimen, a formal D&C should be considered to rule out a coexisting adenocarcinoma. It has been suggested that if gland epithelium is found within the stroma (i.e., stromal invasion) of the curettage specimen, even if the diagnosis is hyperplasia, there is a significant chance that the uterus still contains an endometrial cancer. If a diagnosis of carcinoma in situ is made by endometrial biopsy or D&C, in almost all circumstances a hysterectomy should be performed, because this is not a clearly reproducible diagnosis and actually may represent early invasive cancer or sampling error.

Progestational therapy is very effective in reversing endometrial hyperplasia without atypia. For these patients, either cyclic or continuous therapy is appropriate, using medroxyprogesterone acetate, 10 to 20 mg per day, or megestrol acetate (Megace), 20 to 40 mg per day, for either 14 days each month or daily. Therapy should be continued for 3 months, and then the endometrium should again be sampled to document response. The hyperplasia will revert to normal in 75% to 90% of patients treated with progestins. In patients who desire pregnancy, ovulation induction can be considered using either clomiphene or menotropins (Pergonal). If a patient does not desire pregnancy, oral contraceptive therapy should be considered. In those patients with persistent hyperplasia, definitive surgery should strongly be considered.

Patients with atypical hyperplasia often will opt for a hysterectomy and bilateral salpingo-oophorectomy when made aware of the risk of coexisting adenocarcinoma (approximately 20%) and the malignant potential of these lesions. A truly postmenopausal woman (last menses 2 or more years ago) should be encouraged strongly to undergo hysterectomy, with progestin therapy reserved for patients with severe medical problems that would make them very poor surgical candidates. If the decision is made to treat a patient medically, daily progestin therapy for 3 months is recommended, followed by repeat endometrial sampling. If hyperplasia persists in these patients, a D&C should be performed to rule out a coexisting malignancy, or a hysterectomy should be performed. At the time of hysterectomy, the uterus should be opened intraoperatively, with frozen section if indicated to document the presence and extent of any malignancy so that surgical staging can be performed at the same time, if appropriate.

An interesting, but still experimental, approach is insertion of an intrauterine contraceptive progesterone system (ICPS), which releases continuous therapeutic doses of progesterone or levonorgestrel. Until more experience is gained with the ICPS, it should not be employed outside a research setting. Two preliminary studies reported on the use of danazol (Danocrine) to treat women with adenomatous hyperplasia, and in both studies all women treated were noted to have reversal of the hyperplasia on repeat endometrial sampling. In all premenopausal women, menses resumed within 1 to 2 months following therapy. In the first study, atrophic changes were noted on repeat endometrial sampling even though the patients had normal serum estradiol levels, suggesting a direct effect on the endometrium.

A relatively recently described risk factor for endometrial hyperplasia and carcinoma is the use of tamoxifen citrate (Nolvadex) as an adjuvant treatment for breast cancer. Tamoxifen has been associated with a six-fold to seven-fold risk of developing endometrial cancer and an increased risk of endometrial hyperplasia, polyps, and growth of fibroids. The best method for monitoring women taking tamoxifen is unknown. Obviously, patients should have an annual pelvic examination and Pap smear. Endometrial sampling should be performed in all patients with abnormal uterine bleeding. Because tamoxifen acts as a weak estrogen, it is not unreasonable to consider annual endometrial biopsy or sonographic evaluation of endometrial stripe thickness. This recommendation, however, is not based on prospective studies but rather on an intuitive approach. According to current information, women taking tamoxifen have a greater than 84% chance of developing a thickened endometrium, making this technique relatively insensitive in evaluating the endometrium for pathology. Based on published studies, sonography is useful only for ruling out significant pathology if the endometrial stripe is less than 5 mm in thickness. Therefore, this may not be useful in screening women on tamoxifen.

In summary, the management of endometrial hyperplasia should be individualized, depending on the histologic findings and the patient's age health and reproductive desires. Treatment options include hormone therapy and surgery. Due to the increasing use of tamoxifen, gynecologists should expect to see more women using this medication and should be aware of the risk of both benign and malignant changes of the endometrium and be prepared to evaluate them for these abnormalities.

ENDOMETRIAL CARCINOMA

Incidence and Epidemiology

The American Cancer Society estimated that there were approximately 38,000 cases of epithelial endometrial carcinoma in the United States during 2001, accounting for about 7% of all malignancies in women. It ranks seventh in cause of death from cancer in women and accounts for about 6,000–6,500 deaths each year. At this time, endometrial cancer is the fourth most common cancer in women and is the most common gynecologic cancer. Occurring more frequently than endometrial cancer are lung, breast, and colon cancers. Endometrial cancer generally is thought to be a disease of postmenopausal women. However, one fourth of the cases may occur in women who are premenopausal and about 5% occur in women under the age of 40. Generally, the prognosis is good, with an overall survival rate for all cases of about 75%. Management for this disease has evolved over the past half-century. Preoperative radiation therapy followed by hysterectomy was the standard before the early 1980s, but now almost all patients are staged surgically, and postoperative management is tailored to the risk factors identified at the time of surgical staging. In 1988, this primary operative approach was formalized by FIGO (Federation of International Gynecology and Obstetrics) and now requires surgical staging to accurately assign stages and determine appropriate treatment and progress of this disease (Table 54.2).

TABLE 54.2. *FIGO staging for carcinoma of the corpus uteri*

According to data from the American Cancer Society, the number of deaths from endometrial cancer was about 4,000 in 1990. In 2000, the mortality from endometrial cancer increased to 6,500. The exact reason for this is increase is unclear. Many suggest that this increased incidence is caused by the increased use of estrogen replacement therapy. Several known pieces of information can be used to argue against this. First, death from estrogen-induced endometrial cancer is rare. These cancers usually are well differentiated and carry a low mortality rate. Also, the rate of endometrial cancer is increasing in countries such as Norway and Czechoslovakia, yet estrogens rarely are prescribed in these countries. The incidence of endometrial carcinoma has increased over the last 50 years, most likely because of the aging population, the increased frequency of certain predisposing conditions such as obesity, and improved methods of diagnosis.

Adenocarcinoma of the endometrium is mainly a malignancy of postmenopausal women and is increasingly virulent with advancing age. Peak age at diagnosis is between 50 and 65 years, and approximately 25% of all cases of endometrial carcinoma are diagnosed in premenopausal women and 5% in women younger than 40 years. Usually, but not always, these young women are either obese, chronically anovulatory, or both. Women with endometrial cancer diagnosed at an early age should be queried about family history. Endometrial cancer is the most commonly inherited gynecologic malignancy. It is the second most common cancer described in hereditary nonpolyposis colon cancer syndrome (HNPCC), also known as the Lynch syndrome.

Bohkman proposed that there may be two types of endometrial cancers, designated type I and type II. Type I endometrial cancer is estrogen dependent and is thought to progress typically from hyperplasia to frank cancer in a stepwise fashion. This type of malignancy typically occurs in younger, perimenopausal women with a history of exposure to unopposed estrogen. These tumors tend to arise in areas of hyperplasia, to be well differentiated, and to be associated with a more favorable prognosis. The latter type of cancer occurs in older women without estrogen stimulation of the endometrium, is not often associated with endometrial hyperplasia, and tends to be more commonly associated with poorly differentiated cancer or those of unusual histologic type. It generally carries a worse prognosis. Because cancer is a genetic disease and we now realize that it develops as the result of an accumulation of mutations in genes necessary for normal cellular function, the pathways necessary for the development of these two types of cancers may be different.

The main risk factor for endometrial adenocarcinoma is long-term unopposed estrogen exposure of either endogenous or exogenous origin. Obesity, nulliparity, and late menopause appear to be associated with high endogenous levels of unopposed estrogen. In obese women, there is an increased peripheral conversion of androstenedione to estrone by fat cells. Nulliparity seems to be associated with endometrial cancer, because ovarian dysfunction (chronic anovulatory cycles and polycystic ovaries) contributes to both the infertility and the unopposed estrogen levels. Estrogen-secreting tumors, such as granulosa cell tumors, are associated with endometrial cancer up to 25% of the time. Other risk factors include a history of pelvic irradiation, a history of breast or ovarian cancer, and use of tamoxifen (Table 54.3).

Obesity
Diabetes (not an independent risk factor)
Hypertension
Menopause after the age of 55
High socioeconomic status
Positive family history (60% by age 70 if HNPCC family)
Polycystic ovary syndrome
Unopposed estrogen exposure in postmenopause
Estrogen-secreting tumor
Urban residence
Pelvic irradiation
History of another adenocarcinoma
Tamoxifen use

HNPCC, hereditary nonpolyposis colorectal cancer.

TABLE 54.3. *Factors associated with an increased incidence of endometrial cancer*

Oral contraceptives appear to provide protection from endometrial cancer. At least eight population-based studies suggest that this is so. The use of oral contraceptives appears to decrease the risk of developing endometrial cancer in women 20 to 54 years of age by 50% over those women who never have used oral contraceptives. This protective effect appears to last for at least 10 years in women who used the pill for at least 1 year. Cigarette smoking also decreases the risk of endometrial cancer. There appears to be a dosage relationship to this benefit, such that the greater the number of cigarettes smoked the less the risk of developing cancer. In one study this decrease was quite profound, 30% when one pack was smoked and another 30% if more than one pack was smoked. Furthermore, the greatest risk reduction was in the heaviest women. This is not too surprising, because it is these women who are at the highest risk of developing endometrial cancer, so they might be expected to enjoy the greatest benefit from a factor which decreased their risk. This benefit of risk reduction is strongly outweighed by the increased risk of other health problems of smoking such as heart and lung disease and, therefore, appears to be small consolation.

The relationship between unopposed estrogen exposure and endometrial cancer is well described. Although the risk of endometrial cancer is increased in these women, their prognosis tends to be better. Women with unopposed estrogen use tend to have lower stage, lower grade lesions with better prognosis.

Race is another predictor of survival and type of endometrial cancer. White women have a higher incidence but also have a higher survival rate than black women. This originally was thought to be secondary to socioeconomic status, in that the diagnosis was made later because of less access to health care and, therefore, the cancer was of a higher stage. However, when these variables are controlled for, the survival appears to be less in black women than white. The exact reason for this is unclear. Black women have similar survival to white women when matched for poor prognostic factors. It appears that black women tend to have more poor prognostic variables. Many authors have evaluated this disparity and the etiology is not clear. With the advent of the human genome project, a better understanding of the genetic differences among cancers can be evaluated and understood. This may give us some insight into how they are expressed in different patient populations.

Breast cancer is the most common cancer diagnosed in women in the United States, thereby making tamoxifen a widely used drug in this country. It is estimated that about 80,000 women will start taking tamoxifen each year. Tamoxifen is a selective estrogen receptor modulator, and it has varying effects on estrogen-responsive tissue. The endometrium responds to tamoxifen stimulation much like it does to estrogen. Therefore, the effects of tamoxifen on the endometrium are like those of unopposed estrogen, so the risk of endometrial cancer in women on tamoxifen therapy is increased. In 1985, Killackey reported on three patients with breast cancer who were receiving tamoxifen and who developed endometrial cancer. This and many other reports suggest that there is a significant increase in the risk of developing endometrial cancer while on tamoxifen. The National Surgical Adjuvant Breast and Bowel Project (NSABP) is one of the best studies published on this subject. This study analyzed 2,843 patients with node-negative estrogen receptor–positive breast cancer who were randomized to placebo or 20 mg of tamoxifen a day. There was a significant increase in the risk of endometrial cancer in the tamoxifen arm such that the relative risk was almost 3 times that of the control arm. These data combined with others suggest that the increased risk of endometrial cancer in women taking tamoxifen is between 2 and 3 times that of the population not taking tamoxifen. Women who have breast cancer are also at increased risk to develop endometrial cancer. These studies often do not take this increased susceptibility into account and, therefore, may overstate the risk of endometrial cancer in women taking tamoxifen. The benefits of tamoxifen use for prevention of breast cancer recurrence, more than 120 per 1,000 women, far outweigh the risks of 6 endometrial cancers per 1,000 women.

Genetics

Cancer is the result of accumulation of mutations within the human genome. These mutations can be either acquired or inherited. As we come to understand more through the Human Genome Project and other research, we will come to understand even better the mechanism by which these cancers develop. It is, therefore, essential that clinicians be aware of the information provided by the human genome and use it to better help their patients

Endometrial cancer is the most commonly inherited gynecologic cancer. The clearest hereditary link to this disease is seen in HNPCC, also known as the Lynch syndrome after Henry Lynch, who first described this familial cancer syndrome. Clinical features of HNPCC were described first in the medical literature in 1913 by Aldred Warthin, who identified a clustering of predominantly stomach and endometrial cancers in the family of his seamstress. This inherited pattern of cancers gained little attention over the subsequent 50 years or more until characterized by Henry Lynch as the cancer family syndrome. Subsequently, the pattern of autosomal dominant risk of gastrointestinal cancers and gynecologic cancers became known as HNPCC, although some experts continue to use Lynch syndrome because they

think that it more accurately encompasses both the colorectal tumors and extracolonic cancers.

HNPCC is a clinically defined disease in which the primary genetic defect has been identified as mismatch repair genes. It is an autosomal dominant disease with a risk of penetrance of an inherited mutation of approximately 80%. That means that 80% of the patients who inherit one of these mutations will develop a cancer. During the 1990s, specific genes responsible for HNPCC were identified and are known as the mismatch repair genes, but the syndrome is based on family history. The criteria for defining this disease can be seen in Table 54.4 and Table 54.5. These criteria have evolved gradually from those factors focused on colorectal cancers to those that may encompass all cancers associated with the syndrome. Not all patients who fit the criteria of having clinical HNPCC have a mutation in these mismatch repair genes, indicating that we still have more to learn about the development of this disease. We believe that as many as 10% to 30% of cancers ultimately may be categorized as familial. Most of the inherited abnormalities in this group of patients are unknown. Only about 5% can be characterized as HNPCC or Lynch. Thus, the disease of interest, HNPCC, accounts for an important, but minor, percentage of all colorectal or endometrial cancers. We are just coming to understand that women with relatives with this disease can be at increased risk for other malignancies. This brings home the point that all women with cancers should have a detailed family history taken. This will assess their risk of developing cancers and determine any relative risk for their family members. For instance, the normal population has about a 2% chance of developing a colon cancer, versus 80% cumulative risk in a patient with clear HNPCC. When counseling patients, the cumulative risk of developing a cancer over the course of one's life is the most informative means of conveying this information. An example of cumulative risk assessment for various HNPCC cancers in a patient with HNPCC can be seen in Table 54.6.

I. Patient must meet ALL of the following:
1. Three or more relatives with a histologically verified colorectal cancer, one of whom is a first-degree relative of the other two (FAP should be excluded), AND
2. Colorectal cancer involving at least two generations, AND
3. One or more colorectal cancers diagnosed before the age of 50
II. Patient must meet ALL of the following:
1. Three or more relatives with a histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or kidney), one of whom is a first-degree relative of the other two, AND
2. Colorectal cancer involving at least two generations, AND
3. One or more colorectal cancer cases diagnosed before the age of 50

FAP, familial adenamatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.

TABLE 54.4. *Amsterdam criteria*

Patient may meet ANY ONE of the following criteria:
1. Individual with cancer in families who meet the Amsterdam Criteria
2. Individual with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers: endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter
3. Individual with colorectal cancer and a first-degree relative with colorectal cancer or HNPCC-related extracolonic cancer or a colorectal adenoma; one of the cancers diagnosed at an age younger than 45 years, and the adenoma diagnosed at age younger than 40 years
4. Individual with colorectal cancer or endometrial cancer diagnosed at age less than 45 years
5. Individual with right-sided colon cancer with an undifferentiated pattern (solid or cribriform) on histology, diagnosed at less than 45 years; solid or cribriform pattern defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small glandlike spaces
6. Individual with signet-ring cell-type colorectal cancer diagnosed at age less than 45 years (signet-ring cell type defined as tumor composed of >50% signet-ring cells).
7. Individual with colorectal adenoma diagnosed at age <40 years.

HNPCC, hereditary nonpolyposis colorectal cancer.

TABLE 54.5. *Bethesda criteria*

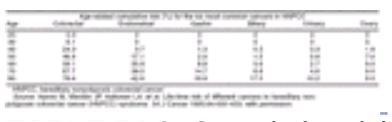

TABLE 54.6. *Cumulative risk*

Interestingly, the risk of a woman with HNPCC developing colorectal cancer may be less than that of a male with HNPCC (60% vs. 80%). Estrogen may play a protective role in this decreased risk. As stated previously, endometrial cancer is the second most common disease in women with HNPCC. An HNPCC mutation confers a significant cumulative risk of developing an endometrial cancer. In the normal population, a lifetime risk is about 1.5%, versus 60% if one has inherited a mismatch repair defect or has clinically defined HNPCC.

Genes responsible for the development of a cancer are oncogenes, which are dominantly expressed cellular control genes, and tumor suppressor genes, which are nondominant cellular control genes. A more recently described set of genes is called *mismatch repair genes.* These genes are responsible for ensuring fidelity in the DNA replicative process. The job of these genes is to search for and identify mismatches that occur during replication and to excise and repair the errors. In humans, they consist of the genes *MLH1, MSH2, MSH6, PMS1*, and *PMS2.* It is these genes that are responsible for the development of HNPCC cancers. When they are mutated and do not repair mismatches in the DNA, errors accumulate through normal division, and eventually an error occurs in a gene(s) responsible for control of cell growth. The importance of these mismatch repair genes is made clear when we see how highly conserved they are across species. The mismatch repair genes of *Escherichia coli* are not that different from the mismatch repair genes we find in humans. We now have the ability to test for mutations in these genes and are, therefore, able to assess the risk of an individual getting a cancer and passing on that risk to offspring. Any patient with endometrial cancer should have a thorough family history taken to detect the possibility of an inherited problem. If genetic testing is deemed appropriate, this may be offered to the patient and family. However, before genetic testing is recommended, the patient should undergo counseling by a trained genetic counselor.

In summary, HNPCC is a clinically defined disease described by the Amsterdam and Bethesda criteria. Over time, the focus on these syndromes has shifted to extracolonic cancers such as endometrial cancer. The Amsterdam Criteria II begin to take this into account, and the Bethesda criteria continued to expand on this concept. Importantly, as gynecologists we see a fair number of synchronous or metachronous ovarian and endometrial cancers. These often occur in younger women and should raise the suspicion of an HNPCC association. Any patient with cancer should have a detailed family history taken to assess her risk of developing another cancer and to help assess her family members' risk of developing a cancer. If appropriate, family members should be offered genetic counseling and possible testing for mutation in the mismatch repair system.

Diagnosis

There are no accepted routine screening methods for detecting endometrial cancer in asymptomatic women or in women at increased risk. Given the low incidence of endometrial cancer, this would be prohibitive from a cost standpoint. Furthermore, the complications of screening may be higher than the benefits. Clinical studies have evaluated routine endometrial biopsy, transvaginal ultrasonography, and Pap smears, but none of these techniques is sensitive or specific enough to be applied to the general population. Even though a routine Pap smear cannot be relied on as a screen for endometrial cancer, this malignancy should be suspected in any nonpregnant woman with atypical endometrial cells or in any postmenopausal woman with normal endometrial cells on a Pap smear. A Pap smear which reveals AGUS in a woman over the age of 35 should be evaluated by colposcopy, endocervical curettage, and endometrial biopsy to rule out endometrial cancer, in addition to a possible cervical lesion.

Abnormal uterine bleeding is the most common initial symptom of endometrial cancer. Any bleeding in a postmenopausal woman must be evaluated promptly, although overall only about 20% of these patients have a genital malignancy. The likelihood that postmenopausal bleeding is indicative of a uterine cancer clearly increases with increasing age. Perimenopausal women with abnormal bleeding must also undergo thorough investigation, with the most suspicious patterns being increased menstrual flow, a decreased menstrual interval, and intermenstrual bleeding. Whenever possible, the diagnostic procedure for evaluating the endometrium should be

an office endometrial biopsy which, under optimal conditions, approaches the accuracy of a formal D&C (greater than 90%). An endocervical curettage (ECC) usually should be performed in the evaluation of postmenopausal bleeding to rule out an endocervical carcinoma as the etiology. If the endometrial biopsy and ECC are satisfactory (with adequate tissue for a diagnosis) and demonstrate no significant abnormality, no further evaluation is necessary. If postmenopausal bleeding is persistent or recurrent or other high-risk factors exist, a fractional D&C should be considered. High-risk factors include atypical hyperplasia or endometrial polyps. Hysteroscopy should be considered if bleeding is recurrent or if either polyps or submucous fibroids are suspected. Many clinical studies now support the usefulness of transvaginal ultrasonography for evaluating the thickness of the endometrium in patients with postmenopausal bleeding. Various investigators have suggested that when the endometrial stripe is thinner than 5 mm, the cause of bleeding usually is related to atrophy, but there have been occasional reports of biopsy-proven malignancy even in patients with thin endometrial stripes. Additionally, almost all women on tamoxifen will have a thickened endometrium, making this test less useful in this patient population.

If endometrial adenocarcinoma is diagnosed, further evaluation of the patient is necessary prior to deciding on the therapeutic approach. A careful physical examination should be performed, with particular attention to supraclavicular and inguinal lymph nodes. A thorough evaluation of the abdomen should be performed, and a bimanual rectovaginal examination to evaluate the size and mobility of the uterus is important. The size and consistency of the cervix, the adnexal structures and parametrium, and the entire vagina, vulva, and rectum are important, and these structures should be evaluated for nodules, masses, induration, and plaquelike lesions that might signify metastatic disease. Any suspicious genital lesions should be sampled for biopsy, and the stool should be tested for occult blood. The histologic subtype and grade of tumor can be determined from the endometrial biopsy or D&C specimen, but it is important to remember that approximately one third of the time the final grade of tumor as determined on the hysterectomy specimen will differ from the original. Additionally, a chest radiograph and routine laboratory studies should be obtained. Based on other risk factors and symptoms, consideration should be given to performing a barium enema examination or a colonoscopy, and preoperative computed tomography or magnetic resonance imaging to evaluate the uterus for depth of invasion and to document occult metastatic disease. An additional test that successfully predicts either deep myometrial invasion or distant disease is the serum tumor marker CA-125. Several studies have documented that 53% to 87% of patients with clinical stage I disease who later were found to have had extrauterine disease at the time of surgery, had elevated CA-125, compared with only 2% to 12% of patients with surgically validated stage I disease. These studies may not be routinely necessary if the decision for full surgical staging can be made intraoperatively (i.e., if the necessary surgical expertise is available to perform pelvic and periaortic lymphadenectomy).

Because endometrial cancer is now staged surgically instead of using the old clinical schema, several practical considerations should be noted. In the past, preoperative irradiation was used in many patients, especially those with grade 2 or 3 lesions, positive ECC findings, or a large uterus. Depending on where the patient was treated, preoperative irradiation could consist of intracavitary radium or cesium for approximately 72 hours or external-beam irradiation of 4,000 to 4,500 cGy to the pelvis. Using these types of treatment plans, many patients received either unnecessary radiation or radiation that did not encompass all of their disease (e.g., paraaortic node metastasis). A second consideration is that all patients should at least be evaluated for full surgical staging, including selective pelvic and paraaortic node dissection. With the adoption of the new surgical staging scheme (see Table 54.2), most patients should undergo primary surgical therapy, including a hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytologic analysis, and selective pelvic and paraaortic node dissection, as indicated. Because endometrial cancer can spread via both the lymphatics and the bloodstream, as well as transmurally or transtubally into the peritoneal cavity, a thorough exploration of the entire abdominal cavity is necessary to document any extrauterine metastasis. Only patients with technically inoperable tumors or medical conditions that make them poor operative candidates should be considered for primary radiation therapy. In these cases, patients should be staged using the older clinical staging schema.

Prognostic Factors

Several well-recognized factors can be used to predict the prognosis of a patient with adenocarcinoma of the endometrium. Preoperative evaluation, coupled with the findings at the time of surgical staging and final pathology, allows individualization of postoperative therapy. These factors are exceedingly important in selecting appropriate postoperative therapy for patients (Table 54.7).

Stage of disease
Histologic differentiation
Histologic type
Depth of myometrial invasion
Lymph node metastasis
Other extrauterine metastasis

TABLE 54.7. *Prognostic factors*

Staging

Until the late 1980s, endometrial cancer was clinically staged using clinical information obtained from examination of the patient and the fractional D&C (Table 54.8). This staging system, however, failed to recognize important prognostic factors, such as deep myometrial invasion and clinically occult extrauterine disease, and often underestimated the extent of disease. Because of these inadequacies, FIGO modified this staging schema in 1988 to reflect the information obtained from surgical exploration and pathologic evaluation of removed tissue. Endometrial cancer is now staged according to the FIGO staging system (see Table 54.2). The recommendation is for all medically operable patients with clinical stage I disease, regardless of tumor grade, to undergo an extrafascial total abdominal hysterectomy and bilateral salpingo-oophorectomy for both staging and therapeutic purposes. A radical hysterectomy may be appropriate in certain circumstances in which the disease is known to involve the cervix or parametrium. The abdominal wall incision should be adequate to perform both pelvic and periaortic lymph node sampling, if indicated by tumor grade and depth of invasion into the myometrium. Immediately after the peritoneal cavity is entered, fluid (either ascites or washing) is obtained for cytologic analysis.

Stage I	Disease confined to uterus
Stage II	Disease extends to cervix
Stage III	Disease extends to pelvis
Stage IV	Distant metastasis

TABLE 54.8. *Clinical staging*

Although the FIGO surgical staging schema has been in effect for more than 10 years, there is still considerable controversy as to which patients should undergo the pelvic and periaortic lymph node sampling as required by this schema. It is also unclear how to select these patients and which preoperative and intraoperative findings can be used to define the patient population most likely to benefit from this procedure. Many institutions send the uterus for frozen section analysis intraoperatively and use the pathologic determination of tumor grade and depth of invasion to determine the need for full surgical staging. Others use preoperative information obtained from the endometrial biopsy specimen and radiographic information, especially when patients need to be referred to another center for surgical staging. Because the error rate for poor prognostic features is high with intraoperative evaluation, more gynecologic oncologists are recommending that all patients undergo staging so that all necessary information is available for postoperative treatment planning.

In a large study by the Gynecologic Oncology Group (GOG) of 621 women with clinical stage I disease, 22% of patients were found to have disease outside the uterus. The sites of distant disease were evenly divided between periaortic and pelvic lymph nodes and positive peritoneal cytology. Adnexal involvement was less likely than nodal involvement or positive peritoneal cytologic findings. Equally important, an additional study documented that only 24% of patients with clinical stage II disease actually had pathologic confirmation of cervical involvement at the time of hysterectomy. On occasion, patients are found to have simultaneous endometrial and ovarian cancers, with a reported incidence rate of 1.4% to 3.8%. Although the difference between metastatic and synchronous primary tumors usually can be determined by routine pathologic examination, this determination occasionally cannot be made with any degree of certainty. The survival of patients with endometrial cancer by stage can be seen in Table 54.9.

Stage	5-Year survival
IA	91%
IB	88%
IC	81%
IIA	77%
IIB	67%
IIIA	69%
IIIB	41%
IIIC	32%
IVA	20%
IVB	5%

Source: FIGO annual report 1990–92. *J Epidemiol Biostat* 1998;3:43, with permission.

TABLE 54.9. *Survival by stage*

Tumor Grade

Grading provides a measure of tumor aggressiveness, and it is now an essential part of the FIGO staging for endometrial cancer. Tumor grade is one of the most important prognostic factors for predicting overall survival. Assignment of tumor grade is based on both architectural patterns, such as gland formation, and nuclear atypia and is affected significantly by interobserver reproducibility. It is also not unusual for the tumor grade from the endometrial biopsy to vary from the final tumor grade from the hysterectomy specimen. The higher the tumor grade, the more likely the patient will have deep myometrial invasion, as well as lymph node and other metastases. Grade is clearly an independent predictor of long-term survival, as well as a predictor of other poor prognostic features. Survival based on grade of the tumor alone can be seen in Table 54.10 and the relationship between grade and the depth of myometrial invasion can be seen in Table 54.11. Examples of the various degrees of differentiation can be seen in Fig. 54.3, Fig. 54.4 and Fig. 54.5).

Grade	Survival
1	96%
2	79%
3	70%

Source: Genest P, et al. *Am J Clin Oncol* 1999, with permission.

TABLE 54.10. *Endometrial cancer differentiation and survival rate*

Myometrial invasion	Grade 1	Grade 2	Grade 3
None	24%	11%	11%
Superficial	53%	45%	35%
Mild	12%	24%	16%
Deep	10%	20%	42%

Source: Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. *Cancer* 1987;60(Suppl): 2035–2041, with permission.

TABLE 54.11. *Differentiation and degree of myometrial invasion*

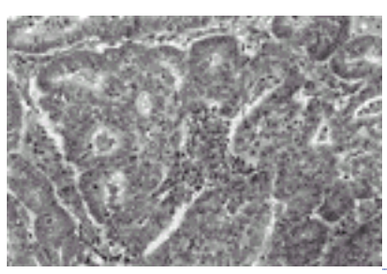

FIG. 54.3. Well-differentiated adenocarcinoma. Back-to-back glands with no intervening stroma.

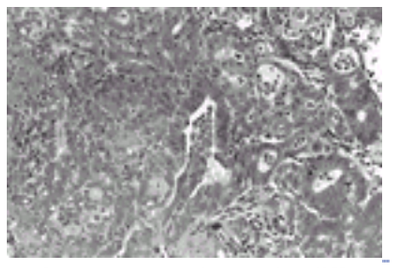

FIG. 54.4. Moderately differentiated adenocarcinoma The left half of this photograph shows back-to-back glands, while the central portion shows solid carcinoma.

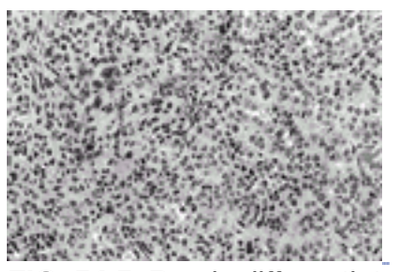

FIG. 54.5. Poorly differentiated adenocarcinoma. Predominantly solid carcinoma with very focal glandular differentiated

Depth of Myometrial Invasion

Depth of myometrial invasion is another important prognostic factor that directly correlates with the likelihood of extrauterine disease. In the new surgical staging criteria, maximum depth of myometrial invasion determines the subcategories within stage I disease. It is believed that increasing depth of invasion is associated with a higher likelihood of access to the lymphatic system, thereby increasing the incidence of both pelvic and periaortic lymph node metastasis. In a study by Boronow and others, only 1% of patients without myometrial invasion had pelvic lymph node involvement, compared with 25% having positive pelvic lymph nodes with outer-third involvement. Survival was also shown to be affected by depth of invasion, with an 80% to 90% 5-year survival with minimal invasion compared with 60% survival with deep invasion. For early-grade lesions, gross evaluation of depth of invasion is quite accurate at about 85% to 90%. As the cancer becomes less well differentiated, the gross evaluation is less accurate because the margins of the cancer are more infiltrative and less pushing. As the cancer becomes less well differentiated, there is a greater likelihood of deep myometrial invasion and an associated decrease in survival (see Table 54.11).

Lymph Node Metastasis

For patients with clinical stage I endometrial cancer, lymph node involvement is the most important independent prognostic factor, being associated with a six-fold increase in the risk of recurrent disease. In these patients, approximately 10% will have positive pelvic lymph nodes, and 6% will have positive periaortic lymph nodes, with periaortic node involvement being the most important predictor of survival. The incidence of lymph node involvement correlates with stage and grade of tumor, depth of myometrial involvement, and location of the cancer in the uterus (i.e., fundal versus lower uterine segment). In patients with clinical stage II disease, lymph node metastasis occurs in approximately 35%.

Adnexal and Intraperitoneal Involvement

Clinically occult adnexal metastasis occurs in approximately 10% of patients with clinical stage I disease, with most having other high-risk factors such as deep myometrial invasion or lymph node involvement. In patients with adnexal metastasis as their only high-risk factor, overall survival seems to be minimally affected. Other extrauterine intraperitoneal disease is associated with a significant decrease in survival.

Tumor Size

Schink and colleagues reported that the size of the endometrial tumor was of prognostic significance. They reviewed tumor size in 91 patients with disease apparently confined to the uterus and found that if the tumor was smaller than 2 cm, the chance of nodal metastasis was about 6%. However, if the tumor was larger than 2 cm, the chance of nodal metastasis was over 20%. In this study, tumor size was an independent prognostic variable.

Histologic Subtype

The histologic subtype of adenocarcinoma may have an independent impact on patient outcome. Approximately 80% of endometrial cancers are of endometrioid histology. These cancers can be of varying degrees of differentiation. There are thought to be of two subtypes as follows: (a) type 1 arises from endometrial hyperplasia, is estrogen dependent, and usually confers a better prognosis; (b) type 2 endometrial cancer tends to be more poorly differentiated, is not dependent on estrogen stimulation, and generally carries a worse prognosis. Squamous differentiation is seen in 15% to 25% of endometrioid tumors. The significance of squamous differentiation is unclear, and its impact has been debated for many years. In the past, the terms *adenoacanthoma* and *adenosquamous carcinoma* were used to identify adenocarcinomas with either benign or malignant squamous differentiation. More recently, Zaino and colleagues recommended that these terms be replaced with the more descriptive term *adenocarcinoma with squamous differentiation.* Although the squamous elements can have varying degrees of differentiation, they usually correlate with the glandular components. Furthermore, the differentiation of the glandular component appears to be the important prognostic feature.

Papillary serous and clear cell cancers of the endometrium are both quite rare (approximately 5% each) but have a significantly worse prognosis compared with that of endometrioid adenocarcinoma. Both of these histologic types are more common in older women, who tend to have distant disease, even when clinically it appears to be stage I (Fig. 54.6 and Fig. 54.7).

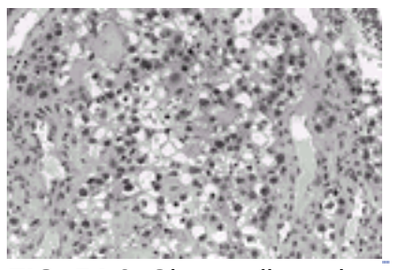

FIG. 54.6. Clear cell carcinoma. The tumor forms sheets of cells with cleared cytoplasm and pleomorphic nuclei.

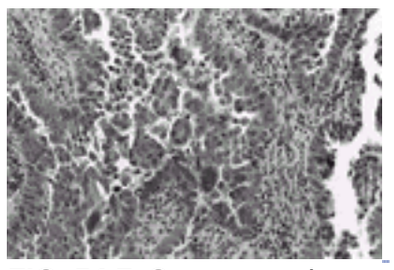

FIG. 54.7. Serous carcinoma. The tumor shows marked intraluminal complexity and high-grade nuclear atypia.

Age

Although it is recognized clearly that advancing patient age at diagnosis is associated with a poorer outcome, there is no agreement as to why this is true. In a study by Lurain and colleagues, increasing patient age was an independent prognostic factor associated with recurrent disease. No patient under age 50 years developed recurrent cancer, compared with 12% of women between 50 and 75 years and 33% of women older than 75 years. For every 1-year increase in age over 50 years, there was a 7% increase in the rate of recurrence. Younger patients tend to have early, well-differentiated lesions with no or minimal myometrial invasion. Younger patients also tend to be in better general health, thereby allowing more aggressive definitive surgery. It has been suggested that older women are more likely to ignore signs of vaginal bleeding, thereby delaying diagnosis until the stage is more advanced. Interestingly, however, the length of time between onset of bleeding and presentation to a clinician does not correlate with tumor stage, and patients with advanced stage disease have not necessarily delayed seeking medical care.

Peritoneal Cytology

The significance of malignant peritoneal cytologic findings obtained during surgical staging for endometrial cancer is controversial. In essentially all published studies, a positive peritoneal cytology result is associated with other high-risk features such as deep myometrial invasion, adnexal spread, positive lymph node metastasis, and cervical involvement. Several studies showed a two-fold to three-fold increase in the risk of recurrent disease in patients with positive peritoneal cytology, but often these patients have one or more other high-risk factors, and many times the recurrent disease is outside the peritoneal cavity. In patients found to have positive cytologic findings, it is unclear whether any currently available therapy would have any impact on eventual outcome.

Race

Even with correction for age and tumor stage, black women with endometrial cancer have a much poorer prognosis than white women. For all stages of endometrial cancer, white women have an 86% 5-year survival compared with a 55% 5-year survival for black women, and within each stage the relative survival is worse for blacks.

Other Factors

Many other factors have been shown to affect prognosis, including hormone receptor status of the tumor, DNA content or ploidy, proliferative index, and oncogene expression. Both estrogen receptor and progesterone receptor levels have been shown to be prognostic factors independent of tumor grade, with the progesterone receptor level being the more important for predicting overall survival. Progesterone receptor levels also can be used to predict which patients with advanced or recurrent disease are more likely to respond to hormone therapy.

Management

The primary management for endometrial cancer is surgery (Table 54.12), consisting of removal of the uterus, cervix, and adnexal structures. Surgical staging procedures, including careful exploration of the abdomen and pelvis and lymphadenectomy, often are done at the same time, as described above. As soon as the uterus has been removed, it should be sent to the pathology laboratory for frozen section to determine tumor grade and depth of invasion, as well as to obtain tissue for estrogen and progesterone receptor levels and other studies, as indicated. For patients in whom lymph node sampling is indicated (see Table 54.12), representative samples of lymph node–bearing tissue from the lower aorta and vena cava are removed. Pelvic lymph node sampling should remove nodes from common and external iliac and obturator regions. An omental biopsy may be performed and is indicated for patients with papillary serous and clear cell cancers. In patients who are very poor candidates for exploratory laparotomy (e.g., morbidly obese), vaginal hysterectomy or laparoscopically assisted vaginal hysterectomy should be considered. Every effort should be made to remove the adnexal structures; therefore, laparoscopically assisted vaginal hysterectomy may be preferable. If appropriate surgical expertise is available, the full surgical staging, including pelvic and periaortic lymphadenectomy, can be performed through the laparoscope. Until additional information is obtained, vaginal hysterectomy should be limited to very select patients who otherwise might be given radiation therapy only. In patients with clinically apparent cervical involvement, radical hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection may be considered.

Risk group (incidence)	Positive pelvic nodes (%)	Surgery
Low risk (30%) Stage IA, IB Grade 1	3	TAH-BSO, peritoneal cytology
Moderate risk (50%) Stage IB Grade 2, 3	9	TAH-BSO, LND, peritoneal cytology
High risk (20%) Stage IC Grade 1, 2, 3	18	TAH-BSO, LND, peritoneal cytology

BSO, bilateral salpingo-oophorectomy; LND, lymph node dissection; TAH, total abdominal hysterectomy.

TABLE 54.12. *Surgical therapy of endometrial cancer*

Following surgery and review of the final pathology report, patients may be divided into risk groups based on the many prognostic factors discussed above. This classification can then be used to individualize the recommended postoperative therapy, if needed. Because formal surgical staging has been utilized widely for less than 10 years, most of the information on recommendations for postoperative radiation therapy are based on clinically staged patients. The risk of pelvic recurrence in patients with high-risk factors but negative surgical staging is largely unknown. The GOG study based on surgicopathologic correlation found that even when sampled lymph nodes were negative, patients with deep myometrial invasion and poorly differentiated cancers were still at a higher risk of recurrence. Even though the surgical staging procedures failed to document extrauterine pelvic disease, postoperative pelvic irradiation was associated with a decreased risk of local recurrence. It is not yet clear whether surgical staging can define a subgroup of stage I patients, other than the already identified low-risk patients, who can be treated without adjuvant radiation therapy.

Treatment for patients with stage II disease remains somewhat controversial. Most studies suggest that patients with cervical involvement are at a higher risk for vaginal vault recurrence, and often recommend adjuvant vaginal cuff irradiation. Whether or not those patients with otherwise negative surgical staging also need pelvic irradiation remains to be confirmed. With clinically apparent cervical involvement, treatment recommendations include either radical hysterectomy or preoperative irradiation followed by extrafascial hysterectomy.

Treatment for patients with documented extrauterine disease (stages III and IV) should be individualized to encompass the true extent of the disease. Therapeutic options include pelvic irradiation, extended-field irradiation to cover the periaortic lymph nodes, whole-abdomen irradiation, and systemic hormone therapy or chemotherapy. In most cases, management of distant metastasis with either high-dose progestins or chemotherapy is palliative only, with little expectation for long-term control of disease. The most widely used chemotherapy agents include doxorubicin hydrochloride (Adriamycin) and cisplatin (Platinol) or carboplatin (Paraplatin).

Progestins have been used for many years in the management of recurrent endometrial carcinoma, with approximately one third of patients having a favorable response. Patients with well-differentiated tumors have a higher response rate than those with moderately or poorly differentiated cancers. Although the role of estrogen and progesterone receptors in endometrial cancer therapy has not yet been accepted widely, it does appear that the responsiveness of recurrent tumor to progestin therapy is related to the content of both estrogen and progesterone receptors. If both receptors are present, the likelihood of a favorable response is good, regardless of tumor grade or other high-risk factors. If the concentration of receptors is low, it is unlikely that the recurrent tumor will respond to progestins, and other chemotherapy should be considered.

Endometrial cancer in approximately 10% to 15% of patients is inoperable, usually because of morbid obesity or severe intercurrent disease. In these patients, primary radiation therapy should be considered. In most cases, a combination of external beam and intracavitary irradiation should be used, and with definitive therapy approximately 85% to 90% of patients with early-stage disease will have control of uterine disease. The overall risk of recurrence in these patients with stage I disease correlates with tumor grade, with a 5-year survival of 94% for grade 1, 92% for grade 2, and 78% for grade 3 tumors.

Posttreatment Surveillance

Many studies have confirmed that after treatment of endometrial cancer, most recurrences will occur within 3 years. Approximately one half of these recurrences will be asymptomatic and, thus, the traditional recommendation has been to follow patients with physical examination and vaginal cytology every 3 to 4 months for the first 2 to 3 years, and then at 6-month intervals for at least 5 years. Serial serum CA-125 measurements also have been suggested for surveillance of patients who have been treated for endometrial cancer, although the level may be normal in patients with early recurrent disease. Because treated endometrial cancer will not recur in the great majority of patients, however, several studies have addressed the cost effectiveness of this traditional recommendation. In a study from the M.D. Anderson Cancer Center, 59% of patients with recurrence were asymptomatic, with over one half being picked up on physical examination, 26% by an elevated CA-125, and only 4% by vaginal cytologic examination. Because of these findings, these authors recommended that physical examination, serum CA-125 assay, and vaginal cytology be performed only every 6 to 12 months on asymptomatic patients. A Canadian study reported that only one recurrence was documented during more than 200 routine follow-up visits after treatment for endometrial cancer, using a schedule of examinations of every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter. There was no difference in the salvage rates of recurrent disease picked up during routine surveillance compared with recurrent disease documented in symptomatic patients. In this study, no recurrence was picked up by vaginal cytology alone. In a third study from Duke University, an analysis of various follow-up techniques demonstrated that routine vaginal cytology and chest radiograph were not cost effective. The recommendation of these investigators is to follow patients every 6 months with examination alone, using additional testing to evaluate any symptoms.

Estrogen Replacement Therapy After Treatment

For many years, it has been thought that a history of endometrial cancer, even successfully treated, was an absolute contraindication to estrogen replacement therapy (ERT), because adenocarcinoma of the endometrium is considered an estrogen-dependent neoplasm. Because no scientific data support the contention that ERT is dangerous for patients who have had a hysterectomy for endometrial cancer and because the body of evidence is increasing in supporting the value of ERT in decreasing morbidity and mortality from heart disease, strokes, and osteoporosis, many physicians and patients are questioning the earlier proscription. During the last decade, there have been several small retrospective studies of patients given ERT following treatment for early-stage endometrial cancer (Table 54.13). In 1986, Creasman and coworkers reported on 221 patients with stage I endometrial cancer, of whom 47 (21%) were given postoperative estrogen replacement for a median of 26 months. Statistical analysis revealed no increased risk of recurrence or death between those who received ERT and those who did not when adjustments were made for tumor grade, myometrial invasion, nodal metastasis, peritoneal cytology, and age. In fact, the risk of recurrence was significantly higher in the untreated group (15% vs. 2%), as was the risk of dying of intercurrent disease. Similar study design and conclusions were reported 3 years later by Lee and others. In both of these studies, selection bias may have contributed to the results, but it does appear that a low-risk group of patients can be selected who can safely take estrogen replacement. Chapman and colleagues retrospectively reviewed information on 123 patients with stages I and II endometrial cancer, of whom 62 received ERT, and again documented no increase in recurrences or deaths from this malignancy. In a Committee Opinion in August 1993, the American College of Obstetricians and Gynecologists concluded that there are no definitive data to support specific recommendations regarding ERT for women previously treated for endometrial cancer. The opinion states that estrogens could be used for the same indications as for any other woman, except that the selection of appropriate candidates should be based on prognostic indicators and the risk that a patient is willing to assume. The gynecologic practice committee, due to the paucity of data, could not evaluate the need for progestational agents in addition to estrogens. A large GOG trial is underway to assess the risk of hormonal replacement in these patients.

TABLE 54.13. *Effect of estrogen replacement therapy on endometrial cancer recurrence*

UTERINE SARCOMAS

Sarcomas of the uterus carry a poor prognosis but, fortunately, they are rare and represent less than 5% of all uterine tumors. The incidence of these tumors is about 1.7 per 100,000 women per year in the United States. The classification of the various histologic types, in order of frequency, can be seen in Table 54.14. There is some retrospective evidence that sarcomas tend to arise more commonly in patients who have undergone pelvic irradiation in the past. A clear cause and effect relationship between irradiation and sarcomas has not been established, and new data have failed to corroborate the older literature.

Mixed homologous müllerian sarcoma (carcinosarcoma)
Mixed heterologous müllerian sarcomas
Leiomyosarcomas
Endometrial stromal sarcomas
Other sarcomas

TABLE 54.14. *Classification of uterine sarcomas by frequency*

These lesions arise primarily from two tissues: endometrial sarcomas arise from endometrial glands and stroma, and leiomyosarcomas from the myometrium itself. The malignant mixed müllerian tumors arise from the pluripotent endometrial stroma. Other sarcomas, such as angiosarcoma and fibrosarcoma, arise in supporting tissues. In general, uterine sarcomas are the most malignant type of uterine tumor and tend to differ significantly from endometrial adenocarcinomas with regard to patterns of spread and prognosis.

The relative incidence of the various subtypes of uterine sarcomas differs significantly in the literature, with mixed mesodermal sarcomas being the most common in recent studies. The staging criteria for uterine sarcomas are based on the FIGO classification for endometrial cancers (see Table 54.2).

Classification

Numerous classification schemes for uterine sarcomas have been proposed, depending on both cell type and site of origin. In 1959, Ober suggested a classification of the endometrial sarcomas. This does not include the pure sarcomas, which are self-explanatory. This classification and can be seen in Table 54.15. Generally, homologous tumors are comprised of tumors that should belong in the normal uterus, such as smooth muscle or endometrial stroma. Heterologous elements are those tissues that normally would not be found in the uterus, such as bone (osteosarcoma) or cartilage (chondrosarcoma). Most pathologists have adopted this classification, which has the advantage of being able to classify these malignancies for study, because most tumors fall into four major groups. Pure tumors are composed of only one cell type; whereas mixed tumors have more than one cell type. Homologous tumors contain tissue elements that are indigenous to the uterus, whereas heterologous tumors are defined as those that contain tissue elements foreign to the uterus (Table 54.15). Because the great majority of uterine sarcomas fall into one of four categories, the GOG has accepted a more simplified classification:

Homologous	Heterologous
Ober Classification	
Pure	
Stromal sarcoma (endolymphatic stromal myosis)	Rhabdomyosarcoma
Leiomyosarcoma	Chondrosarcoma
Angiosarcoma	Osteosarcoma
Fibrosarcoma	Liposarcoma
Mixed	
Carcinosarcoma	Mixed müllerian tumors (mixed mesodermal tumor)
Gynecologic Oncology Group Classification	
Leiomyosarcomas	
Endometrial stromal sarcomas	
Mixed homologous müllerian sarcomas (carcinosarcoma)	
Mixed heterologous müllerian sarcomas (mixed mesodermal sarcoma)	
Other uterine sarcomas	

TABLE 54.15. *Classifications of uterine sarcomas*

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Mixed homologous müllerian sarcoma (carcinosarcoma)
- Mixed heterologous müllerian sarcoma (mixed mesodermal sarcoma)

Leiomyosarcoma

Leiomyosarcoma is a malignancy of smooth muscle. This sarcoma was thought to be the most common of the malignant mesenchymal tumors, a concept that is supported by literature before the 1970s. However, more recent data from the GOG and other sources suggest that leiomyosarcoma is the second most common sarcoma of the uterus and accounts for about 1 out of 7 of all uterine sarcomas, or about 16%. This information is detailed in GOG data published on 447 uterine sarcomas. This malignancy is found in younger women, with a median age at diagnosis between 43 and 53 years. Leiomyosarcoma is more common in black women and is associated with a poorer prognosis in these patients. The patterns of spread for leiomyosarcoma appears to be via both lymphatics and the vasculature, because distant metastases will develop in many patients even if lymph node biopsy results are negative at the time of surgery.

Although there is some disagreement about the exact histologic criteria required for a diagnosis of leiomyosarcoma, the most important factor appears to be the mitotic count of the tumor. Cellular myomas and bizarre leiomyomas may appear to be malignant, but if there are fewer than 5 mitoses per 10 high-power fields (HPF), the lesion is considered benign. Tumors with more than 10 mitoses per 10 HPF are malignant, and those with 5 to 10 mitoses per 10 HPF are thought to have an uncertain potential for malignancy. Many investigators agree that 5-year survival is related to the number of mitoses per 10 HPF, with a 95% to 98% survival with fewer than 5 mitoses per 10 HPF, approximately 40% survival with 5 to 10 mitoses per 10 HPF, and very poor survival (15%–20%) with more than 10 mitoses per 10 HPF. An example of a leiomyosarcoma can be seen in Figure 54.8. The etiology of leiomyosarcoma is unclear. As its name suggests, this tumor was thought to arise within benign leiomyoma. However, in most cases it appears to arise independently of these tumors. Hysterectomy was felt to be indicated for a rapidly enlarging uterus or rapidly growing fibroid tumors for fear that this represented degeneration of leiomyomas into a sarcoma. Investigators from University of Southern California addressed this question best. These authors retrospectively reviewed a large series of patients with “rapidly enlarging” leiomyomas and found the incidence of sarcoma to be very low. They recommended that surgery for a concern of leiomyosarcoma was not warranted for fibroid tumors that were enlarging rapidly, and reasons for surgery should focus on other issues such as symptoms of pressure, pain, or bleeding.

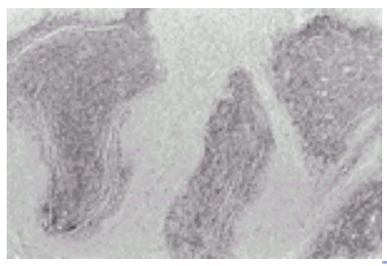

FIG. 54.8. Leiomyosarcoma. Interlacing fascicles of smooth muscle cells exhibit high-grade cytologic atypia and increased mitotic activity. Other areas of this tumor showed coagulative necrosis.

This sarcoma should be treated as any other uterine malignancy. This should include comprehensive staging with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and paraaortic lymph node dissection. The staging system for leiomyosarcomas is the same as for an endometrial cancer (see Table 54.2).

Endometrial Stromal Sarcomas

Endometrial stromal sarcomas are the least common of the three most common uterine sarcomas. The most-often-seen initial symptom of an endometrial stromal sarcoma is vaginal bleeding. These sarcomas are generally yellow in color, fleshy in texture, and often polypoid. At the time of diagnosis and treatment, usually by hysterectomy, 40% of patients have disease outside of the uterus. Endometrial stromal sarcomas are just as aggressive as the other uterine sarcomas and the prognosis is very similar.

Endometrial stromal tumors usually are divided into three groups: benign stromal nodules, endolymphatic stromal myosis and endometrial stromal sarcoma. Benign stromal nodules usually are well-circumscribed tumors with clearly defined pushing margins. These tumors may grow to many centimeters but are always benign. No cases of metastasis or recurrence have been reported. The second histologic type, endolymphatic stromal myosis, is an infiltrative tumor that generally has an indolent course. Another name for endolymphatic stromal myosis is low-grade stromal sarcoma. Gross inspection of the surgical specimen often reveals an infiltrative growth

pattern, and it can project from the cut surface in a worm-like manner that may also extend into blood vessels in the broad ligament. Microscopically, there are little cellular atypia and few, if any, mitoses. The clinical course is slowly progressive and management is usually by surgery alone. However, the tumor can recur many years after initial incidence. It is a hormonally responsive tumor and often grows in the presence of estrogen and can regress or stabilize when exposed to progestational agents. There are reports of low-grade endometrial stromal sarcomas being stabilized for many years with progestational therapy.

Endometrial stromal sarcoma, on the other hand, has a much more aggressive course, with frequent and widespread metastases and a very poor prognosis. As with leiomyosarcoma, the diagnosis of stromal sarcoma versus low-grade stromal sarcoma depends on the number of mitoses per 10 HPF, with 10 mitoses being the cutoff to categorize the tumor as an endometrial stromal sarcoma (Fig. 54.9). Despite this distinction, controversy still exists as to the prognostic significance of the number of mitoses seen. A study from the Mayo Clinic failed to identify this feature as an independent prognostic variable. As with most sarcomas, irradiation may control local disease but has little effect on overall survival. These tumors often exhibit high concentrations of both estrogen and progesterone receptors, and occasional responses have been seen when high-dose progesterone therapy is administered.

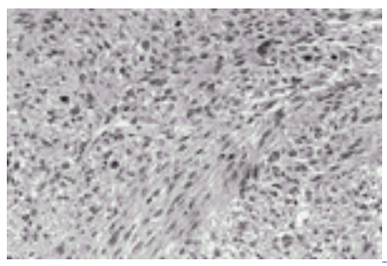

FIG. 54.9. Endometrial stromal sarcoma. Nests of bland endometrial stromal cells diffusely infiltrate the myometrium.

Mixed Müllerian Tumor

This malignancy is the most common uterine sarcoma, accounting for more than 50% of all cases in recent series. This malignancy is aggressive, and more than 60% of patients will have disease outside of the uterus at the time of diagnosis. It tends to metastasize early via lymphatic vessels, blood vessels, and local spread. It is more common in blacks than whites and is associated with prior pelvic irradiation in up to one third of patients. The main initial symptom is vaginal bleeding and, on examination, most patients are found to have an enlarged uterus, often with a polypoid mass protruding through the cervix. This tumor tends to be aggressive, with early metastasis to pelvic and periaortic lymph nodes and adjacent tissue. Hematogenous spread, especially to the liver and lungs, is common.

Histologically, it is composed of both sarcomatous and carcinomatous elements, with the sarcomatous element being divided into homologous types (tissue normally found in the uterus; Fig. 54.10) and heterologous types (tissue such as cartilage or bone not usually found in the uterus; Fig. 54.11). In some series, heterologous elements were associated with a worse prognosis. Rhabdomyosarcoma was the most common heterologous element in these cancers. In the most recent GOG series, the median progression-free interval of homologous tumors was 22.7 months, with a median progression-free interval of 62.6 months in the homologous tumors. Staging is very important in this tumor, because extrauterine disease correlates very strongly with survival. Almost no one with disease outside the uterus is cured of her disease. The single most important factor correlating with survival other than extrauterine disease is depth of myometrial invasion. Recurrences usually occur within the first 2 years and often are comprised of only the carcinomatous elements.

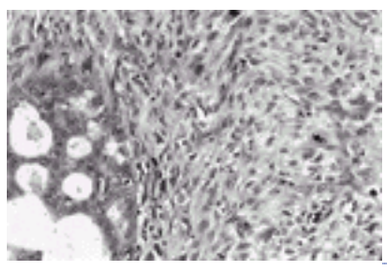

FIG. 54.10. Malignant mixed müllerian tumor, homologous type. Well differentiated.

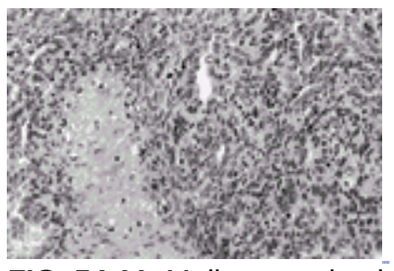

FIG. 54.11. Malignant mixed müllerian tumor, heterologous type.

Other Sarcomas

Pure heterologous uterine sarcomas are rare. Rhabdomyosarcoma is the most common and usually occurs in children. This used to be called *sarcoma botryoides* in children. Management of this rare group of tumors has changed over the last 50 years from primary surgery to chemotherapy. Müllerian adenosarcoma is a rare sarcoma originally described by Skully. This tumor usually causes vaginal bleeding and is of low malignant potential. Its course is indolent and prolonged, with an overall long-term survival rate of about 90%.

Treatment

Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice for almost all uterine sarcomas. Because there is no formal staging system for sarcomas, most authorities feel that the endometrial staging system should be used. Local spread of a sarcoma can be treated with radiation therapy. This may not improve overall survival but will control local disease and diminish the likelihood of the morbidity of a pelvic recurrence. Unfortunately, there are no good prospective randomized trials evaluating the efficacy of postoperative radiation therapy on overall survival. The retrospective studies that do exist show only a benefit for local control. The largest study to address this issue by Salazar comprised more than 900 patients and failed to show a statistically significant survival benefit with postoperative radiation therapy, only a benefit of local control. One can argue that one must obtain control of microscopic local disease before one can cure the cancer. Typically 5,000 to 6,000 cGy is given with or without adjuvant brachytherapy. Investigators from the Mallinckrodt Institute of Radiology noted fewer pelvic recurrences when more than 5,000 cGy were used.

Some patients with leiomyosarcoma may experience an isolated pulmonary metastasis. These sometimes can be resected for cure. Significant 5-year survivals have been recorded in these rare situations. Recurrences of low-grade tumors should be considered for resection no matter where they are.

Recurrences also can be treated with chemotherapy. Many agents have shown activity (Table 54.16). Unfortunately, no therapy has shown a significant increase in overall survival.

Doxorubicin
Ifosfamide
Cisplatin
Etoposide
Mitoxantrone
Paclitaxel

TABLE 54.16. *Active agents in uterine sarcomas in order of response rate*

SUMMARY POINTS

- Uterine cancers comprise a wide variety of histologic types that carry a wide range of metastatic potential and survival.
- Endometrial hyperplasia is a premalignant precursor to endometrioid adenocarcinoma. Simple hyperplasia has a low propensity to progress to a cancer (less than 1%), whereas complex hyperplasia with atypia has a 30% chance of developing into a cancer.
- Endometrial cancer is the most common gynecologic cancer. Type I endometrial cancers are associated with relative estrogen excess. This can be endogenous, as in obese women who have significant conversion of steroids to estrone, or it can be exogenous, as in women who take unopposed estrogen replacement therapy.
- Type II endometrial cancers are not associated with estrogen and are comprised of more aggressive histologic types, such as poorly differentiated endometrioid, papillary serous, and clear cell cancers. These later types have a survival rate as poor as 60%, compared with a greater than 80% survival in the other histologic types.
- Management of endometrial cancers consists of comprehensive staging, including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, pelvic and paraaortic lymph node dissection, and careful abdominal exploration. Management may also include postoperative radiation therapy.
- Postoperative surveillance should include regular examination with Pap smear. The most common site of recurrence is at the vaginal cuff. Radiation treatment of an isolated cuff recurrence has a cure rate of 50% with external radiation therapy.
- Endometrial cancer is the most common inherited form of gynecologic cancer and is associated with HNPCC or Lynch II syndrome. It is important to take a careful family history to assess if the risk is high, and formal genetic counseling and genetic testing may be appropriate.
- Sarcomas are the most lethal of the uterine malignancies, with an overall survival of around 50%. There are several histologic types of sarcomas. The most common is the malignant mixed müllerian tumor, followed by the leiomyosarcoma, and finally by the endometrial stromal sarcomas. Therapy consists of exploratory laparotomy and staging procedure as outlined for endometrial cancers. Postoperative radiation therapy may be recommended, but this is associated only with decreased pelvic recurrence and not improved survival.

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Chapter 55

Ilana Cass and Beth Y. Karlan

Neoplasms of the Ovary and Fallopian Tube

GERM CELL TUMORS OF THE OVARY
Mature Cystic Teratoma
Struma Ovarii and Strumal Carcinoid
Malignant Germ Cell Tumors
Dysgerminoma
Endodermal Sinus Tumor
Immature Cystic Teratoma
Embryonal Carcinoma
Polyembryoma
Choriocarcinoma
Gonadoblastoma
SEX CORD–STROMAL TUMORS OF THE OVARY
Thecoma
Fibroma
Juvenile Granulosa Cell Tumor
Adult Granulosa Cell Tumor
Androblastoma and Sertoli-Leydig Cell Tumor
Sertoli-Leydig Cell Tumors
EPITHELIAL OVARIAN TUMORS
Benign Neoplasms
Tumors of Low Malignant Potential
Malignant Neoplasms
FALLOPIAN TUBE CARCINOMA
Primary Fallopian Tube Epithelial Carcinoma
Fallopian Tube Sarcoma
Metastatic Disease
PRIMARY PERITONEAL CARCINOMA
HEREDITARY OVARIAN CANCER
Hereditary Forms of Ovarian Cancer
Clinical Implications

SUGGESTED READINGS
Germ Cell and Stromal Tumors
Low Malignant Potential Tumors
Epithelial Ovarian Tumors
Fallopian Tube Carcinomas
Primary Peritoneal Carcinomas
Hereditary Ovarian Cancer

Abnormalities of the ovary or fallopian tubes may result from physiologic changes, infectious processes, or benign or malignant neoplasms. Patients may exhibit a pelvic mass with or without other signs or symptoms. These disorders may occur at any age from childhood to senescence. Depending on patient age, the physiologic and pathologic manifestations and implications may differ. For example, teenage patients with a pelvic mass most likely will have a benign germ cell or epithelial ovarian tumor, whereas postmenopausal women have a significantly greater risk of epithelial ovarian carcinoma. The differential diagnosis and the radiologic and tumor marker workups will vary, depending on patient age and the initial complaints. The clinician must be vigilant and willing to evaluate the vague symptoms that are frequently the hallmark of many ovarian and tubal pathologies, especially in women over 40.

In recent years, we have gained an increased understanding of ovarian and fallopian tube tumor biology and molecular genetics, but these advances can be translated only slowly to the clinic. This chapter will outline ovarian and fallopian tube neoplasms, including the common epithelial histologies as well as the rarer germ cell and stromal tumors. Epidemiology and risk factors for these cancers, including inherited cancer susceptibility due to mutations in *BRCA1* and *BRCA2* genes will be discussed, as well as preventive and screening strategies.

GERM CELL TUMORS OF THE OVARY

Germ cell tumors occur most frequently in young women and girls and account for 90% of prepubertal ovarian tumors and 60% of ovarian tumors in women younger than 20 years. These tumors arise from the germ cells originating in the embryonic yolk sac. Patients usually complain of abdominal pain and have an associated pelvic or abdominal mass. Others might have acute abdominal pain as a result of ovarian rupture, hemorrhage, or torsion. A misdiagnosis of acute appendicitis has been made in these circumstances.

Mature Cystic Teratoma

Mature cystic teratomas, also known as dermoid cysts, are the most common benign ovarian neoplasm, with a peak incidence from ages 20 to 40 years. However, they also can be seen in infancy, as well as in menopausal woman. Mature cystic teratomas originate from primordial germ cells and are composed of well-differentiated derivatives of any combination of the three germ layers: ectoderm, mesoderm, endoderm. Ectodermal elements usually predominate. Although these mature tissues are benign in the vast majority of cases, on rare occasion they may undergo malignant transformation, with squamous cell carcinoma being the most frequent malignant histology.

Grossly, the tumors are round or oval with a smooth, glistening, gray-white surface. Most tumors measure 5 to 10 cm in diameter and are bilateral in 8% to 15% of cases. The tumors are usually unilocular but occasionally multilocular, and often are filled with hair and a fatty material similar to sebum (Fig. 55.1). A solid portion located at one pole of the cyst that often projects into the cavity is known as a *Rokitansky protuberance*, where all three germ cell layers are found. Tissues also can be found at the protuberance, including hair, teeth, bone, glia, neural tissue, cartilage, retina, smooth muscle, fibrous and fatty tissue, gastrointestinal and bronchial mucosa, and thyroid and salivary gland tissue. Microscopically, ovarian stroma is noted outside the cyst wall, with the cyst lined predominantly by squamous epithelium with underlying sebaceous and sweat glands (Fig. 55.2).

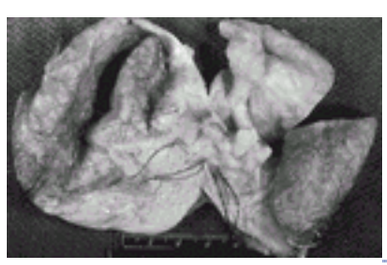

FIG. 55.1. Mature cystic teratoma. This mature cystic teratoma contains hair and teeth.

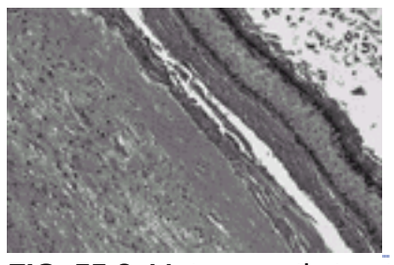

FIG. 55.2. Mature cystic teratoma. Microscopically, there is a keratinizing squamous epithelium on the right and mature glial tissue on the left.

In the past, benign cystic teratomas often were diagnosed on an abdominal radiograph in a young woman with acute abdominal pain, because osseous differentiation or teeth could be seen in the pelvis. Transvaginal sonography, however, has become the diagnostic tool of choice in most centers, although pelvic magnetic resonance imaging (MRI) can be helpful when the diagnosis is uncertain and may be especially useful when the mass is detected during pregnancy. Torsion is a frequent complication, because these are relatively buoyant and mobile tumors. Treatment usually involves ovarian cystectomy, with preservation of normal ovarian tissue and close inspection of the contralateral ovary. This often can be accomplished laparoscopically, when the dermoid cyst can be shelled out from the remaining normal ovary. Although concern for chemical peritonitis resulting from cyst rupture exists, with copious irrigation of the peritoneal cavity this complication can be avoided.

Struma Ovarii and Strumal Carcinoid

Rarely, ovarian teratomas will contain a single specialized tissue type. Struma ovarii is a subset of mature cystic teratomas in which the tumor is composed entirely or predominantly of thyroid tissue. Grossly, the cut surface shows gelatinous red to green-brown colloid, and microscopically mature thyroid tissue is seen (Fig. 55.3). Struma ovarii accounts for less than 3% of mature teratomas, with similar age distribution and similar clinical findings. However, thyroid gland enlargement is seen occasionally, and about 5% of patients with struma ovarii will experience signs and symptoms of thyrotoxicosis. Malignant changes in a struma ovarii are extremely rare, but can occur, and are most frequently of a follicular histology (unlike primary thyroid carcinomas). Approximately 30% of reported cases of malignant struma ovarii are associated with metastatic disease. Evaluation with iodine-131 scanning may be helpful, and treatment is often similar to that given for their thyroid carcinoma counterparts.

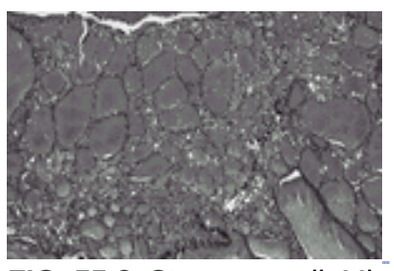

FIG. 55.3. Struma ovarii. Microscopically, the tumor is composed of normal thyroid tissue.

Strumal carcinoids are rare teratomas characterized by a mixture of thyroid and trabecular carcinoid tissues. Primary carcinoid tumors of the ovary account for less than 5% of ovarian teratomas and most likely arise from argentaffin cells found in the gastrointestinal or bronchial tissues that make up the teratoma. These tumors often are hormonally active due to the secretion of serotonin, bradykinin, and other peptide hormones that are secreted directly into the systemic circulation and are not inactivated by a “first pass” through the liver. Approximately 50% of ovarian carcinoids over 4 cm in diameter will be associated with the carcinoid syndrome, including episodic cutaneous flushing, diarrhea, and bronchospasm.

Malignant Germ Cell Tumors

Malignant ovarian germ cell tumors account for less than 5% of all ovarian cancers. Table 55.1 provides a listing of the World Health Organization classification of germ cell tumors of the ovary. Their male counterpart, testicular cancer, is approximately 10 times more common than ovarian germ cell tumors, and many of the chemotherapy regimens that are used for treating ovarian germ cell tumors have been adapted from clinical trials in patients with the corresponding type of testicular cancer. These interesting tumors tend to be diagnosed at an earlier stage than the common epithelial ovarian carcinomas, and they are very sensitive to chemotherapy and, in the case of dysgerminoma, to radiotherapy, as well. Germ cell tumors have distinct histopathologic characteristics and tumor markers that are useful in diagnosis and follow-up. Table 55.2 outlines the serum tumor markers typically associated with germ cell tumors.

Dysgerminoma
Endodermal sinus tumor
Teratomas
Immature
Mature (dermoid cyst)
Monodermal (struma ovarii, carcinoid)
Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Mixed forms
Gonadoblastoma

Source: Serov SF, Scully RE, Robin IH. *Histological typing of ovarian tumors: international histological classification of tumors, no. 9.* Geneva: World Health Organization, 1973, with permission.

TABLE 55.1. *World Health Organization classification of germ cell tumors*

TABLE 55.2. *Tumor markers associated with germ cell neoplasms: likelihood of elevation*

Dysgerminoma

Dysgerminoma is the most common malignant germ cell tumor of the ovary, accounting for 2% of all ovarian malignancies. Approximately 50% of the patients with this tumor are younger than 20 years, and 80% are younger than 30 years. Children with dysgerminoma may exhibit precocious puberty or primary amenorrhea. The serum lactate dehydrogenase level frequently is elevated and may serve as a tumor marker during treatment and follow-up.

Although dysgerminomas tend to be unilateral, approximately 10% to 15% of these tumors are bilateral. They are usually gray-white, smooth, and fleshy in appearance, and on cut surface they are usually solid. Hemorrhage and necrosis may be seen. Cystic areas suggest mixed germ cell elements that would require further careful sampling of the specimen. The microscopic appearance of an ovarian dysgerminoma is similar in histology to its male counterpart, testicular seminoma, with aggregates of tumor cells surrounded by connective tissue stroma containing many lymphocytes and foreign body giant cells (Fig. 55.4). The tumor cells are usually large, with clear or lightly granular cytoplasm containing abundant glycogen. Nuclei are vesicular and large, occupying one half of the cells and containing one or more nucleoli. Mitotic activity is almost always present. In less than 10% of patients, syncytiotrophoblastic giant cells may be detected, producing human choriogonadotropin (hCG) that may be demonstrated in tissue section by immunohistochemical techniques and in the serum by a modestly elevated hCG level. Syncytiotrophoblastic cells in a dysgerminoma do not have prognostic significance; however, serum ß-hCG levels can be used to monitor patients' responses to treatment and during follow-up.

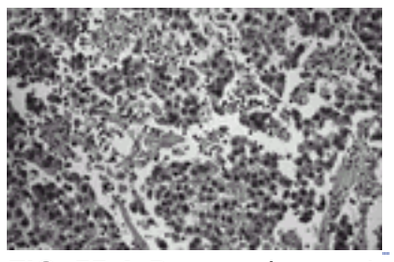

FIG. 55.4. Dysgerminoma. Loose aggregates of tumor cells are separated by connective tissue containing abundant lymphocytes.

Treatment is determined by patient age. Because most patients with dysgerminoma are of reproductive age, unilateral salpingo-oophorectomy and a full staging procedure with preservation of the contralateral ovary and the uterus are recommended, as long as there is no evidence of disease in the contralateral ovary. Table 55.3 is a listing of procedures required when a full staging procedure is performed. Table 55.4 illustrates the widely used International Federation of Gynecology and Obstetrics (FIGO) staging system for all ovarian cancers. Observational studies have revealed identical remission rates for conservative surgical treatment (e.g., unilateral salpingo-oophorectomy and staging) and complete extirpative surgery (e.g., bilateral salpingo-oophorectomy with or without a hysterectomy) in early-stage disease. Routine biopsy of the contralateral ovary is unnecessary if it is normal in appearance. If gross tumor is noted in both ovaries, a unilateral salpingo-oophorectomy of the larger ovary, a contralateral ovarian cystectomy, and a full staging procedure followed by chemotherapy may be appropriate in those patients who desire to retain fertility. Patients with advanced disease may require complete removal of the reproductive organs, which should be performed in consultation with a gynecologic oncologist.

Removal of ascites for cytologic evaluation. If there is no ascites, do peritoneal washing with 50–100 ml, of normal saline in the pelvis, the paracolic spaces, and infradiaphragmatic area.
Thorough examination of all peritoneal surfaces, intestine, and other viscera
BSO ± TAH or USO if tumor is limited to one ovary and future fertility desired
Cytoreductive surgery, reducing tumor size, including lymph nodes, to ≤1 cm residual size whenever possible
If tumor appears to be confined to the pelvis, the following procedures should be carried out:
Infracolic omentectomy
Biopsy of all suspicious areas or adhesions
Evaluation and sampling of paraaortic and pelvic lymph nodes
Routine biopsies from the cul-de-sac, right and left pelvic side walls, and the right and left paracolic spaces
Right diaphragmatic scraping or biopsy
Appendectomy, especially for mucinous tumors

BSO, bilateral salpingooophorectomy; TAH, total abdominal hysterectomy; USO, unilateral salpingooophorectomy.

TABLE 55.3. *Complete staging procedure for ovarian malignancy*

Stage I	Growth limited to the ovaries
Stage Ia	Growth limited to one ovary; no ascites; no tumor on the external surface; capsule intact
Stage Ib	Growth limited to both ovaries; no ascites; no tumor on the external surfaces; capsules intact
Stage Ic	Tumor either stage Ia or Ib but with tumor on the surface of one or both ovaries
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIa	Extension or metastasis to the uterus or tubes
Stage IIb	Extension to other pelvic tissues
Stage IIc	Tumor either stage IIa or IIb but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites containing malignant cells; or with positive peritoneal washings
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes Superficial liver metastasis equals stage III Tumor is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum
Stage IIIa	Tumor grossly limited to the true pelvis, with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIb	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces ≤ 2 cm in diameter Nodes negative
Stage IIIc	Abdominal implants >2 cm in diameter or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV Parenchymal liver metastasis equals stage IV

FIGO, International Federation of Gynecology and Obstetrics.
Source: International Federation of Gynecology and Obstetrics (FIGO), Annual report on the results of the treatment of gynecological cancer, vol 21, Stockholm, FIGO, 1991, with permission.

TABLE 55.4. *FIGO staging for ovarian cancer*

Dysgerminomas are very sensitive to both radiation and chemotherapy. Because they are found most frequently in young women, chemotherapy is the most appropriate postoperative treatment in these patients and should be offered to those with disease more advanced than stage Ia. Combination therapy with (a) vincristine sulfate (Oncovin), dactinomycin (Cosmegen), and cyclophosphamide (Cytoxan) (VAC) or (b) vinblastine sulfate (Velban), bleomycin sulfate (Blenoxane), and cisplatin (Platinol) (known as *VBP*) has been used with excellent results, especially in patients with stage I disease. The combination of bleomycin, etoposide, and cisplatin (BEP) has been even more effective in treating all stages of disease, with a sustained remission in essentially 100% of patients. The M.D. Anderson Cancer Center group and the Gynecologic Oncology Group (GOG) have used BEP in their treatment of dysgerminoma in all stages of disease and have reported a prolonged disease-free interval with three to six cycles of therapy, depending on disease status, residual disease, and tumor markers. In an effort to explore regimens with lower toxicity, the GOG reported a regimen of carboplatin and etoposide for completely staged and resected stage Ib to III dysgerminomas. Despite favorable results, BEP remains the recommended first line based on descriptive studies (type III evidence). In patients with pure dysgerminomas seemingly confined to the ovary (women who were staged inadequately), administration of three cycles of adjuvant BEP is recommended due to a recurrence rate of 20%. However, the scientific merit of this treatment plan requires further investigation. Another option is to offer a repeat surgery to fully stage the disease. There have been several reports of secondary neoplasm, especially hematologic malignancies, after the use of BEP and other etoposide-based regimens. Although these are rare occurrences, careful long-term follow-up and evaluation of risk–benefit ratio may be warranted to assess the efficacy of this regimen with and without etoposide.

Endodermal Sinus Tumor

Endodermal sinus tumor, or yolk sac tumor, is the second most common germ cell tumor, representing 1% of all ovarian malignancies. It may be pure or part of a malignant mixed germ cell tumor. The reported age distribution ranges from 16 months to 46 years, but most patients are younger than 30 years. The serum a-fetoprotein (AFP) level frequently is elevated in these patients (see Table 55.2), making it a useful diagnostic test in the initial workup, in the assessment of response to therapy, and in follow-up for recurrence. Symptoms are typical of those observed with other germ cell tumors. Several cases have occurred during pregnancy. No endocrine manifestations have been seen with the pure form of endodermal sinus tumor. More than 70% of patients with endodermal sinus tumors are diagnosed in stage I, although they are biologically virulent.

Grossly, tumors are usually gray-yellow, large, and solid, ranging from 3 to 30 cm in diameter. Bilateral involvement has been noted only in patients with metastatic spread to other organs. Foci of hemorrhage, necrosis, and gelatinous changes are present. Microscopically, endodermal sinus tumors display a wide range of histologic patterns. The microcystic pattern is characterized by a loose network of channels and spaces forming a honeycomb lined by flat pleomorphic mesothelial-like cells with large hyperchromatic or vesicular nuclei. Hyaline globules or droplets, which are positive with periodic acid–Schiff stain, are found commonly. The endodermal sinus pattern is characterized by perivascular formations called Schiller-Duval bodies (Fig. 55.5). Other patterns include the alveolar–glandular pattern, composed of alveolar, gland-like, or cystic spaces lined by flat or cuboidal epithelium; the polyvesicular vitelline pattern, in which numerous small vesicles are surrounded by connective tissue; and the solid pattern, consisting of aggregates of small pleomorphic undifferentiated cells. These histologic patterns do not have prognostic significance.

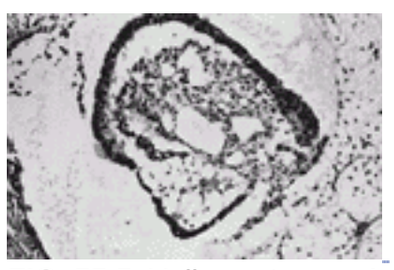

FIG. 55.5. Yolk sac tumor. A characteristic finding in the endodermal sinus pattern is the Schiller-Duval body.

In the past, patients with endodermal sinus tumors, even those with early-stage tumors, did poorly in spite of aggressive surgical and radiation treatments. With adjuvant chemotherapy after conservative pelvic surgery and staging laparotomy (see Table 55.3), there has been a marked improvement in the prognosis of patients with this malignancy. Adjuvant chemotherapeutic regimens for all nondysgerminomatous germ cell tumors (including endodermal sinus tumors, immature cystic teratoma, embryonal cell tumors, and others) are similar, because they are grouped together in treatment protocols in several major studies. The VAC regimen, first

introduced in the 1970s, resulted in a successful cure rate of more than 80% in patients with stage I disease but less than 50% in patients with more advanced stages, as reported by a GOG study and the M.D. Anderson group experience. The VBP regimen has shown superior results, compared with VAC, but toxicity is increased. However, no randomized clinical trials have been performed to compare the two regimens due to the rarity of these malignancies. More recently, the BEP regimen has shown an excellent response rate of over 95% in patients with local or advanced disease and has become the primary therapeutic regimen. Further studies, however, are needed to explore alternative regimens to reduce the rate of toxicity while maintaining the same efficacy. Second-look laparotomy should not be a part of posttherapy surveillance for this tumor or any other germ cell tumors. Salvage therapies, such as surgery followed by chemotherapy, in patients who have failed primary chemotherapy have shown some success; however, they are anecdotal at best due to the limited number of cases.

Immature Cystic Teratoma

Like mature cystic teratoma, immature cystic teratoma is composed of tissues derived from all three germinal layers, except that they also contain embryonic tissue. This group of tumors is the third most common malignant germ cell tumor, representing about 25% of all such tumors in patients younger than 20 years. Unlike mature cystic teratoma, which occurs in all ages but more frequently during the reproductive years, immature cystic teratoma essentially is found during the first two decades of life. It usually grows rapidly through its capsule, forming adhesions to the surrounding structures, and implants in the peritoneal cavity.

Tumors are usually smooth and unilateral, ranging from 9 to 28 cm. A mature cystic teratoma may be present in the other ovary. Tumors are predominantly solid, with some cystic areas filled with serous or mucinous fluid or fatty material (Fig. 55.6). The cut surface is soft and usually gray to pink to brown. Microscopically, the most common immature tissue present is neural, derived from the ectoderm (Fig. 55.7). A histologic grading system was, therefore, proposed based on the relative amount of mature and immature neuroepithelial tissues, mitotic activity, and degree of differentiation:

FIG. 55.6. Immature teratoma. This bulky neoplasm, removed from a 20-year-old woman, weighed 1,800 g. The neuroectodermal elements appeared opaque and friable *(arrow)*.

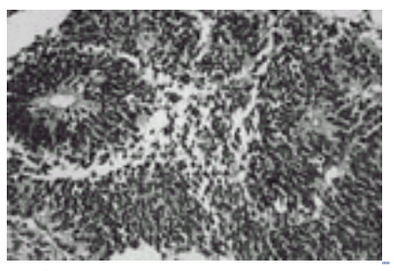

FIG. 55.7. Immature teratoma. These tumors are graded based on the presence and extent of neuroepithelial elements. Note the rosettes.

Grade 0-Mature tissue only
Grade 1-Limited immature neuroepithelial tissue and mitotic activity
Grade 2-Moderate amount of immature tissue and mitotic activity
Grade 3-Large quantities of immature tissue and mitotic activity

Prognosis correlates with histologic grade of tumors, because the presence of immature elements worsens the prognosis. In patients with stage Ia grade 1 disease, surgery alone, consisting of an exploratory laparotomy, unilateral salpingo-oophorectomy, and a complete staging procedure (see Table 55.3), is sufficient. For more advanced disease and high-grade tumors, postoperative adjuvant chemotherapy is necessary. Depending on disease extent, preservation of the contralateral ovary and the uterus is usually feasible. Serum AFP levels may be elevated (see Table 55.2). Chemotherapy is discussed in detail above.

Embryonal Carcinoma

Embryonal carcinoma is rare, accounting for less than 5% of all germ cell tumors. It usually occurs in children, with a median age of 15 years. Like its testicular counterpart, embryonal carcinoma is a highly malignant neoplasm. Because it often is seen as part of mixed germ cell tumors, serum AFP and hCG levels often are elevated. Clinically, it may be associated with precocious puberty, as well as abnormal vaginal bleeding in adults.

The gross pathologic picture is variable, but the tumor is usually large and soft, with a cut surface that is solid and gray-white with areas of hemorrhage and necrosis. Microscopically, embryonal carcinoma consists of primitive, undifferentiated sheets of variably sized epithelial cells (Fig. 55.8). Nuclei are vesicular, and mitoses are frequent. Syncytiotrophoblastic giant cells frequently are seen in the stroma or directly adjacent to clusters of embryonal carcinoma cells.

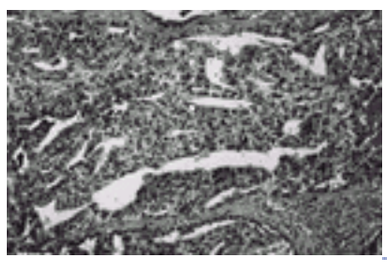

FIG. 55.8. Embryonal carcinoma. Tumor cells form syncytial aggregates that surround cleft-like spaces.

Polyembryoma

Polyembryoma is a rare germ cell tumor, characterized by numerous embryoid bodies that morphologically resemble normal presomite embryos. It is usually part of a mixed germ cell neoplasm and causes similar symptoms. The median age of patients with polyembryoma is 15 years. The tumor is usually unilateral, ranging from 10 cm to a mass that fills the entire abdominal cavity; cut section reveals mostly solid areas with hemorrhage and necrosis. Microscopically, embryonic bodies of varying degrees of differentiation are noted, including an embryonic disk, amniotic cavity, yolk sac, and extraembryonic mesenchyme (Fig. 55.9). Syncytiotrophoblastic cells have been detected, also. AFP, hCG, and sometimes human placental lactogen can be demonstrated in the serum and in cells by immunohistochemical staining.

FIG. 55.9. Polyembryoma. In less differentiated forms, embryoid bodies may have a bizarre appearance.

Choriocarcinoma

Choriocarcinoma is a rare germ cell tumor of either pure or mixed form. Pure choriocarcinoma usually is found in prepubertal children. Isosexual precocious puberty is a common clinical finding in premenarcheal patients. In postmenarcheal patients, the presence of other germ cell components is helpful in distinguishing ovarian germ cell tumors from a gestation choriocarcinoma. A diagnosis of ectopic pregnancy often is entertained in postmenarcheal patients due to the shared signs and symptoms. The gross appearance of choriocarcinoma depends on the composition of the germ cell elements. The tumor is usually arge, unilateral, and solid, with areas of necrosis and hemorrhage. Microscopically, both cytotrophoblasts and syncytiotrophoblasts are present (Fig. 55.10). Treatment is as described previously for the other germ cell tumors.

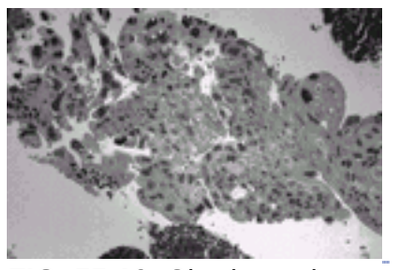

FIG. 55.10. Choriocarcinoma. There is a dimorphic population of malignant cytotrophoblasts and syncytiotrophoblasts. Associated hemorrhage is a common finding.

Gonadoblastoma

Gonadoblastoma almost always arises in a congenitally abnormal gonad, with associated sexual maldevelopment. Patients with gonadoblastoma most often have pure or mixed gonadal dysgenesis or are male pseudohermaphrodites. Predominantly, karyotypes 46,XY, 45,X/46,XY mosaicism and, rarely, 46,XX or 45,X have been associated with this tumor. Gonadoblastoma is much more common in phenotypic females than in phenotypic males, with a ratio of 4:1. It frequently is associated with dysgerminoma and occasionally with other germ cell neoplasms, including yolk sac tumor, embryonal carcinoma, and choriocarcinoma.

Patients with gonadoblastoma usually complain of primary amenorrhea, virilization, or developmental abnormalities of the genitalia. A karyotype should be included in the evaluation of the young women with a pelvic mass and any symptoms of abnormal sexual development. It is during the workup of these conditions that gonadoblastoma is usually diagnosed. It is detected most frequently during the second decade. Hot flushes and other menopausal symptoms have been noted after tumor excision, suggesting estrogen-secreting cells are in these tumors. However, the exact source of the androgen or estrogen production is unknown, because the steroid production was noted in the absence of Leydig or lutein cells.

Gonadoblastoma is more common in the right gonad than in the left and is bilateral in 38% of patients. The tumor can range from a microscopic lesion to a mass, measuring up to 8 cm in diameter, that is soft and fleshy to firm and hard, depending on the degree of calcification. When mixed with other malignant germ cell elements, it can grow even larger. Microscopically, gonadoblastoma is composed of cellular nests containing a mixture of germ cells and immature sex cord–stromal cells, such as Sertoli and granulosa cells (Fig. 55.11). Hyaline bodies and calcification are often present in the nests. In 50% of patients, a supervening dysgerminoma displaces most of the gonadoblastoma, pushing the cell nests to the periphery.

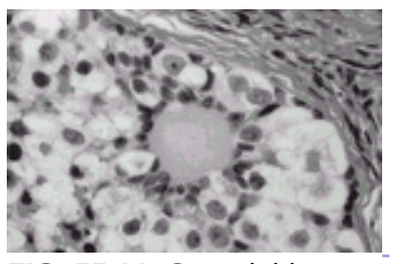

FIG. 55.11. Gonadoblastoma. Large germ cells are admixed with smaller sex cord derivatives that surround rounded hyaline material resembling a Call-Exner body.

Treatment for patients with gonadal dysgenesis is a bilateral gonadectomy, because they have an increased risk for a germ cell tumor, especially gonadoblastoma. If the gonads are not removed and tumors develop, the prognosis of patients with pure gonadoblastoma is excellent, as long as the tumor and the other ovary are both removed. The prognosis in patients with gonadoblastoma associated with dysgerminomatous elements remains very good, even with metastasis. If the gonadoblastoma is associated with other germ cell tumors, such as endodermal sinus tumor, embryonal carcinoma, or choriocarcinoma, the prognosis is poor if untreated. However, combination chemotherapy (BEP) results in significant improvement, as described previously.

SEX CORD–STROMAL TUMORS OF THE OVARY

Sex cord–stromal tumor accounts for approximately 8% of all ovarian tumors. The origin of tumor cells may be the coelomic and mesonephric epithelium or the mesenchymal stroma of the genital ridge. This category includes an array of tumors derived from the sex cords (granulosa and Sertoli cells) and from the gonadal stroma (theca and Leydig cells). The most common types of sex cord–stromal tumor are granulosa cell tumors and fibrothecomas, whose peak age of incidence is approximately 50 years. These tumors have the potential for steroid hormone secretion, with estrogen being the predominant hormone. They usually are not seen in women younger than 20 years, except for juvenile granulosa cell tumors. The classification of sex cord–stromal cell tumors is outlined in Table 55.5.

Granulosa stromal cell tumors
Granulosa cell
Thecoma-fibroma
Androblastoma: Sertoli-Leydig cell tumors
1. Well differentiated
Sertoli cell tumor
Sertoli-Leydig cell tumor
Leydig cell tumor
Hilus cell tumor
Steroid cell tumors
2. Intermediate differentiation
3. Poorly differentiated (sarcomatoid)
4. With heterologous elements
Gynandroblastoma
Unclassified

Source: Serov SF, Scully RE, Robin IH. *Histological typing of ovarian tumors: international histological classification of tumors, No. 9.* Geneva: World Health Organization, 1973, with permission.

TABLE 55.5. *World Health Organization classification of sex cord–stromal tumors*

Thecoma

Thecoma is a benign tumor affecting all ages, with a predominance in the postmenopausal group; it is rare in patients younger than 35 years. It accounts for 2% of all ovarian tumors. Many women with a thecoma have abnormal or postmenopausal uterine bleeding; some have an endometrial adenocarcinoma as a result of unopposed estrogen produced by the tumor. Thecoma is composed of lipid-laden stromal cells resembling theca cells. Rather than arising as a de novo neoplasm, it may represent changes occurring in background cortical stromal hyperplasia.

Tumor size ranges from a nonpalpable incidental finding to a large solid mass with a diameter of 15 to 20 cm. It is usually unilateral and almost never malignant. Its outer surface is smooth, and its cut surface is typically solid, lobulated, and yellow. Cystic change may be seen. Microscopic evaluation reveals masses of oval or round cells with abundant, pale, lipid-containing cytoplasm. Hyaline plaques are noted often. A luteinized thecoma sometimes occurs, usually in younger women.

Treatment for thecoma is tailored to patient age and ranges from a total abdominal hysterectomy and bilateral salpingo-oophorectomy for menopausal or postmenopausal women to a salpingo-oophorectomy or ovarian cystectomy, if possible, in patients who desire to retain fertility.

Fibroma

Like thecoma, fibroma is a benign tumor affecting all ages, although most occur in women aged 40 to 60 years; less than 10% of patients are 30 years or younger. Fibroma is not associated with hormone production. In some cases, hydrothorax and ascites are found in association with a pelvic mass—a constellation of findings known as *Meigs syndrome.* In other cases, fibroma is seen in patients with a hereditary basal cell nevus syndrome, characterized by early-appearing basal cell carcinomas, keratocysts of the jaw, calcification of the dura, and mesenteric cysts.

Fibroma, like thecoma, ranges in size from a nonpalpable incidental finding to larger than 20 cm; it is usually unilateral but multinodular. Cut surface is firm and hard and has a whorled appearance. Microscopically, fibroma is composed of bundles of collagen-producing spindle cells arranged in a storiform pattern (Fig. 55.12). Hyalinization and intercellular edema are characteristic. The cytoplasm of tumor cells may contain small quantities of lipid, making distinction from thecoma difficult.

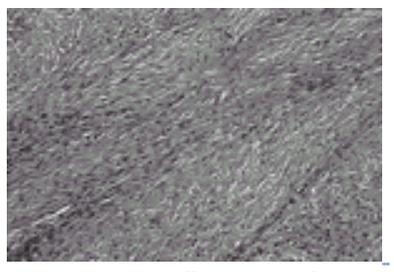

FIG. 55.12. Fibroma. The tumor is composed of intersecting bundles of spindled cells.

Treatment is similar to that for thecoma. In patients with Meigs syndrome, the hydrothorax and ascites usually resolve after resection of the pelvic tumor.

Juvenile Granulosa Cell Tumor

Approximately 44% of all juvenile granulosa cell tumors occur during the first decade of life and 97% during the first three decades. Isosexual pseudoprecocious puberty commonly is associated with this tumor, along with Ollier disease (enchondromatosis), Maffucci syndrome (enchondromatosis and hemangiomatosis), and abnormal karyotypes with ambiguous genitalia. Symptoms usually include abdominal pain, increasing abdominal girth, and hemoperitoneum due to rupture. Occasionally, it may be associated with pregnancy.

The gross appearance of juvenile granulosa cell tumor is commonly a large yellow-to-gray, solid and cystic mass, similar to the adult form. A mixture of granulosa and theca cells may be present. Microscopic features that distinguish juvenile granulosa cell tumor from the adult form are hyperchromatism of the tumor cells, which generally lack grooves, and the frequent luteinization of both the granulosa and theca cells (Fig. 55.13). The follicles are usually immature. Call-Exner bodies, which are pathognomonic of adult granulosa cell tumor, are rarely present in the juvenile form.

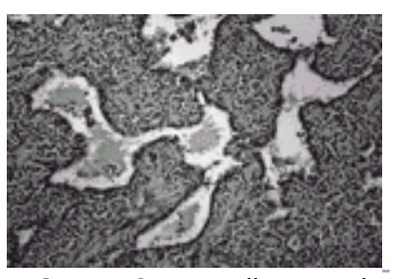

FIG. 55.13. Juvenile granulosa cell tumor. Tumor cells from follicles of varying sizes and shapes that contain weakly basophilic secretions.

Treatment in young women usually consists of a unilateral salpingo-oophorectomy with a complete staging (see Table 55.3), especially if preservation of reproductive function is desired and the tumor appears to be grossly confined to one ovary. Although the survival rate for patients with stage I disease is greater than 90%, juvenile granulosa cell tumor appears to behave more aggressively in advanced disease, with a survival rate of less than 50%. Isolated reports of successful treatment with various combination chemotherapies have been recorded. Due to the rarity of these tumors, a standard chemotherapeutic regimen has not emerged.

Adult Granulosa Cell Tumor

The adult form of granulosa cell tumor accounts for 1% to 2% of all ovarian tumors and 95% of all granulosa cell tumors. Although these tumors average 10 to 12 cm in diameter, a pelvic mass is not always detectable. Peak age of occurrence is 50 to 55 years, and most granulosa cell tumors produce estrogen, which in premenopausal women is manifested by menstrual irregularities such as menorrhagia, amenorrhea due to anovulation, or metrorrhagia. In postmenopausal women, vaginal bleeding results from endometrial stimulation. Endometrial hyperplasia or carcinoma is a relatively common occurrence, approximately twice that seen in premenopausal women. The best estimate for the frequency of associated endometrial carcinoma is 5%.

Grossly, the tumors are solid and gray-white or yellow, with cystic areas and hemorrhage. Microscopically, they are composed of granulosa cells and theca cells or fibroblasts, or both. Theca cells and fibroblasts are most likely a response of the ovarian stroma to granulosa cell proliferation, because only granulosa cells are found in metastatic sites. Granulosa cells may be round, polygonal, or spindle shaped, with scant cytoplasm and round or ovoid nuclei. Many different histologic patterns may be seen separately or together; these include the microfollicular pattern with its distinctive Call-Exner bodies (Fig. 55.14), macrofollicular, insular, trabecular, solid-tubular and, rarely, hollow-tubular patterns. Less differentiated forms include the watered silk or diffuse pattern. Rarely, a granulosa cell tumor undergoes sarcomatous transformation, producing the most aggressive form of the disease. Inhibin may be a useful immunohistochemical marker and serum inhibin levels can be used to monitor the clinical course.

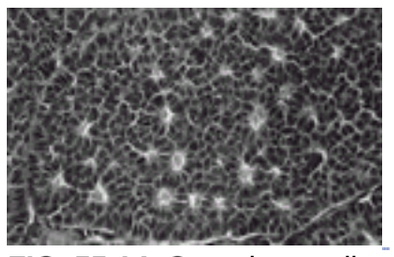

FIG. 55.14. Granulosa cell tumor. The microfollicular pattern is characterized by granulosa cells with angulated nuclei surrounding small cavities that simulate the Call-Exner bodies of the developing follicle.

Although most granulosa cell tumors have a very low potential for malignant behavior, with 90% of tumors being stage Ia, they do have a propensity for late recurrence up to 10 to 20 years or more after initial diagnosis. In addition to full surgical staging (see Table 55.3), surgery should include a total abdominal hysterectomy and bilateral salpingo-oophorectomy in postmenopausal patients. Conservative surgery is indicated in younger patients who wish to maintain fertility, if the tumor is confined to one ovary. Stage appears to be the most important prognostic factor. Although others include capsular rupture, tumor size, nuclear atypia, mitotic activity, and histologic pattern, studies of these factors have not been conclusive. It is difficult to evaluate the efficacy of chemotherapy in this group of tumors. Most retrospective series have been limited by their small sample size and short follow-up. Platinum-based therapy including the PAC, VBP, and BEP regimens have been the most successful, with a 5-year survival of 50%. Radiotherapy also has been used with varying success in studies limited by small numbers. In recurrent disease, surgery may offer the best mode of therapy. Chemotherapy and radiation therapy have been used.

Androblastoma and Sertoli-Leydig Cell Tumor

Hilus Cell Tumor Hilus cell tumor is a subtype of Leydig cell tumor, originating from the ovarian hilus. The other subtype, which is very rare, is a nonhilar-type Leydig cell tumor, derived from ovarian stromal cells and having similar clinical and pathologic features. The average age of patients with a hilus cell tumor is 58 years, and many show symptoms of abnormal menstruation, hirsutism, and virilization. Some may exhibit estrogenic manifestations. Hilus cell tumors are almost always benign. Grossly, this tumor is circumscribed, lobulated, solid, soft, and red to yellow. Tumor enlargement is usually minimal, and the tumor often is physically undetectable. Sometimes, it is discovered incidentally when the ovaries are sectioned for pathology examination for another purpose. Microscopic evaluation reveals circumscribed masses of steroid cells with abundant eosinophilic cytoplasm. Lipochrome pigment may be present, also. The diagnostic elongate eosinophilic crystalloids of Reinke must be found for the tumor to be definitively classified a Leydig cell neoplasm. Treatment of this benign tumor is unilateral salpingo-oophorectomy or ovarian cystectomy if preservation of fertility is desiredSK.

Sertoli-Leydig Cell Tumors

Sertoli-Leydig cell tumors are also termed Sertoli–stromal cell tumors and can be divided further into several subtypes (see Table 55.5). Stage and tumor differentiation seem to be important prognostic factors. Despite the name of these tumors, hormone production is not always associated with them. Tumors that produce hormones may result in masculine or feminine phenotypes, because few of the tumors actually produce estrogen or progesterone.

Sertoli Cell Tumor Sertoli cell tumors are very rare. Patients, ranging in age from 7 to 79 years (median, 33 years), usually exhibit a pelvic or abdominal mass. If the mass is functional, patients may experience some form of estrogenic effect, such as endometrial hyperplasia or isosexual precocious pseudopuberty. Androgenic and progestogenic effects may also occur. Most tumors are stage I unilateral masses that are well circumscribed, averaging about 9 cm in diameter. Cut surface reveals solid, yellow-to-brown, lobulated masses. Microscopic evaluation discloses closely packed hollow or solid tubules lined by Sertoli cells that can also contain abundant cytoplasmic lipid. An association between Sertoli cell tumors and Peutz-Jeghers syndrome has been reported in the literature. Most Sertoli cell tumors are benign or early-stage malignant neoplasms that are cured by surgery. Conservative surgery with a unilateral salpingo-oophorectomy is indicated in many of these patients who are young and desire preservation of ovarian function. Only rarely are these tumors poorly differentiated and aggressive. Experience with chemotherapy in these tumors is limited due to their rarity.

Sertoli-Leydig Cell Tumor Sertoli-Leydig cell tumor accounts for less than 0.5% of all ovarian tumors. It is seen most often in young women, with a mean age of occurrence of 25 years. Less than 10% of these tumors occur in women older than 50 years, and fewer than 5% occur in prepubertal girls. Sertoli-Leydig cell tumor often is associated with androgen production; however, virilization develops in only 50% of patients. This may be due to a lack of hormone production or insufficient androgen production. Typically, patients complain of oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, temporal balding, deepening of the voice, and enlargement of the clitoris. The latter two symptoms may not resolve after tumor removal. Patients without endocrine manifestations may complain of abdominal swelling or pain. Occasionally, symptoms of estrogen production such as menorrhagia or menometrorrhagia may be seen. They are a result of the Sertoli cell component of the tumor or peripheral androgenic conversion. Sertoli-Leydig cell tumor must be distinguished from other virilizing tumors, such as adrenal tumors, which often are associated with an elevated urinary level of 17-ketosteroids; the urinary level of 17-ketosteroids in Sertoli-Leydig cell tumor is usually normal or only slightly elevated. Serum AFP level may be increased and may be useful as a tumor marker. The gross appearance of Sertoli-Leydig cell tumor is highly variable. Overall, it has an average diameter of 12 to 15 cm, and its cut surface is usually tan or yellow and may be cystic. Hemorrhage and necrosis frequently are seen in the poorly differentiated tumors. On microscopic examination, the tumor is composed of a mixture of Sertoli, Leydig, and undifferentiated gonadal stromal cells, with or without heterologous components, in varying proportions and degrees of differentiation. In well-differentiated lesions, Sertoli cells form tubules and Leydig cells are found in the intervening stroma (Fig. 55.15). Sertoli cells are cytologically bland, and mitotic figures are rare. Leydig cells may contain abundant lipochrome pigment or crystalloids of Reinke. Intermediate and poorly differentiated tumors are characterized by more immature components of the Sertoli and Leydig cells. Cartilage, mucinous epithelium, skeletal muscle, and other heterologous elements are found in 20% to 25% of these tumors, most of which are of intermediate differentiation. When heterologous elements have been found in poorly differentiated neoplasms, the tumors are clinically malignant. Sertoli-Leydig cell tumor with a retiform pattern may be seen with prominent hyalinized cores and papillae lined by stratified epithelial cells.

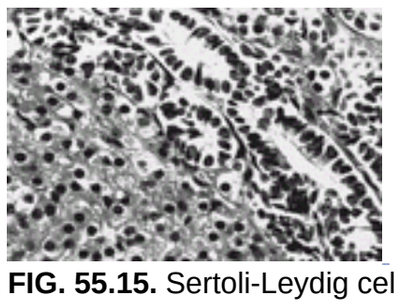

FIG. 55.15. Sertoli-Leydig cell tumor. This well-differentiated tumor is composed of hollow tubules lined by Sertoli cells and adjacent sheets of Leydig cells.

The treatment for Sertoli-Leydig cell tumor usually depends on patient age and tumor stage, degree of differentiation, and presence of heterologous elements in the tumor. The most important prognostic factor is stage. In young women with a stage Ia well-differentiated tumor and who desire future pregnancy, a unilateral salpingo-oophorectomy and a staging procedure are adequate treatment (see Table 55.3). However, more aggressive cytoreductive surgery, including a hysterectomy and bilateral salpingo-oophorectomy, tumor resection, and staging procedure may be indicated in postmenopausal patients or those with more advanced disease. Adjuvant therapy is recommended for patients who have stage Ia lesions with poorly differentiated elements or heterologous components or for those who have metastatic disease. However, due to the limited number of cases, no standard adjuvant therapy has been accepted for these patients. Most of the information available comes from small series and case reports. Treatment of advanced sex cord–stromal cell tumors, unlike that used for germ cell tumors, has not met with much success. Platinum-based therapies have yielded the best results, with an overall survival of approximately 50%. These include the PAC, VBP, and BEP regimens. As with chemotherapy, radiotherapy has been used successfully in a limited number of cases.

Steroid Cell Tumors Not Otherwise Specified Termed lipid cell or lipoid tumors in the past, these are tumors composed entirely of cells resembling typical steroid hormone–secreting cells (e.g., lutein cells, Leydig cells, and adrenal cortical cells), except that specific features such as location of origin in the hilus or crystalloids of Reinke are not identified. Steroid cell tumors not otherwise specified (NOS) account for approximately 0.1% of all ovarian tumors, with a mean age of occurrence of 43 to 60 years. Androgenic changes, occurring in 75% to 90% of patients, may be of many years' duration. Estrogenic and progestogenic changes are noted occasionally. Although the estrogenic manifestations may be a result of estrogen production by the tumors, the aromatization of androgen to estradiol in adipose tissue may be more plausible. Cushing syndrome may be found in some patients, accompanied by elevated serum cortisol levels. Diagnosis often depends on the clinical manifestation of virilization or the rare occasion of isosexual pseudoprecocity. Tumor removal results in rapid resolution of most of the hormonal effects, except for deepening of the voice and clitoromegaly. Grossly, steroid cell tumors NOS are solid, well circumscribed, and yellow to orange-tan, measuring 5 to 8 cm in diameter. Hemorrhage, necrosis, and cystic degeneration occasionally are observed. The cut surface of the tumor is soft and lobulated. Microscopically, tumor cells may resemble Leydig or hilar cells (Fig. 55.16). In other instances, cells have abundant pale cytoplasm, resembling adrenocortical cells. These cells are polygonal to round and larger than Leydig cells, with central nuclei and lipid-rich cytoplasm. The striking resemblance of many of these tumors to adrenocortical tumors has led some to speculate that they may arise from the adrenocortical nests. The association with manifestations of Cushing syndrome would seem to support this theory, and detailed examination has revealed the presence of these nests in the broad ligament and the ovarian hilus. Alternatively, given that steroid cell tumors NOS often are confined to the ovary may simply mean that adrenocortical hormones are being produced by cells of ovarian origin rather than by an ectopic adrenal tumor. Steroid cell tumors NOS are rarely malignant; approximately 10% to 15% of them recur or metastasize.

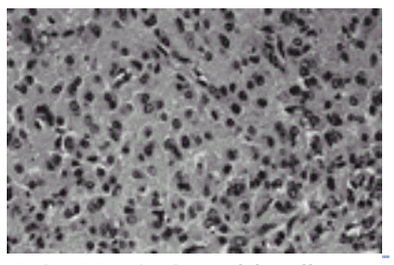

FIG. 55.16. Steroid cell tumor not otherwise specified. If crystalloids of Reinke were identified in these cells, the tumor would be classified a Leydig cell tumor or possibly a hilus cell tumor, depending on the its location. The granular appearance of the cytoplasm in these polygonal-to-rounded tumor cells suggests that they contain little lipid.

A unilateral salpingo-oophorectomy is adequate for stage Ia disease in young, reproductive age women. An abdominal hysterectomy and bilateral salpingo-oophorectomy with staging and resection of all extraovarian disease are indicated in women with advanced disease or in those beyond reproductive age.

EPITHELIAL OVARIAN TUMORS

Benign Neoplasms

Serous Cystadenoma Serous and mucinous cystadenomas are the most common benign epithelial ovarian neoplasms. Serous tumors account for approximately 25% of all benign ovarian neoplasms, with an age range of 20 to 50 years; they are bilateral in 12% to 20% of patients. Symptoms are variable. For many patients, the diagnosis is made during routine pelvic examination. Grossly, serous cystadenoma is a cystic, usually unilocular lesion, ranging from 5 to 15 cm in diameter. The inner lining of the cyst wall may be flat or partially covered by papillary projections. Microscopically, the epithelial lining can range from simple cuboidal cells, resembling the ovarian surface epithelium, to tall columnar cells, resembling the fallopian tube (Fig. 55.17). Ciliated and secretory cells may be present. Mitoses are rare, and nuclear atypia is absent. Psammoma bodies, which are concentric calcifications, are seen in 15% of tumors. Multiple, large, calcified deposits may be visible on radiologic examination of the abdomen. The stroma may vary from fibrous to cellular to hyalinized, with marked stromal edema. The papillary processes are fibrous and lined by a single layer of epithelial cells.

FIG. 55.17. Serous cystadenoma. The lining epithelium commonly appears tubal.

The preoperative workup depends on patient age and the degree of suspicion of malignancy. A unilateral salpingo-oophorectomy usually is performed in patients who have completed childbearing. In those desiring future reproduction, an ovarian cystectomy usually is performed. A bilateral salpingo-oophorectomy may be performed in selected individuals, particularly in those with bilateral tumors. In such cases, discussion of a hysterectomy is reasonable but not necessary.
Mucinous Cystadenoma Mucinous cystadenoma accounts for approximately 25% of all benign ovarian neoplasms, with an age range of 20 to 50; in 2% to 3% of patients it is bilateral. The tumor arises from the surface epithelium of the ovary, resembling müllerian-type epithelium of the endocervix, intestinal-type epithelium, or both these types. Because of the large size that this tumor frequently attains, patients usually have a palpable pelvic or abdominal mass and may have associated pain. Gross evaluation of a mucinous cystadenoma reveals that it is usually multilocular and larger than its serous counterpart, ranging up to 50 cm or more in diameter. The external surface is usually smooth, pinkish gray, and sometimes lobulated. Inside, locules tend to be small and contain thick, sticky, tenacious mucinous material (Fig. 55.18). Microscopically, the epithelium consists of a single layer of uniform tall columnar cells that resemble a picket fence in the endocervical type or may contain goblet, argentaffin, and Paneth cells in the gastrointestinal type (Fig. 55.19). Treatment is similar to that for serous cystadenoma. The appendix should be removed in any suspected ovarian mucinous tumor because of frequent synchronous appendiceal mucinous tumors (mucocele), even in a clinically normal-appearing appendix.

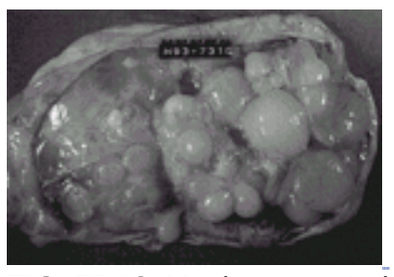

FIG. 55.18. Mucinous cystadenoma. The tumor is multilocular.

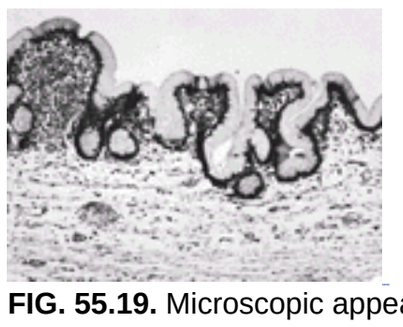

FIG. 55.19. Microscopic appearance of the lining of a mucinous cystadenoma. The “picket fence” epithelium is characteristic of this tumor.

Cystadenofibroma As the name suggests, cystadenofibroma is a variant of serous cystadenoma, containing both cystic and solid components. This benign tumor is usually unilateral and has a similar age distribution to that of serous cystadenoma. It is variably papillary to solid. Papillae are broad, firm, and nonfriable. Microscopically, solid areas are found to contain small cystic structures that are histologically identical to serous cysts. As with other benign epithelial ovarian tumors, treatment is individualized based on patient age and reproductive desire.
Brenner Tumor Also known as transitional cell tumor, Brenner tumor constitutes 2% of all primary ovarian tumors. Patients with this tumor range in age from 30 to 70 years, with a mean age of 50 years. Brenner tumor is thought to be derived from ovarian surface epithelium that undergoes a metaplastic transformation to cells resembling urothelium. It may occur synchronously with mucinous cystadenoma. Most transitional cell tumors are benign, but transformation to a malignant form has been observed. Clinical picture may be variable, because the patient may be asymptomatic or may have a palpable mass or pain. Occasionally, patients may experience vaginal bleeding, probably due to hormonal activity in the stroma. Grossly, the tumor is solid—less commonly cystic—and usually unilateral, although 6% to 7% of tumors are bilateral. Ranging in size from microscopic to as large as 30 cm in diameter, it is usually gray, white, or yellow, with a faintly lobulated cut surface. Microscopic review depicts a characteristic pattern of circumscribed epithelial nests of cells embedded in an abundant fibromatous stroma (Fig. 55.20). Epithelial cells may be round to polygonal, with eosinophilic or clear cytoplasm. When longitudinal grooves of the nuclei are present, the cells are described as having a “coffee bean” appearance. Often, these nests of epithelial cells undergo benign cystic changes lined by either transitional cells or mucinous cells. Treatment is usually resection of the tumor, and this may involve a cystectomy or salpingo-oophorectomy with or without a hysterectomy, depending on patient age and reproductive desires.

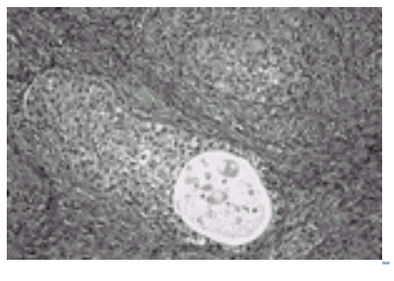

FIG. 55.20. Brenner tumor. Epithelial nests embedded in a fibromatous stroma may show cystic change. Longitudinal grooves in the cells can impart a “coffee bean” appearance.

Tumors of Low Malignant Potential

Epidemiology Ovarian tumors of low malignant potential (LMP), also known as atypical proliferating tumors, comprise a group of tumors showing greater epithelial proliferation than that seen in their benign counterparts although, by definition, they are still noninvasive. Recognized by FIGO in 1971, LMP ovarian tumors account for approximately 15% of all epithelial ovarian cancers; mean age of occurrence is 40 years. A meta-analysis performed by the Collaborative Ovarian Cancer Group found that, as with malignant epithelial ovarian cancer, parity, multiple births, history of breast-feeding, and oral contraceptive use are protective against LMP tumors. A history of infertility and use of fertility drugs may increase the risk of developing an LMP tumor, although these data are weak and controversial. Prospective trials are needed to resolve the controversy surrounding the use of fertility drugs and these tumors.
Clinical Features Patients are usually asymptomatic, but they may come to medical attention with a pelvic mass and complaints of abdominal or pelvic pain or both, increasing abdominal girth, or abnormal bleeding. Ultrasonography or a computed tomography (CT) scan may be helpful in making the diagnosis of an ovarian mass. Serum CA-125 levels are not always elevated. When they are, the tumor is usually of serous histology. LMP tumors usually have an indolent course. Many biomarkers, such as DNA ploidy, tumor markers, oncogenes, and tumor suppressor genes, have been studied in an attempt to define a high-risk group or predict tumor recurrence and thus indicate which patients might benefit from adjuvant treatment. To date, no such marker has been identified.
Pathologic Classification LMP ovarian tumors have been described for all epithelial subtypes; the most common types are serous and mucinous tumors. The absence of stromal invasion is an absolute criterion for making the diagnosis. Careful examination of the tissue blocks is necessary to minimize the potential for “sampling error” or omitting an area of invasive carcinoma in LMP tumors. Approximately 20% to 30% of ovarian tumors diagnosed as borderline by frozen section prove to be carcinomas with review of the permanent sections. The mean diameter of serous LMP tumors is 12 cm, and bilateral tumors are reported in 33% to 75% of patients. These tumors are usually cystic, with mural clusters of papillary projections (Fig. 55.21 and Fig. 55.22).

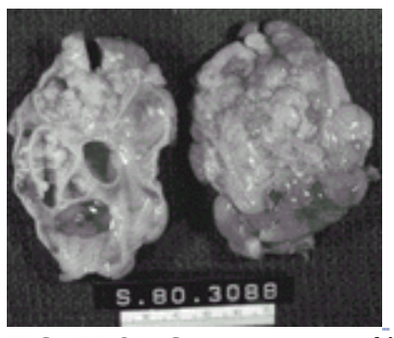

FIG. 55.21. Serous tumor of low malignant potential (atypical proliferating tumor). On the right is the external surface of the ovary; on the left the cut surface. The tumor is multicystic, and within some cysts are complex papillary projections.

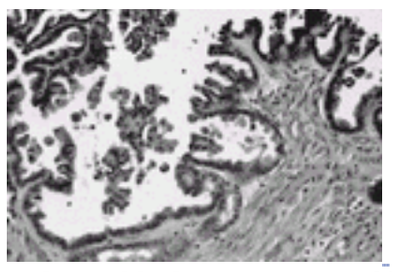

FIG. 55.22. Serous tumor of low malignant potential (atypical proliferating tumor). Ramifying papillae are lined by a relatively bland serous epithelium that forms tufts and seemingly free-floating clusters.

Mucinous LMP tumors are larger than their serous counterparts, with an average diameter of 17 to 20 cm; they are infrequently bilateral. They are characterized by multiloculated cystic masses, with smooth outer surfaces and areas of papillations and solid thickening on the inner surface. Microscopically, the epithelial lining of the cysts consists of tall, columnar, mucin-secreting cells, resembling the epithelium of the endocervix or intestine. Stratified epithelial cells may be atypical with hyperchromatic nuclei and mitotic figures, but without stromal invasion (Fig. 55.23).

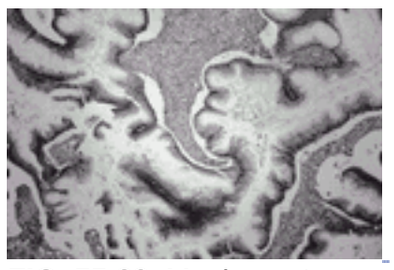

FIG. 55.23. Mucinous tumor of low malignant potential (atypical proliferating tumor). Epithelial proliferation results in pseudostratification and tufting. Mild cytologic atypia is present.

Stage for stage, the 5-year survival rate for patients with LMP epithelial ovarian tumors is far better than that for patients with malignant epithelial ovarian cancer. A review of the literature by several investigators revealed a survival rate of greater than 95% in patients with stage I LMP ovarian tumors. Furthermore, Kurman and Trimble found that a majority of patients with LMP tumors actually died with the disease, not from it, because invasive carcinoma developed in only 8 (0.8%) of 953 patients with a mean follow-up of 7 years. The other patients died from radiation- or chemotherapy-associated complications. Recognizing that a minority of LMP tumors behave aggressively like invasive ovarian carcinomas, Seidman and Kurman have challenged the current classification of LMP tumors in an attempt to develop a nomenclature that better reflects prognosis. These investigators believe that LMP tumors are actually a heterogeneous group of tumors, both histologically and clinically, that can be divided into malignant or benign phenotypes based upon certain features. For serous tumors, they propose that patient outcome depends upon the presence or absence of micropapillary features within the ovarian tumor and invasive versus noninvasive peritoneal implants. In a large meta-analysis of serous LMP tumors, they report that patients with micropapillary serous carcinoma have 5- and 10-year survival rates of 81% and 71%, respectively. Patients with a serous borderline tumor without invasive implants (atypical proliferative serous tumor) had 5- and 10-year survival rates of greater than 98%. However, in serous borderline tumor with invasive implants, survival rates drop to 60% to 70% after 5 and 10 years. The vast majority of patients with invasive implants, or with those which progressed to invasive carcinoma, were found to have micropapillary features within the primary ovarian tumor upon careful sectioning. Thus, atypical proliferative serous tumor and serous borderline tumor without invasive implants follow in a very benign clinical course, while micropapillary serous LMP tumors behave much like invasive ovarian carcinomas. Micropapillary serous carcinoma is characterized by thin, elongated micropapillae with minimal or no fibrovascular support arising directly from thick, more centrally located papillary structures (Fig. 55.24). Mitotic activity may be seen in some of the cases, ranging from one to three figures per 10 high-power fields. The distinction between invasive and noninvasive implants may be difficult. Noninvasive implants usually have a scant epithelial component surrounded by reactive spindle cells with imperceptibly meshed epithelial and stromal cells (Fig. 55.25). On the other hand, invasive implants usually have a more cellular epithelial component, with complex epithelial proliferation composed of multiple micropapillae and small round nests that display a destructive infiltrative growth (Fig. 55.26).

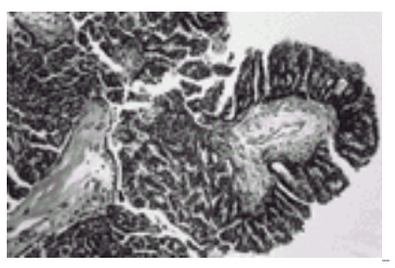

FIG. 55.24. Micropapillary serous carcinoma. In this fully malignant serous carcinoma, strands of neoplastic cells stream from thick, fibrous cores, stimulating a Medusa head.

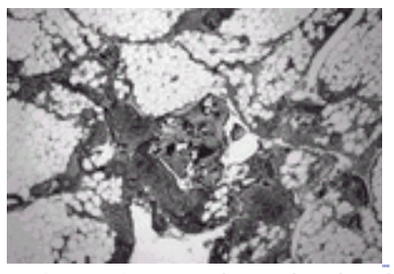

FIG. 55.25. Noninvasive implant in a serous borderline tumor. A circumscribed focus of tumor is surround by fibroadipose tissue that shows no stromal reaction. Cell nests are heavily calcified.

FIG. 55.26. Invasive implant in a serous borderline tumor. The tumor here is more cellular. The invasive implant extends below the peritoneal surface and is associated with reactive desmoplasia.

Mucinous LMP tumors tend to be confined to the ovary. Advanced stage tumors are typically associated with pseudomyxoma peritonei, and frequently represent metastatic disease from the gastrointestinal tract. In such cases, careful histopathological examination of the appendix is necessary to rule out an occult appendiceal primary. Primary mucinous carcinomas of the upper gastrointestinal tract and appendix can present with small primary lesions and large bilateral ovarian masses that stimulate primary ovarian carcinoma. Mucinous ovarian LMP confined to the ovary have an excellent prognosis, while the survival of patients with advanced stage disease is approxmiately 50%.

Pseudomyxoma Peritonei Pseudomyxoma peritonei may accompany mucinous neoplasms of the ovary and is characterized by extracellular gelatinous material in the pelvic and abdominal cavity. The primary site of origin of pseudomyxoma peritonei is debatable. Some series cite that the majority begin in the appendix, while others have described a synchronous origin in the ovary and appendix. Pseudomyxoma is associated most frequently with borderline or well-differentiated ovarian mucinous tumors in approximately 8% of cases and only rarely is seen in mucinous cystadenomas. The mainstay of treatment is cytoreductive surgery; multiple treatment modalities with systemic and intraperitoneal chemotherapies have not demonstrated survival benefit. Patients have a high recurrence rate, with variable times to recurrence. Most series agree that when patients have recurrent disease, repeat laparotomy is required to relieve symptoms. The overall 5-year survival rate is 50%, and most patients die from bowel obstruction.

Treatment The primary surgical treatment for patients with LMP tumors who have completed childbearing is identical to the recommendation for invasive ovarian disease, including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, tumor debulking, and full staging (see Table 55.3). An appendectomy should be performed in patients with a mucinous LMP tumor because of the association with a synchronous primary appendiceal tumor. In younger patients with early-stage diagnosis and a desire for childbearing, conservative surgery with preservation of the uterus, the contralateral ovary, and in some cases the ipsilateral ovary (i.e., cystectomy) may be the appropriate treatment. Consultation with a gynecologic oncologist and pathologist can identify those patients who are candidates for conservative management. Several studies, both cohort and observational, have reported excellent outcome with conservative management of such patients. One of the largest studies reports a 12% recurrence rate for patients treated conservatively with either unilateral salpingo-oophorectomy (n = 110) or ovarian cystectomy (n = 74), versus 2.5% for patients treated with definitive hysterectomy and bilateral salpingo-oophorectomy. Recurrences or progression to carcinoma (1.5%) were more common among patients with invasive implants or advanced stage disease. The feasibility of doing a cystectomy for an LMP ovarian tumor and conserving the rest of the ovarian tissue in early-stage disease has been described but requires further study. LMP ovarian tumors have been diagnosed during pregnancy. Conservative surgery usually is performed, and pregnancy does not appear to be deleterious in regard to the prognosis for these patients. Most patients went on to deliver at full term without any complications.

Postoperative Therapy There is no evidence to suggest that adjuvant chemotherapy for patients with early-stage LMP tumors or with optimal cytoreduction of advanced LMP tumors improves survival. In fact, patients may be more likely to die from the side effects of adjuvant therapy than from the disease itself. Platinum-based therapy may be appropriate for a select group of patients with micropapillary serous tumors and invasive serous implants, based upon the high rates of recurrence in these patients. However, patients must be counseled that available literature does not demonstrate improved survival with chemotherapy. An ongoing prospective GOG trial will address these issues. Second-look laparotomy should not be a part of the standard therapy in treating these patients.

Malignant Neoplasms

Epidemiology Epithelial ovarian carcinomas account for 80% to 90% of all ovarian malignancies. Incidence rates in the United States are about 12 to 15 per 100,000 for white women, compared with about 8 to 10 per 100,000 for the U.S. residents of non-European heritage. The incidence rate continues to increase to about 40 cases per 100,000 women by age 50, and then continues to increase slowly to about 50 cases per 100,000 by age 65. Although the incidence rates in Asian nations are lower, studies have indicated increasing incidence rates in these countries. Other than race, risk factors for ovarian cancer identified by epidemiologic studies include age over 60 years, early menarche, late menopause, nulliparity, infertility, personal history of breast or colon cancer, and family history of ovarian, breast, or colon cancer. In some inherited cases, the increased risk of ovarian cancer may be more than 50%, depending on the type and number of family members affected and age of onset. Other factors that have been implicated but lack adequate epidemiologic evidence include high-fat diets, talcum powder, and infertility drugs. Use of an oral contraceptive, bilateral tubal ligation, and hysterectomy are protective. Epithelial tumors are derived from the ovarian surface epithelium, which is the site of ovulation. One hypothesis suggests that incessant ovulation contributes to ovarian carcinogenesis because of the repeated injury and repair of the ovarian epithelium secondary to monthly ovulation. Repair of the ovarian surface promotes proliferation-associated DNA damage. Data from the United States Collaborative Analysis support the suppression of ovarian activity as a means of preventing ovarian cancer. A study found that a high number of ovulatory cycles was associated with more genetic alterations in patients with ovarian cancer. Oral contraceptives appear to protect against ovarian cancer through suppression of ovulation and a direct antiproliferative effect of the progestins on ovarian epithelium.

Clinical Picture Many patients with epithelial ovarian cancer come to medical attention with advanced stage disease, with symptoms of abdominal fullness, pain, distension, early satiety, and weight loss. Other gastrointestinal symptoms include nausea, dyspepsia, constipation, or diarrhea. Abdominal distension can be due to ascites or a large abdominopelvic mass. Abnormal vaginal bleeding is seen in 30% of the cases. The most common physical signs are ascites, manifested by a fluid wave and the absence of shifting dullness, and a pelvic mass. The mass is frequently firm, hard, and fixed, with multiple nodularities. Small tumors may not be palpated easily in the presence of ascites. Possible sites of spread within the abdomen are multiple (Fig. 55.27).

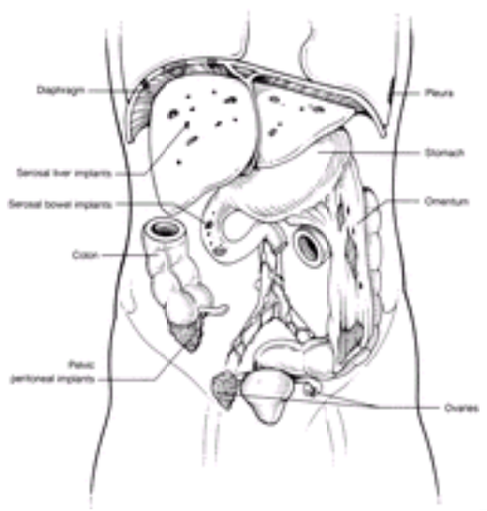

FIG. 55.27. Possible sites of spread of epithelial ovarian cancer.

Preoperative Evaluation All patients should have a complete blood cell count and serum chemistry analysis, including liver function tests, performed. These tests, although routinely done preoperatively, will select patients who may be at higher anesthetic risk. For example, any liver or kidney dysfunction may require further

investigation, or anemia may justify a workup and transfusion prior to surgery. Serum tumor markers should be assayed. Although CA-125 is the best tumor marker for women with epithelial ovarian carcinoma, it can be elevated in a variety of benign gynecologic conditions and other nongynecologic malignancies. CA-125 will be elevated in more than 80% of patients with serous epithelial ovarian cancer. Although it is not useful for screening, CA-125 has higher sensitivity and specificity for detecting ovarian cancer in the postmenopausal patient. Preoperatively, CA-125 may be useful in helping to predict the potential for malignancy and, if elevated, it can be used to follow response to therapy and detect an early recurrence. Chest radiographs are performed routinely to look for malignant pleural effusions, which occur in 10% of patients, and metastatic pulmonary disease, which is very rare. Barium enema examination is not performed routinely but may be helpful in patients with a left lower quadrant mass, blood in the stool, obstipation, or anemia, or in patients with carcinomatosis in whom a primary gastrointestinal tract malignancy must be ruled out. Barium enema examination is not very useful in predicting the need for colon resection. Mammography may be performed to rule out a possible metastatic or synchronous breast carcinoma. Sonography is the most useful diagnostic examination in the evaluation of a pelvic mass. It is an easily accessible and inexpensive imaging modality that provides an accurate description of ovarian morphology. Some characteristics associated with ovarian cancer include irregular ovarian cyst borders, solid elements, papillary projections, bilateral ovarian pathology, and ascites. Color Doppler imaging evaluates blood flow to an ovarian mass and can suggest a malignant process based upon abnormal neovascularization. Several studies suggest that color Doppler imaging improves detection of ovarian cancers, although it lacks the ability to definitively identify malignancy. Three-dimensional ultrasonography has the potential benefit of enhanced imaging of the ovarian architecture and measuring the ovarian cyst volume; however, its application in evaluation of an adnexal mass has not been fully studied. CT scan may be helpful in characterizing the liver, lymphatic spread, the omentum, and the mesentery. CT scan may be helpful in distinguishing a gynecologic malignancy from a metastatic pancreatic neoplasm for which surgery may not be warranted. MRI in patients with an ovarian mass has not been shown to have any clear advantage over CT scanning, except for the evaluation of pregnant patients whose ultrasonographic examination was inconclusive and CT scan would result in undesirable ionizing irradiation. Other studies such as bone and liver scintigraphy do not add any useful information. Intravenous pyelograms or renal scans may be helpful in patients with abnormal renal function or abnormal findings on ultrasonography, but they rarely are used. Immunoscintigraphy using CYT-103 or OC-125 that detects occult extraabdominal or miliary metastasis is experimental but may be helpful in patients prior to second-look laparotomy or in those with recurrent disease. Positron emission tomography (PET) is a form of computer-assisted imaging that uses radionuclide-labeled analogues of glucose labeled with positron-emitting isotopes. Cancer cells are detected by their increased glucose metabolism compared with noncancerous cells. PET has been examined in several preliminary studies involving the preoperative evaluation for suspected recurrent or metastatic ovarian tumors. Although the results are promising, PET's role in the preoperative evaluation of such patients awaits further study.

Staging Staging is a critical step in the treatment of ovarian cancer. It is done at the time of surgical exploration in accordance with the FIGO system revised in 1987 (see Table 55.4). Proper staging is absolutely necessary, because it impacts both prognosis and subsequent treatment method (see Table 55.3). Observational studies have shown that 30% of patients who were thought to have stage I or stage II disease found during initial surgery had more advanced disease with more comprehensive restaging laparotomy. A midline vertical incision is recommended, and it should be extended to above the umbilicus, if necessary, to allow proper exposure of the upper abdominal cavity for tumor debulking. If an ovarian malignancy is discovered unexpectedly through a low transverse incision, the rectus muscle can be either severed or detached from the pubic symphysis to enhance surgical exposure.

Pathology

Serous Carcinoma Serous tumor is the most common epithelial ovarian carcinoma, accounting for 40% to 50% of all such tumors. In most patients, serous tumors are bilateral and are disseminated at the time of diagnosis. They are soft, friable, mostly cystic, containing turbid or bloody fluid and having extensive papillary projections. Papillary excrescences also may be seen on the external surface or attached to adjacent structures (Fig. 55.28).

FIG. 55.28. Serous carcinoma. The tumor forms large, bilateral, solid, and cystic masses that have grown through the capsule. Tumor also involves the uterine serosa.

Microscopic evaluation in well-differentiated serous carcinoma reveals well-formed papillary structures that grow into cystic spaces or on the peritoneal surface of the tumor. Psammoma bodies are present in most cases (Fig. 55.29). With less differentiated tumors, the papillary pattern becomes less visible, the mitotic activity more brisk, and tumors become solid sheets of uniform, dark cells that are often slightly spindled and have a high nucleus-to-cytoplasm ratio.

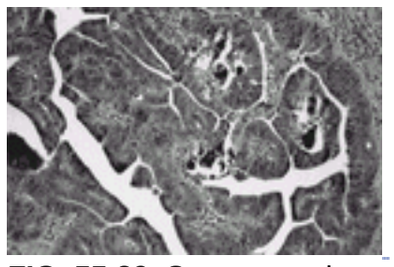

FIG. 55.29. Serous carcinoma. In this tumor, papillae are lined by high-grade tumor cells with prominent nucleoli. Psammoma bodies are present.

Mucinous Carcinoma Mucinous carcinoma represents 5% to 10% of all epithelial ovarian malignancies. Bilaterality is less common, present in less than 15% of cases. Disseminated spread is seen much less frequently than in patients with serous carcinoma. Mucinous carcinoma is usually larger than its serous counterpart, measuring approximately 15 to 30 cm in diameter. The tumor is multiloculated, solid and cystic, and filled with thick, viscous mucin. Microscopically, invasive, well-differentiated mucinous carcinoma typically is composed of more than three layers of epithelium, with prominent mucin production (Fig. 55.30). It may show only subtle irregularities in gland contour and irregular budding, with no other stromal signs of invasion. In moderately differentiated carcinoma, the glands are more back-to-back, with obvious stromal invasion, cellular stratification, and nuclear atypia. In poorly differentiated mucinous carcinoma, cells are disorganized, embedded in a dense reactive ovarian stroma. Signet-ring cells may be present, as in a Krukenberg tumor. Mucinous tumor often contains a wide range of histologic differentiation; therefore, extensive sampling must be performed to obtain the correct diagnosis.

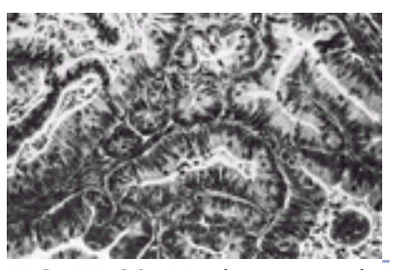

FIG. 55.30. Mucinous carcinoma. Infiltrating, crowded glands are lined by tall columnar cells with pale cytoplasm. Note the atypical, stratified nuclei (original magnification × 160).

Endometrioid Tumor Endometrioid carcinoma accounts for 20% of all epithelial ovarian malignancies. It is the second most common type of epithelial ovarian carcinoma and is bilateral in 30% of cases. In up to one third of patients, endometriosis has been noted in the same ovary or elsewhere in the pelvis. In addition, a synchronous endometrial adenocarcinoma has been seen in 20% of patients; these tumors are superficial and are associated with endometrial hyperplasia. Well-differentiated ovarian endometrioid adenocarcinoma is characterized by well-developed glands lined by tall, columnar, pseudostratified or multilayered epithelium like its uterine counterpart (Fig. 55.31). Squamous differentiation may be seen in about 30% of tumors and is usually benign. As tumors become less differentiated, the glandular pattern becomes less organized, and a solid growth pattern becomes predominant. Mitoses are more frequent, and nuclei are more high grade.

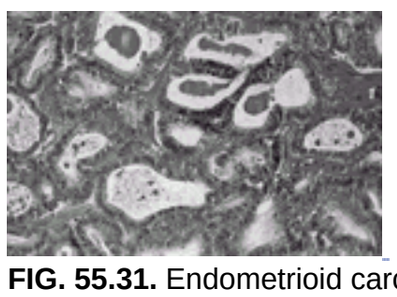

FIG. 55.31. Endometrioid carcinoma. In a well-differentiated endometrioid carcinoma, the glands are smoothly rounded, closely packed, and lined by an endometrioid type of columnar epithelium.

Clear Cell Tumor Clear cell carcinoma constitutes 5% to 10% of malignant epithelial ovarian tumors. It is bilateral in 15% to 20% of patients and confined to the ovary in 60%. Despite the limited spread of disease at the time of diagnosis, clear cell carcinoma is a notoriously virulent tumor. It frequently is associated with endometriosis,

with 25% of tumors arising from the lining of the endometriotic cysts. A mixed form of epithelial ovarian carcinoma with clear cell tumor and endometrioid or serous carcinoma can occur, suggesting a similar histogenesis. Microscopically, clear cell tumor may be characterized by sheets of polyhedral clear cells divided by fine connective tissue septa. Cells usually have abundant glycogen in the cytoplasm that is responsible for the clear appearance of the cells. The other characteristic feature is the tubulopapillary pattern formed by the columnar secretory cells with nuclei that bulge into the lumina of the glands, giving a hobnail appearance (Fig. 55.32). Eosinophilic cells instead of secretory columnar cells may surround tubules or papillae, or a mixture of these cells may be present.

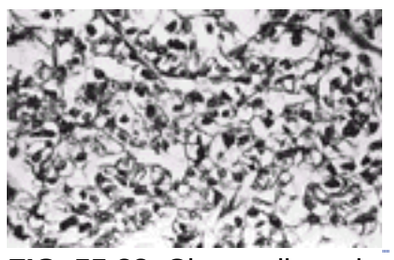

FIG. 55.32. Clear cell carcinoma. In clear cell carcinoma, tumor cells are polygonal, with central nuclei and abundant clear cytoplasm (original magnification × 250).

Undifferentiated Tumor Accounting for 5% to 10% of all ovarian malignancies, undifferentiated tumor exhibits such poor differentiation that it cannot be classified into any of the categories previously described. There is a variable histologic pattern, ranging from sheets of large anaplastic cells, to undifferentiated small cells, to large pleomorphic giant cells with eosinophilic cytoplasm. The prognosis is usually very poor because patients often seek treatment in advanced stages with large tumor burdens.

Brenner Tumor Malignant Brenner tumor is very rare. It ranges from 10 to 30 cm in diameter and is usually unilateral. Microscopically, malignant Brenner tumor exhibits solid sheets of heterogeneous epithelial cells with minimal stroma. Nuclear grade and mitotic activity are high. Histologically, these cells resemble transitional cells, like those in the urologic tract. Differentiation from a carcinoma of urinary origin is based on clinical picture and surgical findings. Origin in the ovary is supported by finding a transition from a benign or proliferating Brenner tumor.

Müllerian Mesenchymal and Mixed Tumors These rare ovarian tumors are divided into subtypes, including adenosarcoma and malignant mixed mesodermal tumor; they are associated with a poor prognosis. Histologically, they resemble their uterine counterparts. Adenosarcoma contains a benign epithelial component and a sarcomatous mesenchymal component. Malignant mixed mesodermal tumor has both malignant epithelial and malignant mesenchymal components (i.e., carcinosarcoma). Similar to epithelial ovarian tumors, these tumors usually are surgically staged. However, optimal cytoreduction and adjuvant chemotherapy regimens for these patients may not be as effective as they are for patients with the other types of epithelial tumors. The chemotherapeutic regimens are also different, but studies are limited by the rarity of these tumors. Agents that have been tried include doxorubicin (Adriamycin), cisplatin, and ifosfamide (IFEX), and paclitaxel (Taxol).

Treatment

Surgery Surgery is the most important aspect in the initial care of patients with epithelial ovarian cancer. Surgery alone is curative for many patients with early-stage ovarian carcinoma. For more advanced disease, surgery establishes the diagnosis and allows appropriate staging and cytoreduction, optimally to less than 1 cm of residual disease. Conservative surgical management of young women who desire to preserve fertility with a unilateral salpingo-oophorectomy with a full staging procedure may be appropriate for stage Ia disease. The contralateral ovary should be evaluated carefully, because there is a 5% chance of occult metastasis or a separate primary carcinoma. Biopsy of the contralateral ovary is no longer recommended unless there are grossly apparent abnormalities. Such patients also must have strict follow-up. Although a hysterectomy and removal of remaining adnexae is recommended for women who have completed childbearing, this recommendation is not based on randomized clinical trials. Primary cytoreduction of ovarian carcinoma has been recommended for almost 30 years. The theory is that removal of large tumor nodules allows better penetration of chemotherapeutic agents and removes potential foci of chemoresistance. Optimal cytoreduction is defined as residual disease smaller than 1 cm. Several reports over the last 25 years have shown that the diameter of the largest residual disease correlates with response rate, progression-free interval, and overall survival. The GOG evaluated survival by maximal diameter of residual disease (data from protocols 52 and 97) and found that the survival rate for patients with residual disease of 2 cm or greater is about 20% after 4 years, compared with a 60% survival rate after 4 years in those with only microscopic residual disease. For patients with residual disease less than 2 cm, the survival rate was 40% after 4 years (Fig. 55.33). Median survival of patients who have received optimal cytoreduction was approximately twice that of patients with suboptimal cytoreduction.

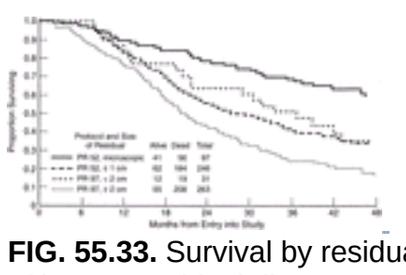

FIG. 55.33. Survival by residual disease: Gynecologic Oncology Group, protocols 52 and 97. (From Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994;170:974–980, with permission.)

There has been great debate in the literature regarding the relative importance of surgical cytoreduction as compared with the inherent tumor biology of the cancer as determinants of patient survival. Patient age, the number and size of tumor nodules at time of diagnosis, and tumor grade have been cited as significant predictors of outcome. Other series have found that optimal surgical cytoreduction did not equate the survival benefit experienced by patients who initially had small-volume disease. Some investigators have suggested that platinum-based therapy has had a larger impact on survival than surgical debulking. Data, including a large meta-analysis, have demonstrated that maximal initial surgical cytoreduction was the most powerful predictor of patient survival. Patients with ovarian cancer are more likely to have optimal cytoreduction under the care of a gynecologic oncologist than with general surgeons or general gynecologists. Despite the benefit of improved survival, most patients with ovarian cancer in the United States never see a gynecologic oncologist. Ongoing efforts to educate physicians and patients regarding appropriate referral to specialized centers are needed. At the end of chemotherapy, patients who are clinically in complete remission may be offered second-look evaluation to determine the success of therapy, as measured by the presence of any residual tumor cells. The reasons for second-look evaluation are as follows: (a) to determine disease presence, thus allowing continued therapy in an attempt to improve survival, (b) to debulk any residual carcinoma, and (c) a prognostic tool for patient survival. Most second-look evaluations can be completed successfully via the laparoscope among surgeons with adequate expertise, and second-look laparoscopy has equivalent rates of detection of residual disease when compared with laparotomy. A laparoscopic approach reduces the length of hospital stay (frequently done as outpatient surgery) and patient recovery time. Older studies have shown that survival rates for those who underwent second-look surgery, as compared with those who did not, were essentially the same, suggesting no benefit for the procedure. However, these studies have not evaluated the effect of newer chemotherapy and more effective salvage therapies. Although second-look surgery should not be considered standard of care, it should be performed in patients enrolled in clinical trials to evaluate the efficacy of newer first-line therapies and the efficacy of better salvage therapies in improving survival. Secondary cytoreduction at the time of second-look laparotomy also has been examined in several studies that revealed a benefit in a select group of patients with gross disease that is reduced successfully to microscopic disease. However, only a minority of patients will have gross residual disease after clinical response to platinum-based chemotherapy. More recent data suggest that the presence or absence of residual disease at second-look surgery is one of the most significant prognostic factors for patient survival. Therefore, until more accurate diagnostic tests can be identified to determine residual disease after standard treatment, second-look surgery may be offered to patients with advanced stage disease in clinical remission to help determine prognosis, with the caveat that the procedure has prognostic value but no impact on survival. Interval debulking surgery is performed after neoadjuvant chemotherapy in patients with advanced ovarian cancer. Although it remains a controversial subject, the Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer conducted a large randomized study documenting the benefit of interval debulking surgery. All patients received three cycles of cyclophosphamide and cisplatin followed by randomization to debulking versus no debulking surgery, and all patients then received three more cycles of chemotherapy. The study revealed that interval debulking surgery resulted in significantly better progression-free and overall survival (Fig. 55.34). Although the 6-month improvement in median overall survival is relatively small, interval debulking surgery may be considered in patients in whom cytoreduction was not optimal during initial surgery, yet who have responded to neoadjuvant chemotherapy.

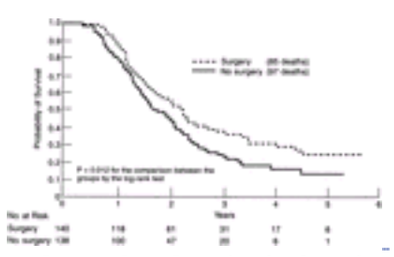

FIG. 55.34. Survival of patients with advanced epithelial ovarian cancer according to whether or not they underwent debulking surgery. (From van der Burg MEL, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. N Engl J Med 1995;332:629–634, with permission.)

Secondary cytoreductive surgery in patients with recurrent epithelial ovarian carcinoma has also been evaluated in several studies. Most of these reports show a statistically significant survival benefit for patients whose cytoreduction was optimal during secondary surgery. The likelihood of successful secondary cytoreduction and improved patient survival increases for patients with a longer disease-free interval (>12 months), unifocal disease, and initial optimal cytoreduction.

Chemotherapy Following surgery, most patients will require chemotherapy. However, for patients with completely staged Ia or Ib grade 1 or 2 ovarian cancers, no survival benefit has been demonstrated with adjuvant chemotherapy. The studies have shown clear benefit to adjuvant chemotherapy in select patients with stage Ia or Ib grade 3 and stage Ic disease compared with observation. The GOG and the Gruppo Italiano Collaborativo in Oncologia Ginecologica studies found that patients with stage Ia or Ib grade 1 or 2 disease had comparable survival with observation and melphalan. In contrast, high-risk patients with stages Ia, Ib, Ic and II disease had improved disease-free intervals with cisplatin-containing regimens compared with observation, intraperitoneal phosphorus-32, or melphalan (Alkeran). The optimal number of cycles of chemotherapy for early-stage disease remains unclear, and it is the objective of a current prospective trial to compare the efficacy of three versus six cycles of paclitaxel and cisplatin in patients with early-stage ovarian cancer. Various chemotherapeutic agents are active against ovarian cancer. Platinum-based therapy has been the mainstay of treatment for ovarian cancer for over 25 years. Combination platinum-based regimens have demonstrated superior response rates to those obtained with single-agent platinum, although there is insufficient evidence to suggest longer overall survival in these patients. The lack of survival benefit in some trials may relate to the high crossover treatment of patients who failed on one treatment arm and received other study treatments, as well as the varied length of patient follow-up in these studies. Paclitaxel, a microtubule stabilizer, was found to have significant activity in many cancers, including epithelial ovarian carcinoma. In 1996, the GOG published a study comparing the efficacy of paclitaxel and cisplatin with cyclophosphamide and cisplatin as first-line adjuvant therapy in patients with suboptimally debulked epithelial ovarian carcinoma (stages III or IV). Disease-free survival and overall survival for the paclitaxel-cisplatin group was statistically longer than for the cyclophosphamide-cisplatin group (median survival 38 to 24 months). Paclitaxel-cisplatin was also more effective in patients with advanced stage ovarian cancer after optimal cytoreduction. Substitution of carboplatin for cisplatin and decreased paclitaxel infusion times have reduced cost and patient side effects compared with the paclitaxel-cisplatin regimen. A subsequent prospective randomized trial replaced paclitaxel with docetaxel (Taxotere), another microtubule stabilizing agent, and found comparable response rates with less peripheral neuropathy. During the last 5 years, many new drugs have been found to be active second-line agents for epithelial ovarian cancer including topotecan, etoposide, altretamine (Hexalen), docetaxel (Taxotere), gemcitabine hydrochloride (Gemzar), vinorelbine tartrate (Navelbine), and doxorubicin hydrochloride liposomal injection (Doxil). Both topotecan, a topoisomerase inhibitor, and doxorubicin have shown promising activity in patients with recurrent, platinum-resistant disease with response rates of 20% to 30%. A large, prospective trial is randomizing patients to one of several combination multiagent chemotherapy regimens using gemcitabine, doxorubicin, or topotecan with paclitaxel-carboplatin as the control arm, to better define the best first-line regimen for patients with advanced stage ovarian cancer. Neoadjuvant chemotherapy to reduce the tumor load before performing a laparotomy is being investigated. Based on available noninvasive testing, it is difficult to predict accurately which patients will not be candidates for a successful cytoreduction. Furthermore, neoadjuvant therapy has been employed only in small retrospective observational series. Although neoadjuvant chemotherapy has resulted in less morbidity from subsequent cytoreductive surgery, this approach has not translated into higher survival rates in the limited number of patients studied. Intraperitoneal therapy allows direct exposure of a tumor to a drug concentration that may be 10-fold to 1,000-fold higher than that achieved with systemic therapy. In theory, this approach may have value for epithelial ovarian cancer, but its superiority has not yet been demonstrated despite extensive study. The clinical situations in which intraperitoneal therapy may be considered include salvage therapy for patients with disease of 5 mm or less, consolidation therapy for patients with surgically documented complete chemotherapeutic response, initial therapy for patients with high-grade early-stage tumors, or combination intraperitoneal therapy with systemic infusion. A randomized trial of intraperitoneal cisplatin and intravenous cyclophosphamide chemotherapy as first-line therapy showed promising survival rates with much less toxicity than older standard intravenous cisplatin-cyclophosphamide regimens. This study suggests that combination intraperitoneal cisplatin with an intravenous agent as primary therapy may be advantageous. However, optimal intraperitoneal regimens remain to be defined and will require randomized trials comparing intraperitoneal infusion with other approaches.

Radiation Therapy Abdominopelvic radiation therapy has been used postoperatively in selected patients who have microscopic or small-volume residual disease; however, with more effective chemotherapy, radiation therapy is an infrequently used adjuvant therapy for ovarian cancer. One of the largest series, compiled by investigators in Toronto, treated patients with stage II and III disease with abdominopelvic radiation and showed a 10-year disease-free survival of 38% (n = 91) for patients with residual smaller than 2 cm and 6% (n = 91) for patients with residual larger than 2 cm. Further studies on the usefulness of radiation therapy for ovarian cancer are warranted.

Prognosis With the addition of improved chemotherapeutic regimens and aggressive surgical cytoreduction, survival has improved in patients with advanced stage ovarian cancer. The overall 5-year survival is approximately 50%. Further strides in the management of ovarian cancer will require more knowledge of the molecular alterations that cause it. Advances in molecular biology indicate that ovarian tumorigenesis results from an accumulation of sequential genetic mutations. With a better understanding of the neoplastic transformation of ovarian epithelium, targeted therapies may be directed against the specific genetic aberrations in an individual cancer to improve patient outcome. Several innovative trials have combined gene therapy or immunotherapy and standard chemotherapy with promising early results. Ongoing efforts in both basic and clinical research are critical for the development of prevention strategies, screening for early detection, and better therapies.

FALLOPIAN TUBE CARCINOMA

Primary Fallopian Tube Epithelial Carcinoma

Fallopian tube carcinoma accounts for approximately 0.1% to 0.5% of all gynecologic malignancies. Peak incidence occurs at ages 60 to 64 years. Epidemiologic data suggest that age and nulliparity are associated with fallopian tube carcinoma, similar to endometrial and ovarian carcinomas. The constellation of symptoms including pelvic pain, a pelvic mass, and serosanguinous vaginal discharge (Latzko's triad) occur in the minority of cases. The most common symptom is vaginal staining or bleeding. Hydrops tubae profluens is characterized by colicky lower abdominal pain relieved by a profuse, serous, watery, yellow, intermittent vaginal discharge. The most common physical sign is a pelvic or abdominal mass. This mass often is thought to be an ovarian mass, with the correct diagnosis made only during surgery. Occasionally, a Pap smear revealing abnormal glandular cells with negative cervical or endometrial findings may lead the clinician to the diagnosis of fallopian tube cancer. Serum CA-125 levels often are elevated in advanced disease, as is noted in patients with ovarian carcinoma. Fallopian tube carcinoma is staged according to the FIGO. In contrast to ovarian cancer, most patients are diagnosed with early-stage disease: stage I, 37%; stage II, 21%; stage III, 31%; stage IV, 10%. (Table 55.6).

TABLE 55.6. *FIGO staging for fallopian tube cancer*

Fallopian tube carcinoma usually is characterized by swollen tubes secondary to intraluminal growth. Most fallopian tube adenocarcinomas are serous and histologically identical to ovarian serous carcinoma (Fig. 55.35). Other types of epithelial fallopian tube carcinoma have been reported but are very rare. Several diagnostic criteria have been established to differentiate fallopian tube malignancy from ovarian and other primary tumors. Microscopically, the tumor must arise from the endosalpinx, with a histologic pattern consistent with tubal mucosal epithelium. The transition from benign to malignant epithelium is helpful for diagnosis. The ovaries and endometrium are either normal or have tumor smaller than that in the tube. As in epithelial ovarian carcinoma, fallopian tube epithelial tumors commonly spread by exfoliation and implantation throughout the peritoneal cavity. The extensive lymphatic channels within the fallopian tube facilitate lymphatic dissemination of tumor, and paraaortic lymph node metastases are common.

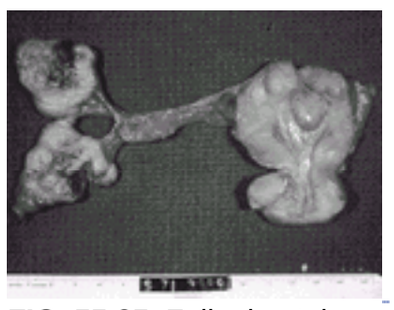

FIG. 55.35. Fallopian tube carcinoma. The fallopian tube lumen and its wall have been replaced by tumor.

Surgery remains the principal treatment, including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, tumor debulking, and a full staging, as with ovarian cancer (see Table 55.3). Treatment of primary fallopian tube epithelial tumors is based on the standard management for ovarian carcinoma, due to the lack of large-scale studies for this rare tumor. Platinum-based therapies are recommended following cytoreductive surgery, based on several series showing superior

response rates and survival compared with those obtained with other agents.

Due to the rarity of fallopian tube cancer, paclitaxel has not yet been widely studied in this disease. However, based on data from ovarian cancer, platinum-taxane chemotherapy is used for patients with fallopian tube cancer. As in ovarian carcinoma, the prognosis is dependent upon the extent of disease and the amount of residual tumor at the end of surgery. Second-look surgery may be helpful in determining treatment efficacy and persistent disease but, as in ovarian carcinoma, it is not considered standard therapy.

Fallopian Tube Sarcoma

Sarcomas of the fallopian tubes may be classified as pure or mixed. They are exceedingly rare—fewer than 50 cases have been reported—and usually are found in postmenopausal women. Abdominal pain and watery or bloody vaginal discharge with signs of peritoneal spread are common findings. An ovarian origin must be ruled out by clearly identifying residual normal ovarian structure. The life expectancy of patients with these sarcomas usually is measured in months. As described in case reports, radiation and chemotherapy have not been effective.

Metastatic Disease

Metastatic fallopian tube disease is more common than primary tumors of the fallopian tubes. It often originates from a primary tumor of the ovary or endometrium and rarely from a primary cancer of the breast, gastrointestinal tract, or uterine cervix. Lymphatic involvement and an intact tubal epithelium distinguish a metastatic tumor from a primary fallopian tube tumor. The diagnostic criteria outlined above assist in differentiating between primary and metastatic fallopian tube tumors.

PRIMARY PERITONEAL CARCINOMA

Carcinoma may arise from the nonovarian epithelium of the peritoneal cavity and can involve diffusely all peritoneal surfaces, with minimal or absent involvement of the ovaries. These tumors share many of the clinical and histologic features of ovarian carcinoma. Most of these tumors are of serous histology. Clinical criteria have been established to distinguish peritoneal serous papillary carcinoma (PSPC) from its ovarian papillary serous counterpart, and molecular analyses of PSPC confirm that it is a distinct entity from ovarian carcinoma. Based upon these criteria, an estimated 7% to 15% of all cases of papillary serous ovarian cancer could be reclassified as PSPC.

The etiology of PSPC remains unknown. Considering the common embryologic origin of ovarian and peritoneal epithelium, a “field effect” of malignant epithelial transformation could involve multiple sites in the müllerian tract. Cases of PSPC have been described following prophylactic oophorectomy in patients with strong family histories of ovarian cancer or with documented *BRCA* mutations. PSPC appears to be another phenotypic variant of the *BRCA*-associated cancer syndromes. PSPC is staged and treated like ovarian carcinoma, with comparable response rates and survival.

HEREDITARY OVARIAN CANCER

Hereditary Forms of Ovarian Cancer

Approximately 5% to 10% of patients with ovarian cancer are thought to have an inherited genetic predisposition. Although this represents a small percentage of patients with ovarian cancer, great emphasis has been placed on these genetic mutations, given their clinical, social, and ethical implications.

Hereditary ovarian cancer syndromes are linked to dominantly inherited genetic mutations. A detailed family history from both maternal and paternal sides of the family must be obtained to determine the genetic susceptibility for the women at risk. Average age at diagnosis for this group of patients is often younger than for the general population, and most tumors are of serous histology.

The breast-ovarian cancer syndrome accounts for up to 85% of all hereditary ovarian cancer cases and is associated most frequently with mutations in the *BRCA1* or *BRCA2* genes. The *BRCA1* and *BRCA2* genes were identified and linked to hereditary breast and ovarian cancer in the 1990s. *BRCA1* is located on chromosome 17q12-21, and *BRCA2* is located on chromosome 13q12-13. Although the precise function of the *BRCA* genes is unknown, they appear to be involved in the recognition and repair of DNA damage. A sample pedigree of a breast-ovarian cancer syndrome family is illustrated in Fig. 55.36. The presence of a *BRCA*-associated syndrome is suspected whenever a pedigree reveals three or more affected relatives in two generations, bilateral or premenopausal breast cancers, a relative with breast and ovarian cancer, or a male with breast cancer in the pedigree (Table 55.7).

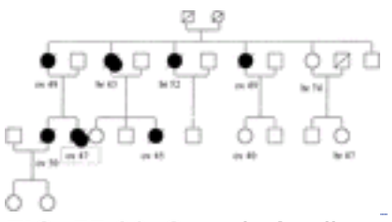

FIG. 55.36. Sample family pedigree.

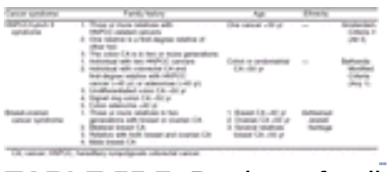

TABLE 55.7. *Pertinent family history—risk factors for genetic mutations*

Many mutations have been described, located throughout the *BRCA1* and *BRCA2* genes, with nonsense mutations or frameshift mutations being predominant. Nonsense mutation occurs when a single nucleotide substitution results in a stop codon, and frameshift mutation occurs when one or more nucleotides are deleted to produce a downstream stop codon. Certain ethnic groups have higher carrier frequencies of founder *BRCA* mutations. Three specific founder mutations, 185delAG and 5382insC on *BRCA1* and 6174delT on *BRCA2*, have been seen in approximately 2% to 2.4% of the Ashkenazi Jewish population. Studies have found that 40% to 60% of Jewish patients with ovarian cancer have a mutation in *BRCA1* or *BRCA2*, in contrast to 5% of non-Jewish women with ovarian cancer.

The lifetime risk of ovarian cancer for patients with *BRCA1* mutations is 20% to 60%, and the risk for a *BRCA2* mutation carrier is 10% to 35%. Patients with *BRCA1*-associated ovarian cancer appear to be diagnosed at a younger age than patients with sporadic ovarian cancer or *BRCA2*-associated ovarian cancer. Studies show that *BRCA2* mutations also are associated with other malignancies, including cancer of the pancreas, biliary tract, and prostate and melanoma (Table 55.8).

Cancer site	Gene mutations	Cancer risk with mutation (by age 70)	Population cancer risk
Breast	*BRCA1*	87%	11%
	BRCA2	87%	
Ovary	*BRCA1*	20%–60%	1.0%–1.5%
	BRCA2	10%–35%	
	MMR	9%–12%	
Fallopian tube	*BRCA1*	Increased	3.6/1,000,000
	BRCA2	Increased	
Endometrium	*MMR*	42%–60%	1.5%
Colon	*MMR*	54%–82%	2%

MMR, mismatch repair.

TABLE 55.8. *Cancer risks by site for gene mutation carriers*

Data have also demonstrated that fallopian tube carcinoma can occur in patients with an inherited genetic predisposition to ovarian cancer by virtue of germline mutations in the *BRCA* genes. A large population-based series of patients with fallopian tube cancer found that 16% of patients had inherited mutations in *BRCA1* or *BRCA2.* Based upon these data, fallopian tube carcinoma should be considered a clinical component of the *BRCA*-associated breast-ovary cancer syndrome. Patients with germline *BRCA* mutations who elect to have prophylactic surgery should have both ovaries and fallopian tubes removed, with careful histologic evaluation to eliminate occult fallopian tube carcinoma. It is unknown whether hysterectomy is necessary, in addition to salpingo-oophorectomy, in order to remove the cornual portion of the fallopian tube as surgical prophylaxis for these patients.

Hereditary nonpolyposis colorectal cancer (HNPCC) syndrome accounts for approximately 10% of all hereditary ovarian cancer cases. It is an autosomal dominant genetic syndrome characterized by three or more first-degree relatives with colon cancer (over 70% in the proximal colon) or endometrial cancer, where one is a first-degree relative of the other two, and two of them must be diagnosed with cancer before age 50 years. Four genes that are part of the DNA mismatch repair (MMR) pathway have been identified as being responsible for the HNPCC phenotype: *hMSH2* (chromosome 2p), *hMLH1* (chromosome 3p), *hPMS1* (chromosome 2q), and *hPMS2* (chromosome 7p). Most affected patients are found to have defects in either *hMSH2* or *hMLH1.* An inherited defect in any one of these genes increases an individual's risk of developing cancer because of an impaired ability to repair somatic genetic mutations. Family members with HNPCC syndrome are at risk for cancer at other gastrointestinal sites, the urologic tract, and the ovary. The risk of endometrial cancer among women in the HNPCC syndrome is estimated to be 40% to 60% by the age of 70 compared with 1.5% in the general population. Limited studies have reported a 3.5-fold increase in the risk of ovarian cancer in members of these families (see Table 55.8).

Clinical Implications

Genetic Testing Although hereditary cancers account for only 10% of ovarian malignancies, individual risk assessment and appropriate genetic testing can identify those individuals with significant lifetime risk. The first concern in genetic testing is the scientific and technical utility of the tests: the reliability of tests, their predictive value, their interpretation, and ultimately their ability to prevent cancer in patients who have positive test results. The second major concern relates to the ethical, legal, and social implications of gene testing. The proper selection of patients for testing is very important. Genetic counseling is imperative. As testing for these genes becomes more available to the public in both commercial and academic settings, clinicians and patients must work together to ensure that the results are used in a fashion that will consider carefully the ethical, legal, and psychosocial issues that may arise from genetic testing. Multidisciplinary services that include pretest and posttest counseling, screening, treatment, and psychosocial sessions have been established in the major referral centers. Patients must be counseled regarding the potential advantages and disadvantages of genetic testing, as well as the utility of screening and prophylactic measures that are available. American Society of Clinical Oncology guidelines recommend offering testing to anyone with a greater than 10% risk of carrying a mutation based on pedigree analysis, and only if the test result will influence medical management. First- and second-degree relatives of an affected individual from a family with breast-ovarian cancer syndrome should be offered genetic testing if they carry a mutation of the *BRCA1* or *BRCA2* gene. Certain ethnic groups, such as Ashkenazi Jews, are at increased risk for carrying a *BRCA* mutation, and a lower threshold for genetic testing may be appropriate in these individuals. Genetic testing for the MMR genes should be considered when there is a first-degree relative with a known mutation and when the patient meets the Amsterdam or the Bethesda Criteria for HNPCC syndrome (see Table 55.7). A comprehensive family history can provide an estimate of an individual's risk of carrying a genetic mutation; however, genetic testing provides more accurate information regarding the chance that an individual patient will develop cancer. The best way to determine if a cancer-associated mutation is present in a family is to test an affected family member, who is usually the most likely proband to carry a deleterious mutation. The first family member often will need comprehensive gene sequencing, and subsequent individuals can then be tested for the identified mutation, which may be unique to the particular family. In the Ashkenazi Jewish population, genetic testing for the three founder mutations is required because of the high carrier frequency in this population and occasional reports of individuals carrying both *BRCA1* and *BRCA2* mutations. Test results may come back positive or negative for an identifiable mutation or may report a mutation of indeterminate clinical significance. When a test result returns negative, interpretation will depend on the patient's family history. If an affected family member has tested positive for a mutation, then the patient has likely not inherited the deleterious mutation, and her cancer risk approximates that of the general population. If there is no documented positive mutation in the family, it is still possible that the patient has a cancer-associated mutation that is not detectable with testing. Approximately 12% of testing results are genetic variants or polymorphisms, reported as indeterminate clinical significance. Further study of these genetic variants and associated cancer risks in large populations will help reduce the number of indeterminate reports.

Follow-up and Management

Screening Follow-up and treatment of patients with an inherited genetic predisposition to ovarian cancer is complex due to the variable penetrance of genetic alterations and the lack of effective early detection methods. Serum CA-125 levels and transvaginal ultrasonography with color Doppler flow are the two modalities that have shown potential usefulness in surveying these patients. CA-125 levels may be elevated in other benign diseases and may not be elevated in early stage I ovarian cancer; thus, it lacks sufficient sensitivity. Transvaginal ultrasonography is very sensitive in detecting adnexal masses; however, it cannot differentiate between malignant and benign masses, resulting in a high false-positive result rate and unnecessary surgery, especially in premenopausal women. Consequently, screening of the general population is not warranted with the currently available technology. There is no conclusive evidence to support screening patients with higher risk of ovarian cancer. Ovarian surveillance modalities have not improved significantly the detection of early-stage invasive epithelial ovarian cancers, with minimal impact on the survival among the screened patients. One prospective study of high-risk women demonstrated enhanced survival among the screened population versus historic controls; however, conclusions are limited by small patient numbers. Despite the available data, the National Institute of Health *Consensus Statement on Ovarian Cancer* and the Cancer Genetic Studies Consortium recommend screening starting at ages 25 to 35 years as part of the annual or semiannual routine examination for women with germline *BRCA1* or *BRCA2* mutations. The benefit, however, is not proven, because the evidence is based on expert opinion only. Table 55.9 lists the provisional recommendations for cancer surveillance for the carriers of *BRCA1* and *BRCA2* mutations. Screening and prophylactic surgery for patients with HNPCC-associated mutations is also based on expert opinion, although colonoscopy and stool occult blood testing have been shown in randomized clinical trials to reduce the incidence of and mortality from colon cancer (see Table 55.9).

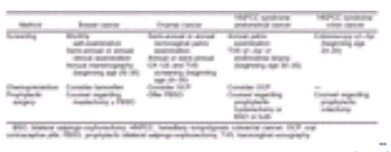

TABLE 55.9. *Recommendations for treatment of women at high genetic risk for gynecologic malignancies*

Prevention Chemoprophylaxis with oral contraceptive pills (OCP) for 5 years decreases ovarian cancer risk by 50% in the both general population and in high-risk women. A case-controlled study of 207 known *BRCA* mutation carriers and their sister controls found a 60% reduction of ovarian cancer risk with OCP use. Other risk-reducing strategies such as tubal ligation and hysterectomy have also demonstrated reduced incidence of ovarian cancer among many high-risk women.
Prophylactic Salpingo-oophorectomy Prophylactic bilateral salpingo-oophorectomy (PBSO) is another preventive strategy for patients with *BRCA* mutations to reduce cancer risk. Given that most hereditary ovarian cancer occurs after the age of 35 to 40, prophylactic oophorectomy is an option in carefully selected patients at unequivocally high risk for ovarian cancer who have completed their childbearing. This procedure can be performed laparoscopically, and the decision for concomitant hysterectomy is individualized. The surgical pathologist must be alerted to perform a careful examination of the high-risk patient's ovaries and fallopian tubes given the reports of occult ovarian and tubal carcinoma in these specimens ranging in frequency from 2% to 15%. The efficacy of PBSO in hereditary breast-ovarian cancer syndrome has been evaluated in several studies. Prospective studies have documented a significant reduction in both ovarian, peritoneal, and breast carcinoma among *BRCA* mutation carriers following PBSO, one study of 248 patients found a 98% decrease of ovarian and primary peritoneal cancers, and a 50% reduction in subsequent breast cancer compared with age-matched controls. This supports the findings of another prospective study that documented a 50% reduction of breast cancer with PBSO among premenopausal and postmenopausal *BRCA* mutation carriers that persisted irrespective of the use of hormone replacement therapy. Despite oophorectomies, primary peritoneal cancer has been reported in 0.4% to 10.7% of high-risk patients, and patients must be counseled regarding this disease. It is believed that that all coelomic epithelium, including the peritoneal covering of the entire abdominal pelvic cavity, is prone to malignant transformation in *BRCA* mutation carriers. Several other significant issues remain unresolved regarding the physiologic adjustments to premature surgical menopause and the safety of hormone replacement therapy in this group, especially in those at high risk for breast cancer. Recommendations from other agencies or groups are as follows:

- American College of Obstetricians and Gynecologists (1992). Women with familial ovarian or hereditary breast-ovarian cancer syndromes who do not wish to maintain their reproductive capacity may be offered PBSO. Such women should have a documented familial syndrome, preferably established via a full pedigree analysis by a geneticist. These women should be informed that removal of the tubes and ovaries does not provide 100% protection; primary peritoneal carcinoma has been reported after bilateral salpingo-oophorectomy in some cases.
- National Institutes of Health *Consensus Statement on Ovarian Cancer* (1994). The probability of a hereditary ovarian cancer syndrome in a family pedigree increases with the number of affected relatives, with the number of affected generations, and with young age of onset of disease. Therefore, prophylactic oophorectomy should be considered in these patients after careful weighing of the risks and potential benefits. The risk of ovarian cancer in women from families with hereditary ovarian cancer syndrome is sufficiently high to recommend prophylactic oophorectomy at age 35 years or after completion of childbearing.

SUMMARY POINTS

- Germ cell tumors are the most common gynecologic malignancy in young women. The cure rate is 90% due to the significant advancement of chemotherapeutic regimens. The most commonly used regimen is BEP. The risk of secondary malignancy, especially hematologic, with the use of etoposide must always be considered when this regimen is administered.
- Sex cord–stromal tumors, such as granulosa cell and Sertoli-Leydig cell tumors, have the potential for steroid hormone secretion, with estrogen being the most frequently produced hormone. Aside from juvenile granulosa cell tumors, sex cord–stromal tumors rarely occur in women under 20 years. Primary treatment usually entails primary tumor resection and staging. When the pathology is malignant, the need for chemotherapy must be individualized, because no standard treatment regimen has been established.
- Tumors of LMP account for approximately 15% of epithelial ovarian cancers and have an earlier age of onset, around 40 years. All epithelial histologic subtypes of LMP tumors exist, with serous being the most common. Pseudomyxoma peritonei, characterized by extracellular gelatinous material in the peritoneal cavity, may accompany mucinous LMP tumors. Therapy for LMP tumors is surgical excision and appropriate tumor staging and, when necessary, debulking.
- Although significant strides have been made in the treatment of epithelial ovarian cancer, the 5-year survival rate remains approximately 50%. Continued efforts are needed to understand the etiology of these tumors, which ultimately will result in the development of prevention strategies, early detection, and improved therapies. Optimal cytoreductive surgery followed by platinum-taxane combination chemotherapy is the current standard treatment for advanced stage disease.
- Identification of the genes that are responsible for several familial ovarian cancer syndromes, especially *BRCA1* and *BRCA2*, has opened up new areas of investigation and provided valuable information for understanding the development of both hereditary and sporadic ovarian carcinomas. Although there is no level I evidence to support the use of screening and prophylactic surgery in patients who are at high risk for ovarian cancer, these modalities may be considered to reduce the chance of disease development. Oral contraceptive pill use may also decrease ovarian cancer incidence in these high-risk women.

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Chapter 56

Linda Van Le

Management of the Adnexal Mass

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DISTRIBUTION OF ADNEXAL MASSES BASED ON AGE
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Mucinous Tumors, Benign and Malignant
Endometrioid Tumors, Benign and Malignant
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Transitional Cell Tumors
Other Common Benign Tumors
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SPECIAL CLINICAL SITUATIONS
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SUMMARY POINTS

SUGGESTED READINGS
Radiologic Evaluation of the Adnexal Mass
Surgical Evaluation
Tumor Markers
Special Clinical Situations
Laparoscopic Approach to the Adnexal Mass

The optimal management of the adnexal mass has perplexed clinicians for many years. As long as women have been offered medical care, the adnexal mass has presented a diagnostic as well as therapeutic problem. During the 21 st century, we have made many inroads into understanding the development, complications of, and malignant potential of the adnexal mass. Additionally, we have made some advancements in its management: operative laparoscopy has been developed carefully and is approaching appreciable levels of sophistication such that recovery from surgical intervention is at a minimum.

Some considerations of management of the adnexal mass include the following: What is the mass? Should it be followed? How should it be followed? Should a woman have surgery for this? What route of surgery should be undertaken? Should an oncologist assist in the surgical management in the event that the mass is malignant? All of the above questions are timely and ideally should have precise answers such that we may offer optimal care for women. However, many of these issues still are being explored. With the advent of genetic discovery and technical advancement, we hope we will be able to better understand the etiology of the adnexal mass as well as offer management with minimal morbidity.

In this chapter, general background information, modes of diagnosis, ancillary studies, and surgical management of the adnexal mass will be discussed. Our hope is that with the tools available, a rational approach toward the adnexal mass will be presented such that the right choice will be offered for each patient with a minimum of concern for the physician and patient. Efficient diagnostic evaluations should be performed, with the goal of offering the appropriate patient a surgical procedure and expectantly following patients for whom one might predict the mass would resolve, thereby sparing a trip to the operating room. Management of the adnexal mass should be made with confidence and a clear schema and treatment plan. Taken altogether, management of the adnexal mass should be well understood by everyone in clinical gynecologic practice. A triage scheme should be available and understood such that for every patient and every kind of mass a treatment plan is readily available, one that will minimize the chance of malignancy and minimize morbidity should the patient need surgical management.

GENERAL OVERVIEW

In the grand scheme of things ovarian cancer is considered rare; however, it is often fatal. In light of this, management of the adnexal mass is a serious endeavor. Five to ten percent of all women in the United States will undergo surgical evaluation for an adnexal mass and, of these, up to one fifth will have ovarian cancer. Up to 300,000 women are hospitalized each year for evaluation of an adnexal mass and the majority of these patients undergo surgery. The skill then lies in determining which masses will be malignant such that the appropriate surgical preparations will have been undertaken; additionally, masses that may not need exploration then can be followed. Thus, the appropriate evaluation is important and includes a complete history, physical examination, and radiologic studies, as well as serum markers.

Adnexal mass refers not only to ovarian abnormalities but to masses originating in the fallopian tube, ovary, broad ligament, bowel, as well as uterine masses that lateralize (Table 56.1). Taking a pertinent history is, therefore, important. In addition to ascertaining the quality, severity, and duration of abdominal symptoms, review of menstrual cycle characteristics in premenopausal women, history of pelvic infectious disease, and any gastrointestinal syndromes may guide the diagnosis to one area or another.

Ovarian
Ovarian neoplasm
Ovarian cyst
Simple ovarian cyst
Tubal-ovarian abscesses
Adnexal torsion
Tubal masses
Ectopic pregnancy
Pyosalpinx
Tubal neoplasms
Tuberculosis salpingitis
Uterine
Myoma
Gastrointestinal
Colon cancer
Diverticulitis
Appendicitis
Appendiceal tumor
Genitourinary
Pelvic kidney

TABLE 56.1. *Masses occurring in the adnexal region*

Review of the family history, in particular for the occurrence of ovarian cancers, is extremely important. Scientific discoveries within the last decade have determined that specific gene mutations may increase the risk of ovarian cancer in certain subsets of the female population. In the general population, the lifetime risk of ovarian cancer is in 1 in 70 women, approximately 1.7%; however, even without the a specific gene mutation, having one family member with ovarian cancer increases a patient's risk to 5%, and with two relatives with ovarian cancer the risk increases to 7%. Regardless of how alarming it is to identify a family member with the disease, however, less than 10% of ovarian cancer patients will have this significant family history. The most common syndrome associated with familial transmission of ovarian cancer is hereditary breast-ovarian cancer. Of all hereditary cases, this syndrome accounts for the majority of familial ovarian cancers. Many of these cases are associated with germ-line mutations in *BRCA1* and *BRCA2* genes. *BRCA1* is a tumor suppressor gene that, in a “normal” format, controls and regulates abnormal cell growth. In a patient affected by a mutation, this gene does not function to regulate cellular growth and, thus, malignancy evolves. Although advances in science have enabled us to identify many of these mutations, there are other abnormalities in this gene may contribute to not only ovarian cancer but breast cancer. Further investigations are underway to identify these additional gene mutations. *BRCA2* is another well-known gene associated with breast-ovarian cancer. In particular, an abnormality in this gene has been found in 1% of the Ashkenazi Jewish population and, presumably, ovarian cancer in this population has been associated with germ-line mutations in *BRCA2.* If a mutation is found in *BRCA1*, a lifetime risk of ovarian cancer is estimated between 28% and 44%, and up to 27% in patients with a *BRCA2* abnormality. Ovarian cancer also can be part of a constellation of cancers which include colorectal cancer, stomach cancer, endometrial cancer, and ovarian cancer. This is referred to as *hereditary nonpolyposis colorectal syndrome.* The risk of ovarian cancer is increased to up to 10% of patients who have this syndrome. In the face of germ-line mutations in these genes, ovarian cancer develops at an earlier age, often premenopausally, than in the majority of ovarian cancer cases, which tend to develop postmenopausally. Given the identification of familial risk, registries have been developed to investigate further the association of ovarian cancer in patients and their relatives. For patients with *BRCA* mutations, increased surveillance is recommended. Monthly breast examinations are encouraged beginning at an early age; some recommend beginning between ages 18 and 21. Additional examinations by a physician are recommended twice a year beginning in the mid-20s. Yearly mammograms are recommended also, beginning at this time. There is some interest in chemoprevention, such as tamoxifen to reduce the risk of breast cancer,

and bilateral prophylactic mastectomy is being explored to reduce the risk of incurring breast cancer. Additionally, if a *BRCA* mutation is present, surveillance for ovarian cancer is recommended. This includes transvaginal ultrasonography and measurement of serum CA-125 beginning in the mid-20s. Bilateral prophylactic oophorectomy may be recommended after a woman has completed her family. Chemotherapeutic prevention of ovarian cancer may be instituted in the form of oral contraceptives. It is well accepted that oral contraceptives reduce the risk of ovarian cancer for women in the general population and may also decrease the risk in women carrying a *BRCA* mutation.

During the physical examination, a full female-oriented examination should be performed including a node survey and breast, abdominal, and pelvic examination. In cases of advanced cancer, nodular masses often are found in the abdomen and pelvis. However, for the most part, this would be quite clear when a patient with ovarian cancer arrives. Thus, in regard to determining whether an adnexal mass is malignant in the early stages, the physical examination may not be helpful. Lastly, the radiologic study and evaluation of a patient with, perhaps, mild symptoms would be of utmost importance.

DISTRIBUTION OF ADNEXAL MASSES BASED ON AGE

One way to approach the adnexal mass is to think of it in regard to the patient's age. The majority of ovarian cancers occur postmenopausally. For the young woman in her late teens and up to mid-20s, the majority of ovarian cysts are, of course, benign. Hemorrhagic corpora lutea and follicular cysts are common. In this age range, however, tubal abnormalities should be strongly considered. They include ectopic pregnancies and sequelae from tubal infections. Of concern in this age group, however, is the solid mass. The germ cell tumors, which for the most part are solid and unilateral, occur rarely but only in this age group. In these cases, preoperative consultation with a gynecologic oncologist may be in order.

In the older yet still reproductive age group, benign masses still prevail. Again, hemorrhagic corpora lutea and follicular cysts are common, as are dermoid cysts. Ultrasonographic characteristics of the ovarian mass in these cases will be helpful. Again, ovarian cancer in this age group is not common. Lastly, the age group for which there is most concern is the postmenopausal group. Albeit infrequent, ovarian cancers predominate, although the majority of masses in the this group are benign.

COMMON EPITHELIAL MASSES

The majority of ovarian masses are benign and, of these, the most common histologic type is epithelial, whether benign or malignant. The epithelial tumors are, for the most part, of the following types: serous, mucinous, endometrioid, clear cell, and transitional cell.

Serous Tumors, Benign and Malignant

Serous tumors are the most common histologic type and account for approximately 50% of all ovarian cancers. The benign counterpart accounts for 50% to 70% of all benign ovarian neoplasms. Although a patient of any age can manifest a benign serous tumor, the average age is 40 years. These tumors appear to be simple on ultrasonographic evaluation in that for the most part, although there may be some small internal echoes, these are purely cystic in appearance. They can be large and are mostly fluid filled. Benign serous tumors are bilateral in 20% of cases.

In contrast, invasive serous ovarian carcinomas account for 50% of all ovarian epithelial cancers. They are often bilateral and occur menopausally. The serous tumor is the prototype for invasive ovarian cancer, the “garden variety” histologic type. As with most ovarian cancers, the tumors are widely disseminated at the time of diagnosis.

Mucinous Tumors, Benign and Malignant

Benign mucinous tumors, mucinous cystadenomas, account for 25% of all benign ovarian neoplasms. They occur at a slightly younger age than serous benign tumors and can occur in young women, as well. They are less often bilateral, with both ovaries involved in only 3% of cases. They tend to be large and can be multiloculated. These are the tumors that have been reported to weigh up to 100 kg. Histologically, the cells are mucin filled and show endocervical or intestinal differentiation. These are the second most common type of ovarian neoplasm. Their invasive counterpart, the mucinous cystadenocarcinoma, represents 15% of invasive ovarian epithelial cancers.

Endometrioid Tumors, Benign and Malignant

The third epithelial type is the endometrioid neoplasm. These neoplasms recapitulate the endometrium and, thus, the epithelial component resembles the endometrial glandular cell. Benign tumors of this histologic type are less common and are associated histologically with changes of adenofibroma or cystadenofibroma. The endometrioid malignant ovarian neoplasm represents up to 25% of ovarian epithelial cancers and is usually moderate in size, ranging up to 20 centimeters. Most ovarian endometrioid neoplasms are malignant. The malignant form tends to be bilateral in 30% of cases. When an endometrioid ovarian invasive cancer is found, up to 25% of patients will have concomitant uterine endometrial cancer or endometrial hyperplasia. Pelvic endometriosis may be found also, and one hypothesis is that these lesions arise from preexisting endometriosis. When an endometrioid invasive cancer is found in the ovary it is the duty of the pathologist to clarify whether this is a metastasis from a primary uterine cancer.

Clear Cell Tumors

The fourth general category of epithelial ovarian neoplasms is the clear cell tumor. Benign clear cell tumors rarely are diagnosed. However, the invasive form of this, the clear cell carcinoma, represents 10% of all ovarian cancers. The clear cell component usually coexists with another epithelial type. The clear cell histology also is associated with endogenous endometriosis in the pelvis in up to 25% of cases.

Transitional Cell Tumors

Lastly, transitional cell tumors, which mimic the epithelium found in the bladder, are rare. The Brenner tumor is a well-known transitional cell tumor and accounts for 2% of all ovarian epithelial tumors. Brenner tumors are considered benign, although a malignant variant has been identified.

Other Common Benign Tumors

The dermoid cyst is a common benign tumor found in all ages. This tumor is comprised of three germ cell layers, which explains the term teratoma. The three germ layers include the ectoderm, mesoderm, and endoderm. It is the most common type of ovarian germ cell neoplasm and occurs frequently. This teratoma accounts for 25% of all ovarian neoplasms and is most commonly found in the reproductive age group; however, it can be found in younger women and in postmenopausal women. The mature teratoma can grow to quite a large size before a patient has pain or notices abdominal swelling. Up to 15% of cases are bilateral and these tumors can grow to a large size, weighing several kilograms (Fig. 56.1). These tumors are well known for their smooth, glistening, pearly white surface. Either cystectomy or adnexectomy can be performed to treat these neoplasms effectively. These tumors are interesting because of a radiologic finding of teeth or bone or cartilage on plain film. Additionally, they have a characteristic finding on ultrasonography and computed tomography (CT) scan. Within the cyst wall is a protuberance called *Rokitansky protuberance.* These neoplasms are well known for the greasy sebaceous material associated with hair, bone, or teeth found within the cyst. Thyroid tissue, salivary gland tissue, and gastrointestinal and bronchial epithelium can be found, associated with bone, cartilage, and smooth muscle. Other ectodermal tissues, including brain, neural, retina, and choroid plexus, are also found. Clinical complications associated with the presence of these neoplasms include torsion rupture and infection. More uncommonly, hemolytic anemia and malignant transformation may also occur.

FIG. 56.1. Removal of a large dermoid cyst.

Endometriomas of the ovary involve bilateral ovaries in up to 50% of cases. These cysts often are associated with dense adhesions to the broad ligament or cul-de-sac and are difficult to excise. The contents are usually chocolate colored and thickened. Cystectomy can be performed successfully in many cases. The presence of endometriomas indicates advanced endometriosis, and usually other pelvic sites are involved, such as the cul-de-sac or other peritoneal structures. Bilateral salpingo-oophorectomy is curative, if clinically appropriate, in that estrogen drives the growth of these cysts. Ovarian endometrioid carcinoma can be associated with these benign neoplasms.

Physiologic cysts can appear as adnexal masses. These include follicular cysts and corpus luteal cysts, which are most common in the reproductive age group and range from small to moderate in size. Follicular cysts are unilocular, and the ultrasonographic image should be that of a simple cyst; however, if there is a region of clotted blood this area will appear as cystic or solid. The interpretation of this is dependent upon the ultrasonographer. However, given that these benign physiologic cysts prevail in the reproductive age group, a laparoscopic approach could be offered should surgical evaluation be necessary.

RADIOLOGIC EVALUATION OF THE ADNEXAL MASS

Whether suspicion of an adnexal mass arises as a result of a patient's symptoms or suspicious findings during a pelvic examination, radiologic imaging is usually the next step in the diagnostic evaluation. For gynecologic problems, fortunately, transvaginal ultrasonography gives the best visualization of the adnexal region. Previously, transabdominal ultrasonography was used routinely to visualize the adnexa. However, the transvaginal approach, by virtue of the proximity of the probe to the adnexa, gives startlingly clear characterization of the adnexal region.

Description of an adnexal mass should include qualitative modifiers. If the mass is cystic, comments such as whether the cyst is simple (indicating that there are no internal echoes or populations of suspicion) or complex should be made. The size and whether there has been interval growth should be noted.

Additionally, solid components are important, because malignant masses often will have solid sections. Several studies have indicated that the incidence of malignancy increases when masses are multiloculated and contain solid areas. Other reports indicate that the most suggestive finding of malignancy is inner wall abnormalities, such papillations, or a solid area. Other important features found on ultrasonography actually can be reassuring, such as calcium found next to fat as noted in dermoid tumors. Thus, adnexal masses that have solid components, inner wall papillations, or nodularity should not be observed further and surgical evaluation would be in order (Fig. 56.2).

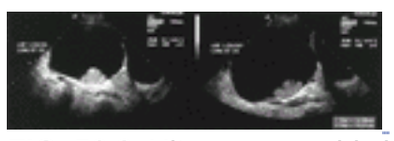

FIG. 56.2. Ultrasonographic image of an ovary with internal wall papillations. The final pathology of this ovarian cyst was clear cell adenocarcinoma.

An ultrasonographic evaluation can clarify the etiology of the mass. Although not definitive, suggestions that the masses may arise from the tube, such as the form of hydrosalpinges or tuboovarian abscesses, can be helpful. This is operator dependent and, as such, obtaining an ultrasonographic examination from a quality center would be of utmost importance in managing patients with adnexal masses (Fig. 56.3 and Fig. 56.4).

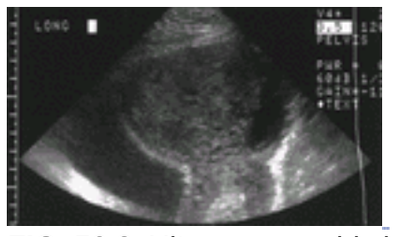

FIG. 56.3. Ultrasonographic image of a tuboovarian abscess.

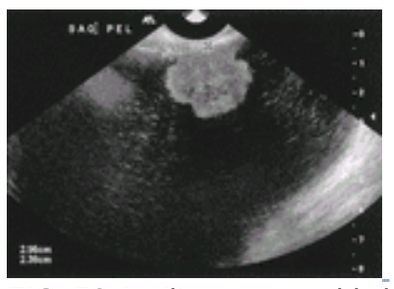

FIG. 56.4. Ultrasonographic image of a cystadenofibroma.

Most ovarian malignancies occur in the postmenopausal group. In addition to the abnormal findings noted above for which surgery is recommended, growth of a mass in any age group is most likely an indication for surgical evaluation. It has been suggested, however, that in the postmenopausal population, a cystic mass that is simply cystic, that is has no nodularity, papillations, nor solid areas, may be managed conservatively. In a study of over 7,000 postmenopausal women, unilocular ovarian cysts measuring less than 10 centimeters in diameter in asymptomatic women were infrequently malignant. The patients in whom unilocular cysts were detected were observed, and 50% of the masses resolved within 60 days. Of the residual patients, all the masses were found to be benign when evaluated during surgery. Thus, these findings should be reassuring for the postmenopausal patient with unilocular cysts, in particular if the cysts are stable over several ultrasonographic examinations.

In addition to ultrasonographic findings, Doppler sonography may add some information. Doppler ultrasonography allows an evaluation of ovarian blood flow. With emission of a sound wave from a stationary source, reflection of the sound wave from a moving target is relative to its velocity. The strategy of using Doppler ultrasonography in ovarian masses would be to detect abnormal blood flow associated with neoangiogenesis often associated with ovarian malignancy. Thus, several indices have been developed for standardization of the study of ovarian blood flow. These include systolic-to-diastolic ratio, resistance index, and pulsatility index. Doppler analysis of flow is performed at multiple points, then color coded according to the direction of blood flow and superimposed on the anatomic location. A Doppler study can be performed quickly and is felt to add to the sonographic diagnosis. In a normal ovary, pulsatility and resistance indices are low. These indices also show changes relative to phases of the menstrual cycle. In contrast, in ovarian tumors, are associated with development of new blood vessels required to support growth of the aberrant tissue, the newly formed vessels have no smooth muscle vasculature, and thus the Doppler signalling is abnormal.

In the event that ultrasonographic findings are uncertain or more information is needed before surgical evaluation is undertaken, CT can be helpful. The conventional CT scan obtains images one slice at a time. Slice thickness is usually 8 to 10 millimeters, and patient immobilization is critical for obtaining clear views. Each slice is then reconstructed by the computer to result in a full image of the pelvis. Usually radiopaque oral agents are used to opacify the gastrointestinal tract. Intravenous contrast can be administered to visualize vascular and genitourinary structures. Ovarian nodularity, septations, and fat can be characterized well by CT scan. Additionally, if there is a concern that ultrasonographic findings may be reflecting a loop of bowel, CT can clarify this by using contrast. CT scans are fairly accurate for diagnosing a dermoid cyst given the combination of fat and calcification in these neoplasms (Fig. 56.5). If there is some concern that an adnexal mass may be uterine, such as in the case of myomas, CT can clarify this. Lastly, if an abdominal and pelvic CT scan is ordered, information regarding the rest of the lower abdomen and upper abdomen can be obtained.

FIG. 56.5. Computed tomography image of dermoid cysts. **A:** Internal calcification.

Magnetic resonance imaging (MRI) uses magnetic fields and radio waves. As compared with CT scan, which uses x-ray attenuation, multiple tissue characteristics are analyzed by MRI. One of the advantages is that no ionizing radiation is used for MRI. Patients with electrical pumps or implants such as pacemakers cannot undergo MRI evaluation. Gadolinium is used as intravenous contrast to better visualize organs and abnormalities. Compared with MRI, the CT scan is less expensive and usually more readily available. When evaluating disease, MRI may provide additional information but, for the most part, similar information is gained from either modality when evaluating the adnexal mass.

A new modality, positron emission tomography (PET), is undergoing investigation for clinical use in the evaluation of gynecologic malignancies. This radiologic test is based on the uptake of 18F-fluoro-2-dioxyglucose. This scan differs greatly from previous scans, which measure the differences between normal tissue and cancerous tissue; it is hypothesized that cancer tissues process this glucose analog differentially such that when a PET scan is performed, the emission of images is different in abnormal tissues. Theoretically, then, this technique is potentially more sensitive than classic imagining methods for detecting metastatic disease. The glucose analog is given intravenously, then the scan is performed and images are displayed for interpretation. This study usually is performed in the nuclear medicine department. Some investigators have suggested that the PET scan is more sensitive than CT or MRI for detecting the recurrence of ovarian cancer. Other investigators differ and note that the false-negative and false-positive result rates are quite high. The PET scan is an experimental modality; its use may increase with more experience. We have yet to understand fully its use in the evaluation of gynecologic malignancies, and insurance reimbursement issues still exist.

TUMOR MARKERS

The purpose for using tumor markers is two-fold as follows: (a) to measure these preoperatively to try to predict the malignant nature of the mass in question so that surgical preparations may be undertaken and (b) to follow disease once established. Traditionally, the most important tumor marker for epithelial ovarian cancers is CA-125. This antigen is expressed epithelially when a CA-125 level is ordered, and the amount of expression is measured by antibody assay using OC-125. CA-125 is relevant in particular to epithelial ovarian cancers, for which a cutoff of 35 U/mL has been determined to divide normal from abnormal levels. This has been accepted as the standard for clinical practice in the United States. Numerous studies have shown CA-125, drawn preoperatively, to be unreliable as a predictor of the malignant nature of a mass. During early stages of cancer, such as stage I disease, only 50% of patients will have elevated levels. Additionally, many other adnexal masses and disease processes may express elevated levels of CA-125 (Table 56.2 and Table 56.3). For screening purposes, many investigators have moved on to a combination of CA-125 with other tumor markers or with ultrasonographic findings. To date, there have been no successful screening protocols using serum and ultrasonographic preoperative data to accurately predict adnexal malignancy. Lastly, in the event of an ovarian epithelial neoplasm, preoperative CA-125 levels have been found to be controversial in regard to final outcome.

Gynecologic
Endometriosis
Leiomyomata
Adenomyosis
Pelvic inflammatory disease
Luteal phase menstruation
Ovarian hyperstimulation
Pregnancy (normal or ectopic)
Ovarian cystadenoma
Nongynecologic
Congestive heart failure
Chronic renal failure
Chronic liver disease
Colitis
Pneumonia
Systemic lupus erythematosus
Peritonitis of any etiology
Poorly controlled diabetes
Pancreatitis

TABLE 56.2. *Benign conditions associated with elevated CA-125*

Colon cancer
Lung cancer
Breast cancer
Pancreatic cancer
Vaginal cancer
Endometrial cancer
Fallopian tube cancer

TABLE 56.3. *Other malignancies associated with elevated CA-125*

For following disease progression and regression, however, CA-125 levels have been invaluable. For monitoring responses to treatment, elevated levels accurately reflect progression or regression of disease in over 90% of patients. Thus, CA-125 is useful preoperatively as a baseline for ovarian cancer and is one of the main methods of following disease progression, in combination with radiologic imaging and clinical examination.

CA-125 levels can be elevated postoperatively because of surgical manipulations of the abdominal organs. If a preoperative CA-125 level was not drawn and a diagnosis of cancer is made intraoperatively, a postoperative CA-125 level should be measured, taking into consideration that elevated levels may be seen due to surgery. The elevation may not be so important, because it will be the rate of decline and actual resolution of elevated levels that would be most indicative of disease prognosis. Of note, the half-life of CA-125 is 20 days.

Numerous other markers have been studied to attempt to predict ovarian malignancy preoperatively and to follow cancer should it be diagnosed. Other tumor antigens include CA-15-3, CA-72-4 (TAG-72), CA-130, and CA-19-9. However, only CA-125 is in common use, and our clinical protocols include this antigen for following disease. The other tumor markers have not been as successful, in that their accuracy is less than that of CA-125 and many assays may not be readily available. A new tumor marker, lysophosphatidic acid (LPA), has been studied and may be promising in ovarian cancer. This lipid mediator can be assayed in serum and has been found to be elevated in patients with cancer.

SURGICAL EVALUATION

Once it has been decided that a mass requires surgical evaluation, the patient is scheduled for surgery and the surgeon must decide which approach to attempt. Gynecologists have been trained to make essentially two kinds of incisions when using an open approach. The most common transverse incision is the Pfannenstiel incision, also known as the *bikini incision.* Usually performed at the superior aspect of the pubic hair region for cosmetic reasons, its exposure is limited. When space is not a consideration for node dissection or removal of a large mass, the Pfannenstiel is useful in that it heals well, is reportedly less painful, and is associated with a lower incidence of wound dehiscence as compared to vertical incisions. Other transverse approaches include the Cherney and Maylard incisions. To perform a Cherney incision, a transverse skin incision is made, and the rectus muscles are identified at the insertion into the pubic synthesis and divided, commonly using electrocautery. With the rectus muscle out of the way, pelvic exposure is greatly enhanced and, thus, this incision is very useful when additional pelvic exposure is needed, yet the cosmetic aspects of a transverse incision are preserved. Closure of this incision is straightforward. The rectus tendons should be reapproximated to the inferior tendon of the rectus sheath using permanent sutures. Thus, in this incision, the rectus muscles are preserved. Alternatively, another space-endowing incision is the Maylard. Again using the transverse skin incision, once the rectus muscles are identified, the inferior epigastric vessels which reside in the lateral aspect of the rectus muscles are identified and ligated. The rectus muscles are divided using electrocautery. If approached cautiously and slowly, division of the rectus muscles is not complicated by bleeding. As with the Cherney incision, the Maylard incision affords greater exposure to the pelvic region than does a Pfannenstiel.

Alternatively, when a malignancy is suspected and surgical staging may be required, a vertical incision is used because of accessibility to the upper abdomen should this be needed; clearly, transverse skin incisions are limiting for exploration and management of disease found in the upper abdomen. There are two major vertical incisions, the paramedian incision and midline vertical incision. In performing a paramedian incision, the skin incision is just lateral to midline. Some consider these incisions stronger because of the displacement of the skin defect over the rectus muscle defect. The incidence of incisional hernia formation is decreased. However, the midline incision is used most commonly. With the need for upper abdominal exposure, the midline incision is ideal because of the ability to extend the incision superiorly.

Exposure is usually ideal with the midline incision, although in many cases the Cherney and Maylard incisions offer better exposure of the pelvis. Because the midline facial area is less vascular, the entry in the midline can be performed quickly, with minimal damage to rectus muscles and nerves. Also, blood loss is decreased with a midline incision. However, this is considered one of the weaker incisions and hernias, dehiscence, and eviscerations occur more readily with this incision than with others.

In summary, several incisions are available to gynecologists. Choice of incision is critical to successful evaluation of the gynecologic problem at hand. If malignancy is suspected, then the midline incision is recommended. However, suspicion of malignancy is based on a thorough knowledge of the risks, taking into consideration the radiologic characteristics of the mass and the patient's age. Thus, by a “best guess” scenario of the malignant potential of the adnexal mass being evaluated, the incision should be chosen.

Once the abdomen is open, it is recommended that washings be obtained before manipulation of the pelvic organs, so that a true assessment of cytologic spread can be undertaken. This can be performed in many ways. Simply, a large syringe can be used to inject the pelvis with fluid, and then the fluid is withdrawn using the empty syringe. Alternatively, various suction devices are available for use in the operating room to efficiently remove pelvic washings. The solution recommended for pelvic washings is isotonic so that lysis of cells does not occur. Plasmalyte warmed to body temperature is recommended. When obtaining washings, it is helpful to cup one's hand in the abdomen and aspirate the collective washings from this so as to not to aspirate epiploica. A small amount of heparin is added to the collection, which is then transported to the cytology department for evaluation.

After washings are obtained, a thorough exploration of the upper and lower abdomen is in order. In the upper abdomen, the diaphragm and omentum should be palpated for possible metastatic sites. Also, by reaching under the omentum for the root of the mesentery, the periaortic region should be palpated for adenopathy. Because the intent is to pack away bowel so that pelvic visualization is optimized, lysis of adhesions may be necessary to release small bowel loops that may be adherent in the pelvis. After doing so, using laparotomy sponges to collect the bowel, a retractor can be placed. Care should be taken in thin patients not to compress the psoas muscle and cause femoral nerve damage. Then the adnexal mass of interest is examined. If the pelvic mass is an ovarian cyst, either a cystectomy or an oophorectomy can be performed, depending upon the preoperative discussion with the patient and the index of suspicion for malignancy. For most postmenopausal women, an oophorectomy is planned. If there is any question as to whether the mass is truly malignant and the patient desires preservation of her ovaries, a cystectomy can be performed; if malignancy is suggested by frozen section, completion of the oophorectomy can be performed later during the surgery. In a quality hospital, frozen section analysis should have high correlation, upwards of 90%, with the final pathology findings.

Classically, when a malignancy is found in a postmenopausal woman, complete surgical staging, including total hysterectomy and bilateral salpingo-oophorectomy, is performed. Washings from the pelvis, both gutters, and diaphragm should be obtained. Bilateral pelvic sidewall, paracolic gutter, cul-de-sac, and anterior vesical biopsy samples should be obtained. These can be obtained by lifting a small portion of peritoneum and excising sharply. If there is bleeding at the biopsy site, the area can be cauterized for hemostasis. In lieu of obtaining a diaphragm biopsy, which can be performed using a cervical biopsy forceps, a scraping of this area can be performed. The right side of the diaphragm is scraped with a Pap smear spatula. The dominant hand is extended into the right upper quadrant and the diaphragm scraped. Cells are smeared from the spatula onto a slide and fixed with traditional preservative or submerged in liquid cytology media. When only an ovary(ies) is(are) affected without evidence of extraovarian spread, pelvic lymph node and periaortic node sampling should be performed, as well as omental biopsy. Lymph node dissection is not commonly performed by the general gynecologist so will not be described here; however, several excellent references describe the technique. Possible resources for the gynecologist who does not often perform lymph node dissection ideally include consultation with a gynecologic oncologist. However, if one is not available, a surgical oncologist or a urologic oncologist may be of assistance.

After ascertaining that all sites are hemostatic and sponge and instrument counts are correct, the abdomen is closed. For vertical incisions, two running sutures meeting in the midline should be sufficient for a fascial closure. If there is any concern that this closure would not be durable, as in patients who are malnourished or are on steroids or other immunosuppressive agents, interrupted closure with a permanent suture may be undertaken. Successful closure of the abdomen often is taken for granted but is a very important part of any surgical procedure. Wound infection and skin separations are unpleasant for the patient; however, serious complications such as fascial dehiscence can result. Although the Smead-Jones closure traditionally has been felt to be the most secure, it is very time consuming and may not afford any extra advantage for the patient when compared with mass abdominal wall closure. When using the Smead-Jones closure, monofilament permanent suture often is used. Alternatively, single interrupted sutures encompassing the entire abdominal wall can be used. However, using two sutures and running the fascia from the opposite poles to the midline is equally effective. This, of course, shortens operating room time and the amount of time the patient is under anesthesia.

There are many compelling reasons to stage an ovarian cancer. First of all, the extent of tumor is clearly described within our staging system, thus making communication among physicians and the clinical implications quite clear. Given a certain stage of disease, a patient may obtain appropriate therapeutic or adjuvant chemotherapy or radiation therapy. Staging in ovarian cancer is particularly important, because microscopic metastases are serious implications for postoperative treatment. In a classic study, up to 30% of patients thought to have stage I ovarian cancer based on incomplete surgical staging were upgraded to a more advanced stage when microscopic metastases were discovered during a later surgery. Therefore, if full staging, which includes pelvic and periaortic lymph node dissection, had not been included, these patients would have been treated incorrectly. Unfortunately, despite the availability of gynecologic oncologists in this country, full staging still is not offered to all patients. Not only are node dissections omitted, full palpation of the upper abdomen and omental biopsies are omitted. Although the missing staging procedures sometimes can be attributed to a skill issue such as lymph node dissection, failure to evaluate the diaphragm or perform straightforward peritoneal biopsies usually reflects the surgeon's lack of understanding of the necessity of full staging for ovarian malignancies. Complete staging is described in Table 56.4.

Total hysterectomy
Bilateral salpingo-oophorectomy
Omentiectomy
Pelvic node excision
Paraaortic node excision
Peritoneal biopsies (cul-de-sac, vesical peritoneum, right and left paracolic gutters, and pelvic sidewalls)
Peritoneal washings from pelvis, paracolic gutters, and infradiaphragmatic areas
Biopsy or scraping of right side of diaphragm

TABLE 56.4. *Complete staging for ovarian cancer*

SPECIAL CLINICAL SITUATIONS

Ovarian cancer is usually a disease of postmenopausal women. Thus, when faced with surgical evaluation of an adnexal mass, should a total hysterectomy and bilateral removal of adnexa be required, the implications are not as striking. However, in the case of a young woman with an incidental malignancy found during surgery, there is the added dilemma of how to address the unaffected organs after removal of the adnexa. For the young woman in whom a malignancy is suspected, conservative treatment is recommended (Table 56.5). Conservative surgery may be considered in women who are nulliparous with only suspected stage I disease (cancer confined to an ovary). After conservative surgery, should more advanced disease be diagnosed after pathologic evaluation of resected specimens, additional surgery may be undertaken as needed after consultation with an oncologist.

Unilateral salpingo-oophorectomy (includes removal of the ovary at the infundibulopelvic ligament)
Pelvic lymph node sampling
Periaortic lymph node sampling
Omentiectomy
Peritoneal biopsies from cul-de-sac, vesical peritoneum, right and left pelvic sidewalls, and paracolic gutters
Biopsy or scraping of right side of the diaphragm
Peritoneal washings from pelvis, paracolic gutters, and infradiaphragmatic areas
Biopsy of the contralateral ovary if it appears suspicious

TABLE 56.5. *Surgical staging for ovarian cancer in young women*

For young patients who wish for preservation of fertility options, all efforts should be made to perform a cystectomy. Samples can be sent for frozen section to determine if the ovarian mass is benign or malignant. If there is a question of malignancy, staging should be performed. Care should be taken to understand the patient's wishes for reproduction before performing surgical staging. In these cases it is clearly best to discuss all possible options preoperatively with the patient; in general, masses in premenopausal women are benign. However, in the event that a malignancy is found, if the contralateral ovary appears to be normal the uterus and ovary can be preserved, and the rest of the staging is as for the postmenopausal woman. That is, pelvic and periaortic node dissection, peritoneal and omental biopsies, and washings should be obtained. In the young patient, if there are bilateral masses and it is suspected that both ovaries are involved, thought should be given to preserving the uterus, given the advances made in assisted reproductive technology. Egg donation and other services may be available for this patient should

removal of both ovaries be indicated.

Another special scenario is management of the mass with borderline histology, also known as tumors of low malignant potential. Ovarian low malignant tumors have been described for all of corresponding invasive epithelial ovarian neoplasms. Serous and mucinous histologies make up the largest proportion of these tumors. Histologically, low malignant tumors differ from truly invasive lesions in that invasion into ovarian stroma is not detected; the epithelial lining is multilayered, and only mild nuclear atypia is present. These tumors account for up to 16% of ovarian malignancies. As compared with truly invasive ovarian cancers, the majority of tumors of low malignant potential are early stage and confined to one ovary. Once resected, regardless of stage, the role of adjuvant or therapeutic chemotherapy is unclear (unlike that for invasive epithelial ovarian cancers); this disease is felt to not benefit from adjuvant chemotherapy and remains a surgically treated disease. CA-125 levels are elevated in some patients with tumors of low malignant potential. In these cases, monitoring this marker for the recurrence of disease may be useful.

In the postmenopausal population, management is straightforward. At the minimum, unilateral salpingo-oophorectomy is performed and, more frequently, a bilateral salpingo-oophorectomy and often hysterectomy are performed. Again, the majority of tumors of low malignant potential are of early stage and prognosis is good. In the young population, a cystectomy is a possibility. Although recurrence rates may be higher after cystectomy, mortality rates from recurrent disease appears to be unchanged. When cystectomies are performed in these cases, women desiring children may be able to gain a few years and complete a family before undergoing or requiring more definitive surgery.

Adnexal masses in the young women may also be of germ cell origin. This is a special clinical scenario in that these neoplasms occur exclusively in young women. The main complaints include abdominal pain, with a pelvic mass found during examination. Some patients have acute abdominal pain resulting from torsion or rupture and hemorrhage of these masses. When evaluating a patient whose condition is not acute, the radiologic image usually reflects a solid mass with some cystic changes. The most common germ cell ovarian tumor is a dysgerminoma (Fig. 56.6). This is also the most common ovarian malignancy for young and pregnant women. This germ cell tumor is unusual in that it has a high incidence of bilaterality. Should a solid tumor be found and a germ cell tumor suspected, a-fetoprotein, human chorionic gonadotropin, and LBH levels may be drawn preoperatively, although none of these is necessarily predictive of finding a germ cell tumor. During surgery, given that most of these patients have not completed childbearing and that germ cells tumors most often are confined to the ovary, a conservative approach such as unilateral adnexectomy can be performed. Routine biopsy of the contralateral ovary in the case of a dysgerminoma is not recommended, even though the bilaterality rate is higher than with other germ cell tumors.

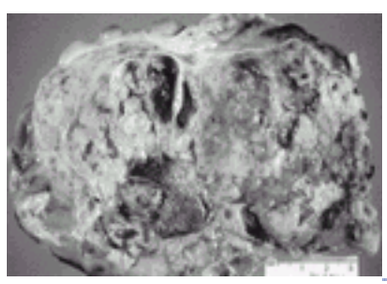

FIG. 56.6. Dysgerminoma in a 17-year-old girl.

Another germ cell neoplasm that occurs in young women is the endodermal sinus tumor. This tumor is classically associated with elevated a-fetoprotein and may be found in conjunction with a dysgerminoma. These tumors confer a worse prognosis. The malignant counterpart of the dermoid cyst, a malignant teratoma, may also be found in this population. These tumors are uncommon. In summary, if a germ cell tumor is diagnosed in a young person, a unilateral procedure may be performed if there is no suspicion of metastatic disease to the contralateral ovary or pelvis. If in doubt, a conservative approach would be best, with preservation of other reproductive organs and the possibility of returning for another laparotomy should this be indicated.

LAPAROSCOPIC APPROACH TO THE ADNEXAL MASSES

The role of laparoscopy in the management of the adnexal mass has advanced tremendously over the last decade. Laparoscopic technique has been developed and equipment is available such that laparoscopic surgery has never been easier. The advantages of a laparoscopic approach to management of the mass include shorter hospital stay, less pain, shorter recovery time, less expensive process by virtue of fewer days of hospitalization, and the potential to minimize the development of adhesions. Alternatively, the risks and complications of a laparoscopic approach differ from those associated with laparotomy. Although striking when reported and laparoscopic complications such as puncture of a vessel can be severe, altogether they are uncommon. Minimal requirements for a laparoscopic approach to the adnexal mass include adequate surgical skill to perform competently either a cystectomy or adnexectomy, accurate and prompt frozen section services, and the availability of staging in a timely fashion should rupture or advanced disease be diagnosed (Table 56.6). With the laparoscopic approach, once the mass is removed frozen section is completed as usual. Should the mass be malignant, staging should be undertaken as usual, either laparoscopically if the surgeon is skilled or by proceeding to laparotomy. If rupture of the mass occurs and the frozen section confirms malignancy, in general it is recommended that staging be performed promptly. However, should there be spill of ovarian contents inadvertently or in the process of performing a cystectomy, although the stage is upgraded to stage Ic ovarian cancer, it is unclear that the prognosis is much worse; however, in many cases the patient would be committed to adjuvant chemotherapy.

Surgical skills appropriate for performing cystectomy or adnexectomy
Prompt and accurate frozen section services
Personnel and facilities for timely surgical staging available

TABLE 56.6. *Criteria for laparoscopic removal of adnexal mass*

A unique complication associated with the laparoscopic approach to the mass with malignant potential is the occurrence of port-site implants. Studies have reported port-site dissemination and metastasis in 20% to 50% of patients. The mechanism for metastasis to these sites is direct tracking of tumor cells through port sites. Suggestions for decreasing the risk of port site metastasis in the event ovarian cancer is found at laparoscopy include resection of the port site or copious irrigation at the time of removal of instruments through the port site.

The key to successful laparoscopic management of an adnexal mass then returns to the main issue, selection of the appropriate patient given a best guess scenario of whether a mass is benign or malignant. A postmenopausal woman with a complex mass has a higher chance of malignancy and, therefore, the surgeon planning a laparoscopic approach should absolutely have a contingency plan should malignancy be discovered. Alternatively, because the chance of malignancy is less frequent in the premenopausal group, laparoscopic approach usually is appropriate in this age group. Until we can predict absolutely which masses are malignant, a combination of age and radiologic appearance, in particular ultrasonographic findings, should be integrated to determine the best approach for each patient.

SUMMARY POINTS

- Inroads have been made into the management of the adnexal mass. These include conservative management of the simple cyst in the postmenopausal woman and offering a laparoscopic approach to adnexal masses.
- An ideal method for determining preoperatively whether a mass is benign or malignant has not been discovered. Should we be able to predict this, plans and preparations could be made accordingly.
- All surgeons managing the adnexal mass should know the appropriate cancer staging procedures for the postmenopausal woman and the young woman desiring preservation of fertility. Even if the surgeon is not technically equipped to perform the actual node dissection, assistance frequently can be arranged. In the event a malignancy is diagnosed, appropriate staging is imperative to save the patient another surgical procedure and to determine the extent of the disease so that adjuvant therapy can be prescribed.
- New tumor markers and radiologic approaches are being pursued fervently such that soon we may be able to more accurately distinguish malignant from benign adnexal masses. In the meanwhile, appropriate medical and surgical management of the adnexal mass is the responsibility of all gynecologic surgeons.

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Chapter 57

Andrew J. Li and Beth Y. Karlan

Gestational Trophoblastic Neoplasms

HYDATIDIFORM MOLE
Complete Hydatidiform Mole
Partial Hydatidiform Mole
Invasive Mole
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Surgery and Radiation in Trophoblastic Disease

Gestational trophoblastic neoplasia (GTN) encompasses a broad spectrum of benign and malignant tumors derived from the trophoblast of the human placenta. Although they are rare in incidence, they have the potential to become rapidly fatal diseases that afflict young women in their peak reproductive years.

Traditionally, GTN is divided into three histologic categories: hydatidiform mole, invasive mole (chorioadenoma destruens), and choriocarcinoma. Partial hydatidiform moles and placental site trophoblastic tumors (PSTT) are further recognized as histologically and clinically separate entities under the broad classification of GTN.

Despite the apparent diversity of GTN, these diseases are all derived from the human placental trophoblast and the paternal genome, with only occasional maternal genetic contribution. Human chorionic gonadotropin (hCG) is secreted by these neoplasms and serves as a sensitive tumor marker that correlates well with the clinical course for all GTNs except PSTT.

In 1956, metastatic gestational choriocarcinoma, the most malignant form of these diseases, was shown to be curable with chemotherapy. Many studies have now demonstrated the curability for most of these women, although individualization of therapy remains fundamentally important.

Patients may be treated for *malignant* GTN on the basis of clinical, radiographic, and serologic (hCG level) determinations without a definitive histologic diagnosis. For this reason, the generic term of *GTN* is useful, especially when treating patients with metastatic disease that is not readily accessible for pathologic evaluation. Except for PSTT, the initial histologic features of any lesion identified as GTN are less important than the clinical data and hCG level.

This chapter will review the wide spectrum of these human neoplasms and discuss important concepts regarding diagnosis, management, and surveillance for women with GTN.

HYDATIDIFORM MOLE

Two distinct types of molar gestations are recognized: partial and complete hydatidiform moles, both of which have distinct cytogenetic origins, pathologic features, and clinical behavior. Although it is not as clear whether partial hydatidiform mole represents a form of GTN or an extreme form of hydropic degeneration of the placenta in a chromosomally abnormal pregnancy, partial moles should be considered a variant of complete hydatidiform moles with risk of malignant sequelae. Most patients with primary molar gestations do not require adjuvant chemotherapy and may be monitored after therapeutic evacuation with serial hCG level determinations until either spontaneous regression occurs or the patient develops criteria for malignant disease.

Complete Hydatidiform Mole

Complete hydatidiform mole is identified macroscopically by edema and swelling of virtually all chorionic villi, without identifiable fetal parts or amniotic membranes. Hydropic villi are usually 1 to 3 centimeters in diameter, giving the gross appearance of grapelike vesicles. Microscopically, the chorionic villi are hydropic with marked interstitial edema. Fetal vessels are absent in the stroma of the villi. Proliferation of cytotrophoblast and syncytiotrophoblast is observed. Regardless of the degree of trophoblastic proliferation, all patients should be followed in similar fashion. All hydatidiform moles secrete hCG, and this marker is used to monitor tumor regression after evacuation.

Complete moles are almost uniformly diploid with completely paternal chromosomal composition. Most are 46,XX, although a minority will demonstrate a 46,XY karyotype. The most common origin of complete hydatidiform mole is fertilization of an empty egg by a haploid sperm followed by reduplication, although some may result from dispermic fertilization of an empty egg.

Unlike women with partial hydatidiform moles, approximately one third to one half of these patients have uterine enlargement greater than expected for gestational dates. Fetal heart tones are absent. Patients often have vaginal bleeding and spontaneous abortion of the atypical hydropic vesicles. Theca lutein cysts are detected clinically in approximately 20% of patients with complete moles. Pulmonary decompensation, pregnancy-induced hypertension, and hyperthyroidism are observed occasionally. The clinical diagnosis of molar gestation is supported by a characteristic mixed echogenic “snowstorm” image filling the uterus on an ultrasonographic scan.

Partial Hydatidiform Mole

Approximately 1% of pregnancies have a triploid karyotype and resolve following spontaneous abortion; partial hydatidiform moles represent a subset of these pregnancies, with placental histologic features that share features with complete hydatidiform moles. A comparison of karyotypic, pathologic, and clinical features of partial and complete hydatidiform moles is shown in Table 57.1. Partial moles often are associated with identifiable fetal parts or amniotic membranes. Grossly, the placenta demonstrates a mixture of normal and hydropic villi. Microscopic features include normal and hydropic chorionic villi with focal mild hyperplasia of trophoblastic elements. Scalloping of the hydropic villi is common, with trophoblastic inclusions in the stroma. Fetal vessels frequently are observed, with nucleated fetal erythrocytes within the vessels. Normal amniotic membranes are identified often, even if a fetus is not found.

TABLE 57.1. *Features of complete and partial hydatidiform moles*

Partial moles almost always are associated with one haploid maternal and two haploid paternal sets of chromosomes. Presumably, this results from dispermic fertilization of a haploid ovum or fertilization of a haploid ovum with a diploid sperm.

Women with partial hydatidiform mole usually have a clinical diagnosis of spontaneous abortion or missed abortion. Often, hydropic villi are not identified on ultrasonography, and the diagnosis is not suspected until after evacuation of the pregnancy. Initial hCG levels are lower than those seen in patients with complete hydatidiform mole, and prompt postevacuation regression of hCG levels occurs in most cases. Unlike patients with complete moles, who have a 10% to 30% incidence of malignant sequelae, fewer than 5% of the patients with partial moles develop criteria requiring chemotherapy. Regardless of this low risk of malignant sequelae, all women with partial hydatidiform moles should undergo hCG surveillance after evacuation, similar to that recommended for patients with complete hydatidiform mole. If there is any doubt that the products of a conception are molar, postevacuation hCG monitoring should be done.

Invasive Mole

Invasive moles (chorioadenoma destruens) are histologically identical to complete moles, but with invasion into the myometrium without intervening endometrial stroma. Invasive moles usually are diagnosed within 6 months of molar evacuation. Untreated invasive moles tend to invade the uterine wall locally, which can result in uterine perforation and hemorrhage. Direct vascular invasion and metastasis may occur rarely. In these cases, biopsies of distant metastases reveal hydropic villi consistent with invasive mole instead of solid sheets of anaplastic cells consistent with choriocarcinoma.

The identification of an invasive mole from uterine curetting may be difficult unless there is sufficient myometrium to document direct myometrial invasion. Most frequently this is a clinical diagnosis made when persistent, nonmetastatic GTN is diagnosed.

Choriocarcinoma

Choriocarcinoma is a highly anaplastic malignancy derived from trophoblastic elements. No chorionic villi are identified. Grossly, the tumor has a red, granular appearance on cut section with focal, often extensive, central necrosis and hemorrhage. Histologically, the lesion consists of mixed syncytiotrophoblastic and cytotrophoblastic elements with numerous abnormal mitoses, multinucleated giant cells, and extensive areas of necrosis and hemorrhage. Choriocarcinoma rapidly invades the myometrium and uterine vessels, and systemic metastasis results from hematogenous embolization. The lung and vagina are the most common sites of metastasis, with secondary dissemination to the central nervous system (CNS), kidney, liver, and gastrointestinal tract.

Choriocarcinomas may develop after any type of pregnancy. Approximately 50% of cases are preceded by hydatidiform mole, and the remaining are distributed equally between a normal antecedent term gestation and abortion or ectopic pregnancy. Gestational choriocarcinoma has been observed several years after the last known pregnancy. Spontaneous regression of the primary uterine site has been well documented from autopsy series of patients before the development of effective chemotherapy.

Placental Site Trophoblastic Tumor

PSTTs are locally invasive neoplasms derived from intermediate cells of the placenta. These rare neoplasms are composed of a monomorphic population of intermediate cytotrophoblast cells that secrete human placental lactogen (hPL) and relatively small amounts of hCG. Typically, there is local myometrial invasion with rare systemic metastasis. PSTTs are significantly more resistant to standard chemotherapy than other forms of GTN, and hysterectomy is the initial therapy of choice.

INCIDENCE AND EPIDEMIOLOGY

Approximately 3,000 cases of hydatidiform mole and 500 to 750 cases of malignant GTN are diagnosed in the United States each year. Hydatidiform mole is identified in approximately 1 in 1,500 to 2,000 pregnancies in the United States. There is a marked geographic variation in the incidence of this disease, with rates 5- to 15-fold higher in the Far East and Southeast Asia than in the Western industrialized nations. Some of this variation may be accounted for by the methodology of studies reporting the incidence of molar gestation, because many data were reported from the experience at referral centers and may overestimate the true incidence of molar pregnancies in the general population. Racial differences also may account for some of the geographic variations; Japanese immigrants to Hawaii have an incidence of molar gestation intermediate between that of native Hawaiians and native Japanese. Nutritional factors may also be important in the development of hydatidiform mole, including deficiencies of protein or animal fat and fat-soluble carotene.

Known risk factors for hydatidiform mole include previous molar pregnancies and maternal age. Women with a history of hydatidiform mole have a 4 to 5 times higher risk for development of a subsequent molar gestation. Women at the extremes of reproductive age are also at increased risk of developing a hydatidiform mole. Several studies have confirmed that risk increases with advanced maternal age, and others have suggested an increased risk for younger women or adolescents. The impact of paternal age on the incidence of hydatidiform mole is difficult to separate from the effect of maternal age.

The incidence of partial hydatidiform mole is unknown. Presumably, many are undiagnosed due to insufficient histologic analysis of tissue from spontaneous and induced abortions. Some pathologists may not be familiar with the diagnosis of partial hydatidiform mole, and karyotyping seldom is performed on material obtained from spontaneous abortions. One report reclassified approximately 10% of all moles in their studies as partial hydatidiform moles on the basis of histologic analysis.

Invasive mole follows approximately 15% to 20% of complete hydatidiform moles. In the United States, choriocarcinoma will follow in approximately 1 in 40 moles, 1 in 5,000 ectopic pregnancies, 1 in 15,000 abortions, and 1 in 150,000 normal pregnancies.

MANAGEMENT

The basic principles of management of the patient with hydatidiform mole include establishment of the diagnosis, evacuation of the molar gestation, and close surveillance of hCG levels after evacuation. Patients with complete hydatidiform moles frequently have spontaneous abortion of hydropic villi, which are pathognomonic for molar pregnancy. Absent fetal heart tones, uterine enlargement different from that expected for the gestational age, hyperemesis, preeclampsia, and a markedly elevated hCG level are clinical indications that may suggest a hydatidiform mole. Ultrasonography is now the diagnostic method of choice for evaluating patients with suspected hydatidiform mole. Ultrasonography demonstrates a characteristic image of multiple echogenic regions within the uterus corresponding to hydropic villi, focal intrauterine hemorrhage, and absence of fetal parts (Fig. 57.1).

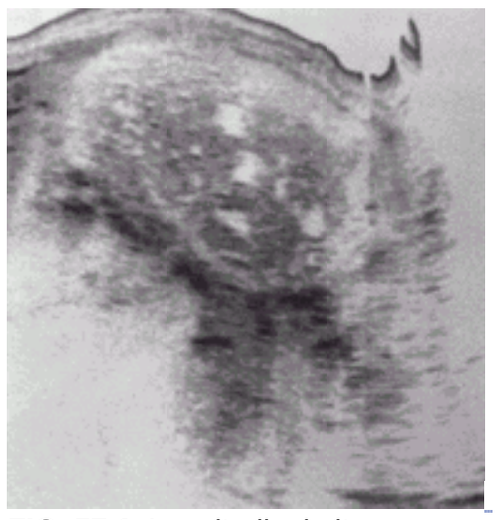

FIG. 57.1. Longitudinal ultrasonography reveals a hydatidiform mole. The mixed echoic pattern is caused by hydropic villi and focal intrauterine hemorrhage.

Evaluation of the patient before evacuation of the hydatidiform mole is directed toward preparing the patient for evacuation, obtaining baseline hCG level information, screening for occult metastatic disease, and screening for associated hyperthyroidism. The following studies are recommended:

- Complete physical and pelvic examinations
- Complete blood count determination
- Blood chemistry levels, including renal, hepatic, and thyroid function tests
- Baseline serum hCG level
- Chest radiograph
- Pelvic ultrasonography

Suction dilation and curettage (D&C) offers a safe, rapid, and effective method of evacuation of hydatidiform mole in most patients. Some patients who do not desire preservation of reproductive function may benefit from primary hysterectomy for evacuation of hydatidiform mole and concurrent sterilization. However, these patients must be followed closely after hysterectomy, because malignant sequelae may still develop. Hysterotomy or induction of labor for molar evacuation is not recommended.

Suction D&C for evacuation of hydatidiform mole has a low complication rate in patients with uterine sizes corresponding to less than 16 weeks of gestation. Oxytocic agents are administered immediately after cervical dilation to aid in postoperative hemostasis. Patients with excessive uterine enlargement have a higher risk of pulmonary complications associated with D&C, which may be related to trophoblastic deportation, preeclampsia, fluid overload, anemia, and hyperthyroidism. In patients with hydatidiform mole complicated by uterine enlargement greater than that of 16 weeks of gestation, baseline arterial blood gas analysis should be obtained preoperatively, with consideration of invasive hemodynamic monitoring (Swan-Ganz catheterization) during the procedure. Evacuation should be performed only after a euvolemic status has been established and blood products readily available for possible transfusion.

Primary hysterectomy is a reasonable alternative for termination of molar gestation in patients with hydatidiform mole who have completed childbearing and desire sterilization. Hysterectomy reduces the incidence of malignant sequelae after evacuation of hydatidiform mole from approximately 20% after suction D&C to less than 5% after hysterectomy. However, this does not eliminate the need for careful follow-up or complete hCG surveillance after termination of hydatidiform mole, because malignant GTN may develop even after hysterectomy. Concurrent surgical extirpation of the adnexae should be considered, as with hysterectomy for benign indications.

Theca lutein cysts are detected clinically in approximately 20% of patients with molar gestations. These cysts are thin walled and highly vascular, and develop as a response to ovarian hyperstimulation from the high hCG levels produced by hydatidiform moles. They typically regress spontaneously over several weeks following molar evacuation. It is preferable to avoid surgery or ovarian manipulation in patients with uncomplicated theca lutein cysts. Rarely, because of abdominal distension and respiratory compromise, they may require aspiration with ultrasonic guidance. Enlarged cysts may undergo torsion, infarction, or rupture, and oophorectomy should be considered in these circumstances.

Some centers prescribe prophylactic short courses of methotrexate or dactinomycin chemotherapy at the time of molar evacuation to decrease the incidence of malignant sequelae in patients with high-risk features. However, prophylactic chemotherapy does not eliminate the chance of subsequent malignancy nor the need for hCG surveillance. Routine prophylactic chemotherapy at the time of molar evacuation for patients with uncomplicated hydatidiform mole is not recommended if reliable hCG surveillance is available.

Surveillance Following Molar Evacuation

The wide availability of sensitive hCG assays provides a backbone for postmolar evacuation triage and therapy. Several sensitive hCG assays are available, measuring the ß-subunit of hCG by radioimmunoassay or by radioimmunometric assay. These assays can detect hCG levels elevated above the baseline variations of pituitary gonadotropins. These sensitive hCG assays should be used to monitor patients with GTN after evacuation of hydatidiform mole and during therapy of patients with malignant GTN. Urinary or serum pregnancy screening tests should not be used to follow patients with GTN, because the assays do not have sufficient sensitivity to permit detection of minimal elevations of hCG levels.

The recommendations for postmolar follow-up include determination of serum ß-hCG levels every 1 to 2 weeks after evacuation until hCG level is undetectable. Subsequently, hCG levels should be determined for 2 to 4 weeks after the first normal level to confirm spontaneous hCG regression, followed by hCG surveillance every 1 to 2 months for 6 months after the first normal hCG level. In addition, hCG levels should be checked 6 weeks after all subsequent pregnancies due to the patients' elevated risk of subsequent GTN.

Most women with molar pregnancies undergo hCG level regression after evacuation to normal limits and require no further therapy. Strict contraception is recommended during hCG surveillance to avoid an intercurrent pregnancy that would interfere with monitoring. The hCG elevation of an early normal pregnancy may mask the hCG rise associated with postmolar malignant GTN.

Although an early report implicated oral contraceptives as a risk factor for postmolar malignant GTN, subsequent investigators found no significant increase in the risk of malignant GTN associated with the use of oral contraceptives after molar evacuation. After completion of 6 months of hCG level surveillance with normal results, patients may attempt pregnancy if desired. Because the risk of recurrent molar pregnancy is about 1%, they should undergo early screening of all pregnancies with ultrasonography to exclude recurrent molar gestations. Figure 57.2 illustrates an algorithm for diagnosis and follow-up of patients with hydatidiform mole.

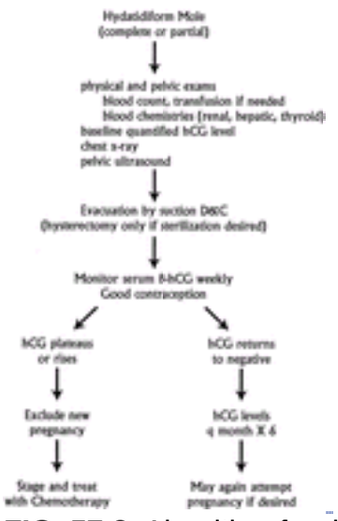

FIG. 57.2. Algorithm for diagnosis and treatment of a patient with hydatidiform mole.

False-positive hCG Test Results

The sensitivity and specificity of serum ß-hCG levels makes it an ideal tumor marker in both diagnosis and surveillance of GTN. However, hCG, a glycoprotein comprised of both a- and ß-subunits, linked by eight oligosaccharides, has significant heterogeneity in its structure and antigenicity. Free subunits, degraded molecules, molecules with irregular side chains, and fragments of hCG are present in sera of women in pregnancy, with trophoblastic disease, and with nontrophoblastic neoplasms. Furthermore, hCG variants that include hyperglycosylated hCG, nicked hCG, hCG missing the ß-subunit C-terminal peptide, free ß-subunit, and nicked free ß-subunit may also be present. Although all professional laboratory hCG assays use antibodies to different sites on the ß-subunit, variations in antibody use may lead to measurements of different hCG-related molecules.

The heterogeneity of hCG and the variability between different hCG assays may result in false-positive test results. The phenomena of “phantom hCG” and “phantom choriocarcinoma” have resulted in erroneous diagnoses of invasive GTN and choriocarcinoma, with unnecessary subsequent chemotherapy and hysterectomy. The U.S.A. hCG Reference Service recommends that when false-positive hCG results are suspected, urine hCG testing for detection of the ß-core fragment, the terminal

degradation product of hCG and its variants, should be performed. Evaluation also should include serum testing by a laboratory using a different ß-hCG assay. In cases with absence of urine hCG and failure to detect serum ß-hCG by an alternative laboratory, the initial elevated level likely represents a false-positive test result.

False-positive results also may be due to the presence of heterophilic antibodies. These antibodies are able to complete with hCG in antibody binding used in commercial hCG assays, and may result in persistent positive results. Treatment with a heterophilic antibody blocking reagent has been shown to reduce the incidence of false-positive results, and these reagents have been added to the protocol used by the U.S.A. hCG Reference Service.

MALIGNANT GESTATIONAL TROPHOBLASTIC NEOPLASMS

Malignant Sequelae Following Molar Evacuation

The spectrum of malignant sequelae after evacuation of hydatidiform mole includes intrauterine molar proliferation without invasion (i.e., retained mole), invasive mole, choriocarcinoma, and the clinical identification of metastatic GTN without a histologic diagnosis. The purpose of hCG level surveillance is early detection of trophoblastic neoplasia before the development of complications related to local proliferation, uterine invasion, or distant metastasis.

Before the development of effective chemotherapy for GTN, approximately 9% of women required hysterectomy for malignant sequelae after evacuation of hydatidiform mole. Many series of patients have been reported since the development of chemotherapy, with a wide range in the rate (9% to 36%) of patients requiring therapy after evacuation of hydatidiform mole. These observed differences in the frequency of malignant GTN may reflect inclusion of partial moles in some studies, a different incidence of metastatic disease in patient populations, or different hCG level regression criteria used to define malignant GTN and assign therapy in the various studies.

Histologic and clinical features can be used to define high- and low-risk groups of patients after molar evacuation but are of little value in determining the need for therapy in individual patients. Trophoblastic proliferation, uterine enlargement, theca lutein cysts, respiratory distress syndrome after molar evacuation, and postevacuation uterine hemorrhage all are associated with a higher frequency of postmolar malignant GTN. Prompt uterine involution and regression of theca lutein cysts are favorable prognostic signs. However, the definitive method for predicting development of postmolar malignant GTN is observation of the pattern of hCG regression.

Serial hCG levels are obtained at 1-week intervals with chest radiographs every 2 to 4 weeks as long as the hCG levels are elevated. Patients are treated with chemotherapy according to several criteria as follows: hCG level rise, hCG level plateau for 3 or more consecutive weekly levels, appearance of metastasis, or histologic evidence of invasive mole or choriocarcinoma.

Diagnosis

Malignant GTN is diagnosed in women with rising or paltering hCG levels or identification of metastasis after evacuation of a hydatidiform mole. Histologic diagnosis of invasive mole or choriocarcinoma is a criterion for malignant GTN. Patients who developed malignant GTN after nonmolar gestations often sought treatment for atypical symptoms attributable to distant metastases. Gastrointestinal or urologic hemorrhage, hemoptysis, or neurologic symptoms due to cerebral hemorrhage may be the clinical features. Irregular uterine bleeding or amenorrhea may be observed. Rarely, patients have clinical hyperthyroidism. Under these circumstances, the diagnosis of malignant GTN is facilitated with serum hCG testing and the exclusion of normal pregnancy. The possibility of metastatic GTN should be considered in any woman of the reproductive age group who has metastatic disease involving the lungs or distant sites from an unknown primary site of malignancy.

After the diagnosis has been made, the following clinical, laboratory, and radiographic evaluations are recommended for a patient with malignant GTN:

- Physical and pelvic examinations
- Baseline hCG level
- Complete blood count and baseline chemistry determinations
- Chest radiograph
- Pelvic ultrasonography
- Computed tomography (CT) of brain, chest, and abdomen–pelvis

Before a woman is treated for malignant GTN with chemotherapy, it is essential to exclude an intrauterine pregnancy with a pelvic ultrasonographic scan. Approximately 50% of patients with malignant GTN have pulmonary metastasis detected by routine chest radiographs. The clinical significance of small pulmonary metastases detected only by whole-lung CT scans is unknown. Because CNS and hepatic metastases may develop without clinical or radiographic evidence of pulmonary or vaginal metastases, the remainder of the radiologic studies are recommended strongly, regardless of whether abnormalities are detected by physical examination or chest radiograph. The role of magnetic resonance imaging studies or positron emission tomography in the evaluation of women with GTN is not yet defined.

Occult CNS metastases may be detected using lumbar puncture with simultaneous serum and cerebrospinal fluid (CSF) hCG determinations. The plasma-to-CSF hCG ratio is normally greater than 60:1 in the absence of CNS metastasis and is usually less than 60:1 in patients with CNS metastasis. Some investigators have reported falsely lowered plasma-to-CSF hCG ratios for patients without GTN undergoing first-trimester abortions and for patients with nonmetastatic GTN. CSF hCG determinations are most frequently utilized in evaluation of patients who have developed resistance to chemotherapy, with residual disease documented by elevated serum hCG levels, when the site of disease is obscure. Routine CSF hCG determination, however, is not part of initial GTN staging.

Surgery may be useful for patients with malignant GTN, but it rarely is indicated for staging or diagnosis alone. Histologic evaluation of tissue obtained by D&C may confirm the diagnosis and may be useful in the patient experiencing vaginal bleeding, but the procedure carries the risk of uterine perforation and hemorrhage. Laparoscopy, craniotomy, and thoracotomy rarely are justified to establish the primary diagnosis of malignant GTN, because this diagnosis can be made on the basis of elevated hCG levels with radiographic evidence of metastasis after excluding pregnancy.

All patients with malignant GTN must be thoroughly evaluated for metastatic disease. Selection of the initial therapy and subsequent survival largely depend on identification of poor prognostic factors in patients with metastatic disease. Figure 57.3 demonstrates an algorithm of management of malignant GTN.

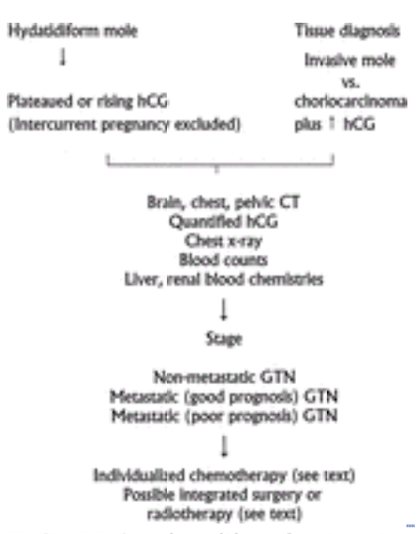

FIG. 57.3. Algorithm for treatment of a patient with malignant gestational trophoblastic disease.

Staging and Classification

Due to considerable overlap in the clinical course of the histologic entities that constitute malignant GTN, and because a complete histologic evaluation of an individual patient with GTN is rarely possible, a variety of classification and staging systems have been used to assess risk and assign initial therapy and prognosis for these

patients. Several clinical findings are important in categorizing patients for treatment, and any classification system must take these factors into consideration to be clinically useful.

A simple clinical classification system based on risk factors for malignant sequelae may be used to assign initial therapy for patients with malignant GTN. This system takes into account factors that predict failure of initial single-agent chemotherapy to effect cure and allows identification of patients who would benefit from initial aggressive multidrug chemotherapy (Table 57.2). After radiographic studies have been completed, the patient is considered to have nonmetastatic GTN if there is no evidence of extrauterine spread of disease. This category is not subdivided into good-prognosis and poor-prognosis categories because these patients can achieve approximately 100% remission rates using current chemotherapeutic regimens. The histologic diagnosis of choriocarcinoma mandates treatment but does not change the initial choice of therapy. If there is any clinical or radiographic evidence of extrauterine metastasis, the patient is classified as having metastatic GTN. These patients are divided further into good-prognosis and poor-prognosis categories on the basis of factors that predict the failure of primary single-agent chemotherapy with methotrexate or dactinomycin.

I. Nonmetastatic GTN
A. Not defined in terms of good versus poor prognosis
II. Metastatic GTN
A. Good prognosis (i.e., absence of high-risk factors)
1. Pretreatment serum β-hCG level <40,000 mIU/mL
2. Less than 4-month duration of symptoms attributable to disease
3. No evidence of brain or liver metastasis
4. No significant prior chemotherapy
5. No antecedent term pregnancy
B. Poor prognosis (i.e., any single high-risk factor)
1. Pretreatment serum β-hCG level >40,000 IU/mL
2. More than 4-month duration of symptoms attributable to disease
3. Brain or liver metastasis or both
4. Failed prior chemotherapy
5. Antecedent term pregnancy

GTN, gestational trophoblastic neoplasms; hCG, human chorionic gonadotropin.

TABLE 57.2. *Clinical classification of malignant gestational trophoblastic neoplasia*

The International Federation of Gynecologists and Obstetricians (FIGO) developed a staging system for GTN that is based on the anatomic site of disease, conforming to the FIGO staging systems for other gynecologic malignancies:

Stage I: Disease confined to the uterine corpus
Stage II: Metastasis to the vagina or pelvis
Stage III: Metastasis to the lung
Stage IV: Other extrapelvic metastasis

Although essentially all patients with stage IV disease are at high risk, this system does not recognize the prognostic importance of other factors, such as the initial hCG level, other direct and indirect measurements of tumor burden, or duration of disease.

The World Health Organization (WHO) devised a prognostic index scoring system (Table 57.3) based on Bagshawe's analysis of the prognostic factors of his patient population. In addition to using a weighted scale for risk factors analyzed by the clinical classification, such as hCG level and duration of disease, the system identifies a graded range of additional risk factors. Ectopic pregnancies and abortions have an intermediate risk between molar and term pregnancies. Blood types and age contribute to the score. The size of the largest tumor, the number of metastatic sites, and site of metastasis are considered indirect approximations of tumor burden. After computation of each risk factor, the patient is considered to be at low risk if the score is 4 or less, at intermediate risk with a score of 5 to 7, and at high risk with a score of 8 or more. The WHO prognostic index scoring system has been found to correlate well with survival after conventional combination chemotherapy protocols. Not all of the WHO factors, however, have been evaluated critically to determine whether the graded scoring system is valid. Figure 57.3 illustrates a plan of evaluation and therapy for patients with malignant GTN.

TABLE 57.3. *World Health Organization prognostic scoring system for gestational trophoblastic neoplasia*

Therapy

Before the development of effective chemotherapy against malignant GTN, surgical therapy was not successful in curing most patients, even women with nonmetastatic disease confined to the uterus. Since the introduction of methotrexate in the 1950s, malignant GTN has become the most curable of human solid tumors. Therapy should be conducted by physicians who have considerable experience in the management of these diseases, and a reliable hCG assay should be available so that therapeutic changes can be instituted quickly when necessary. Although chemotherapy has largely supplanted surgery and radiation therapy as the first-line management of malignant GTN, these modalities continue to play an important role in the management of patients with malignant GTN.

Chemotherapy The initial chemotherapy should be selected on the basis of one of the systems of classification of malignant GTN (Table 57.4). Patients with nonmetastatic and good-prognosis GTN are treated initially with single-agent chemotherapy regimens using methotrexate or dactinomycin. Patients with poor-prognosis metastatic GTN require initial chemotherapy using combinations of active agents. Currently, the most frequently used combination is the EMA-CO regimen (etoposide, methotrexate with folic acid rescue, dactinomycin alternating with cyclophosphamide, and vincristine [Oncovin]).

TABLE 57.4. *Chemotherapy for malignant gestational trophoblastic neoplasms*

Chemotherapy for Nonmetastatic Disease The most widely used initial chemotherapy regimen for patients with nonmetastatic GTN includes courses of alternating doses of methotrexate (1 mg/kg [maximum 50 mg] on days 1, 3, 5, and 7) and folinic acid rescue (0.1 mg/kg on days 2, 4, 6, and 8), both administered intramuscularly. A variety of other agents and schedules, including daily and “pulsed” dactinomycin, also have been used to treat nonmetastatic GTN, with essentially equivalent remission rates. Reports indicate that weekly courses of methotrexate administered intravenously as a single dose of 30 mg/m ^{2} have an advantage over other schedules of methotrexate in reducing cost and toxicity and are equally effective. Close hematologic and renal and liver chemistry monitoring must be done during therapy. Multiple studies show remission rates in this stage of disease to approach 100% when patients are treated appropriately. Although methotrexate and dactinomycin continue to be the mainstays of treatment for low-risk disease, there is no consensus on a single superior regimen. The Gynecologic Oncology Group, a multicenter collaborative clinical trials association, is accruing patients into a randomized, phase III trial of weekly intravenous methotrexate versus pulsed dactinomycin as primary management for low-risk GTN. The major goals of therapy for patients with nonmetastatic GTN include administration of active, relatively nontoxic regimens of chemotherapy with close hCG level monitoring. For most of these patients, chemotherapy alone is adequate treatment, and surgery is unnecessary. However, primary hysterectomy may be used for patients who desire sterilization, because this may reduce the number of cycles of chemotherapy necessary to achieve remission and cure.

Chemotherapy for Good-prognosis Metastatic Disease Initial therapy with repetitive cycles of 5-day courses of single-agent methotrexate or dactinomycin is preferred for patients with good-prognosis metastatic GTN. For these patients without high-risk factors, the ultimate sustained remission rate also approaches 100%. Patients are treated initially with repetitive 5-day cycles of methotrexate administered intravenously at a dose of 0.4 mg/kg per day or dactinomycin administered intravenously daily at a dose of 500 μg. Chemotherapy is repeated every 14 days. Again, hematologic and renal and liver chemistry monitoring must be done, and colony-stimulating factors may be required to keep the treatment on schedule. Remission rates with either agent are approximately 60%, and most patients with drug-resistant disease are salvaged with the alternative single agent. Occasionally, patients may require hysterectomy or other surgical procedures to extirpate loci of persistent disease or else require a change in therapy to a multidrug chemotherapy regimen.

Chemotherapy for Poor-prognosis Disease Multidrug chemotherapy is used as the initial therapy for patients with poor-prognosis metastatic GTN. Survival is poor for this group if the initial therapy is with only a single agent, and it is important to diagnose poor-prognosis, high-risk features in these patients so that appropriate initial therapy may be instituted in a timely fashion. The most successful and least toxic multiagent regimen is EMA-CO. Other salvage regimens include MAC (methotrexate,

actinomycin D, and cyclophosphamide [Cytoxan]), and the modified Bagshawe regimen of hydroxyurea, methotrexate, vincristine, cyclophosphamide, dactinomycin, and doxorubicin (Adriamycin). Because VP-16, cisplatin, 5-fluorouracil, vinca alkaloids, and bleomycin all demonstrate activity against GTN, other salvage regimens are based on combinations employing some of these agents. Regardless of regimen, another cycle of chemotherapy is administered as soon as toxicity from the previous cycle has cleared. Use of stem cell factor support should be used when needed to keep the treatment on schedule. Although toxicity may be marked with these combinations, aggressive initial multiagent chemotherapy usually is necessary to ensure optimal survival for patients in this category. Patients with poor-prognosis metastatic GTN should be treated at centers that specialize in the therapy of patients with GTN. Physician experience with GTN and these aggressive multimodality therapies appears to improve the outcome for these patients. Patients with poor-prognosis metastatic GTN who have failed standard chemotherapy regimens are extremely challenging when designing appropriate coordination of chemotherapy and other therapeutic modalities to achieve salvage. Frequently, patients must be treated without regard for toxicity and must be supported through episodes of profound bone marrow suppression, sepsis, and nutritional deprivation to have a chance at salvage.

Surgical and Radiation Therapy

Hysterectomy Due to improvements in chemotherapy, hysterectomy rarely is indicated as the initial therapy for women with malignant GTN. However, for patients with nonmetastatic or good-prognosis metastatic GTN with uterine disease, hysterectomy appears to decrease the duration of hospital stay and number of courses of chemotherapy required to achieve remission. Delayed or secondary hysterectomy is required as salvage therapy for approximately 10% of patients in these categories, but chemotherapy alone is successful in curing approximately 85% of patients with nonmetastatic and good-prognosis metastatic GTN. Among women with poor-prognosis metastatic GTN, preservation of childbearing capacity must be of secondary importance, but primary or delayed hysterectomy does not appear to offer as many benefits as in the therapy of patients with low-risk disease. Surgical procedures for the purpose of removing sites of GTN are performed during a cycle of chemotherapy. Theoretically, this prevents dissemination of disease caused by embolization of GTN during the surgical manipulation of tissues. The complications of surgery and wound healing do not appear to be increased using this approach.

Thoracotomy Thoracotomy with pulmonary segmental resection has been the most frequently performed procedure other than hysterectomy to remove drug-resistant disease. The radiographic regression of pulmonary nodules may lag far behind the response measured by hCG levels, and the persistence of a lung nodule after hCG normalization should not necessarily be interpreted as indicating persistent disease. There have been reports of success with resection of solitary pulmonary nodules in carefully selected women with drug-resistant disease. Before considering pulmonary resection, it is important to exclude the possibility of disease elsewhere. If the patient has not had a hysterectomy, occult pelvic GTN should be evaluated with arteriography or other imaging techniques, such as magnetic resonance imaging. Prompt hCG remission after pulmonary resection predicts a favorable outcome.

Brain and Liver Metastasis Whole-brain and whole-liver irradiation are used often as adjuncts to chemotherapy in the treatment of patients with metastasis to these sites. Whole-brain irradiation of 3,000 cGy over 10 days should be instituted immediately in conjunction with chemotherapy after brain metastasis is diagnosed. The rationale for this treatment is to prevent hemorrhage from these highly vascular metastases. With this approach, survival rates of approximately 85% are achieved for patients receiving primary therapy for brain metastasis; survival rates of approximately 50% are achieved for all patients with brain metastasis, including those developing metastasis during chemotherapy or at the time of recurrence. An alternate approach includes the combined use of high-dose systemic methotrexate with intermittent intrathecal methotrexate. Craniotomy is not often required for the primary therapy or diagnosis of brain metastasis from GTN and usually is not successful when used alone. However, neurosurgical consultation should be obtained early in the course of therapy in the event that hemorrhage into brain lesions occurs and craniotomy is required for stabilization of the patient. Whole-liver irradiation of approximately 2,000 cGy delivered over 10 days may be used to treat liver metastasis and prevent hepatic hemorrhage. Some investigators have not used hepatic irradiation to avoid exacerbation of the toxic hepatic effects of chemotherapy. Others have advocated selective occlusion of the hepatic artery by means of ligation or embolization when bleeding has occurred. Patients with hepatic metastasis have a poor prognosis and require aggressive chemotherapy, with careful monitoring during therapy to maximize the chances for survival. Whole-organ irradiation does not appear to compromise tolerance of aggressive chemotherapy.

Placental Site Trophoblastic Tumors PSTT is a rare placental neoplasm that is histologically and clinically distinct from other forms of GTN. PSTTs lack significant volume of syncytiotrophoblast elements and do not secrete high levels of hCG. As such, serum hCG levels are not a reliable tumor marker for PSTT as they are in other forms of GTN. PSTT usually is locally aggressive, with invasion into the myometrium. It typically is resistant to traditional chemotherapeutic agents. Most women with PSTT require hysterectomy, although anecdotal reports suggest a minority may be cured by D&C alone. Rarely, PSTT may pursue a more aggressive course, characterized by distant metastasis and rapidly progressive disease.

Monitoring Therapy

Laboratory Evaluations During chemotherapy, hematologic, renal, and hepatic indices should be monitored carefully. Toxicity from methotrexate-based and dactinomycin-based chemotherapy is relatively predictable. Unless a patient is receiving salvage chemotherapy for drug-resistant or recurrent GTN, new cycles of therapy should be withheld unless the total leukocyte count is greater than 3,000 cells/mm ^{3}, the platelet count is greater than 100,000 cells/mm ^{3}, and the renal and hepatic indices are normal. Radiographic studies of metastatic lesions and pelvic examination should be repeated frequently to monitor response to therapy. More important than radiographic surveillance is closely following the hCG level response during therapy. Sensitive assays of the hCG levels should be performed at 1-week intervals during therapy. Chemotherapy should be changed if the hCG titer has not dropped at least 25% after a treatment cycle or if toxicity does not permit adequate dosage or frequency of administration.

Human Chorionic Gonadotropin Level Remission and Surveillance Complete remission is defined as three consecutive weekly hCG levels in the normal, undetectable range. After remission has been achieved, hCG levels should be followed every 1 to 2 weeks for the first 3 months after completion of therapy, every 2 to 4 weeks for the subsequent 3 months, and every 1 to 2 months for the completion of the first year of surveillance. Recurrent episodes of GTN usually develop within a few months after completion of therapy, but late recurrences develop in a few cases. The assay of hCG levels should be repeated indefinitely at 6-month intervals. Patients are counseled to avoid pregnancy through the first year of hCG surveillance; most are treated with oral contraceptives for efficiency and to avoid low-level interference with the hCG assays caused by luteinizing hormone.

Prevention of Recurrent Disease

Despite the accuracy of hCG assays, a tumor burden of 10 ^{4} cells may exist despite normal serum hCG levels. Recurrence rates after therapy for GTN have been 3% to 26%, depending on the patient population being studied. Patients with poor-prognosis metastatic GTN usually have a much higher recurrence rate than patients with low-risk disease. Most investigators agree that consolidation chemotherapy should be administered beyond the first normal hCG level. Typically, patients undergo one additional cycle of chemotherapy beyond the first normal hCG level for nonmetastatic disease, two cycles of consolidation chemotherapy for good-prognosis metastatic GTN, and three to four cycles of maintenance chemotherapy for poor-prognosis metastatic GTN. Toxicity must be considered in continuing therapy for these patients.

Reproduction After Therapy

Most women treated for GTN are cured by chemotherapy without resorting to hysterectomy. Several reports have documented that there is little or no increased risk of congenital malformation of infants during subsequent pregnancies. There may be a slight increase in the incidence of spontaneous abortions in this population, but this increase may be an artifact of increased hCG surveillance and identification of preclinical pregnancies in women who have previously received treatment for GTN. There is also an increased incidence of repeat molar gestation in patients who have had a hydatidiform mole (approximately 1%). Patients who have received intensive therapy for poor-prognosis metastatic GTN often undergo hysterectomy during therapy or may develop ovarian failure as a result of prolonged multidrug chemotherapy. Only a few patients in this category with uterine conservation are able to conceive or desire to attempt pregnancy after therapy.

Although the risk of congenital anomalies is not increased significantly after chemotherapy for malignant GTN, obstetric complication rates may be. Major obstetric complications can be observed in as many as 9% of these pregnancies. The incidence of placenta accreta, in particular, appears to be increased.

Women who have been treated successfully for GTN should be advised that pregnancy should be deferred for at least 1 year after therapy to allow for hCG level surveillance. They should be reassured about the low incidence of congenital malformations and recurrent GTN in subsequent pregnancies. An ultrasonographic scan should be performed early in pregnancy to exclude the possibility of recurrent molar gestation. A chest radiograph and serum hCG level should be obtained 6 to 8 weeks after delivery to screen for the rare case of recurrent choriocarcinoma developing after a subsequent normal pregnancy.

SUMMARY POINTS

- Gestational trophoblastic neoplasia represents a spectrum of human tumors, ranging from benign with potential malignant sequelae to highly malignant.
- Primary hydatidiform mole (complete) usually becomes apparent as a pregnancy with threatened first-trimester vaginal bleeding. Other frequent findings include discordant uterine size, ovarian cystic enlargement, and hyperemesis, but may include hyperthyroidism and preeclampsia.
- Evacuation of hydatidiform mole is best done by suction D&C, with caution used regarding trophoblastic deportation and pulmonary embolization.
- Individualization of therapy is critical for successful treatment of patients with GTN. Although chemotherapy is the primary modality for therapy, surgery and radiotherapy may also have a role.
- The hCG level is a sensitive and reliable marker for GTN and can be used effectively to aid in diagnosis, monitor therapy, and maintain follow-up evaluation.

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Chapter 58

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Medical Ethics

MEDICAL ETHICS
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MEDICAL ETHICS

Physicians in obstetric and gynecologic practice confront ethical concerns and issues that arise when the physician's judgment about what is in the patient's interest differs from the patient's judgment about what is in her or her fetus's interest. One way to manage such differences is to assert the primacy of the physician's judgment. This strategy has been discredited in medical ethics, because it leads to paternalism in the care of patients. Paternalism can occur when medical judgments fail to take account of the patient's values and beliefs regarding her own health and medical care. To avoid paternalism, one might opt for the alternative of the primacy of the patient's judgment. The problem with this approach is that it reduces the physician to the status of a mere technician and may require the physician to act in ways that contradict reasonable medical judgment.

In this chapter we apply the methods of ethics to the problem of differences between the obstetrician-gynecologist and the patient about what is in the patient's interest in a way that avoids these two extremes. We develop a framework for clinical judgment and decision making about the ethical dimensions of the obstetrician-gynecologist–patient relationship. To achieve this goal, we first define ethics, medical ethics, and the fundamental ethical principles of medical ethics, beneficence, and respect for autonomy. Second, we show how these two principles should interact in gynecologic clinical judgment and practice. Third, we show how these two principles should interact in obstetric judgment and practice, emphasizing the example of cesarean delivery. Fourth, we examine ethical issues in managed care, emphasizing the virtues of the physician as a professional. We emphasize a preventive ethics approach that appreciates the potential for ethical conflict and adopts ethically justified strategies to prevent those conflicts from occurring. Preventive ethics helps to build and sustain a strong physician–patient relationship.

ETHICS, MEDICAL ETHICS, AND ETHICAL PRINCIPLES

Ethics is the disciplined study of morality and draws on the disciplines of the humanities, especially philosophy. Medical ethics is the disciplined study of morality in medicine and concerns the obligations of physicians and health care organizations to patients, as well as the obligations of patients. It is important not to confuse ethics with the many sources of morality in a pluralistic society. These include, but are not limited to, law, our political heritage as a free people, the world's religions (most of which now exist in our country), ethnic and cultural traditions, families, the traditions and practices of medicine (including medical education and training), and personal experience. These sources of morality are useful reference points for ethical inquiry.

The traditions and practices of medicine, including education and training, constitute an obvious source of morality for physicians. They provide an important reference point for ethics in medicine, because they are based on the obligation to protect and promote the interests of the patient. This obligation tells physicians what morality in medicine ought to be, but in very general, abstract terms. Providing a more concrete, clinically applicable account of that obligation is the central task of medical ethics.

To make concrete the general obligation of protecting and promoting the interests of the patient, medical ethics focuses on the question of “How *ought* the physician conduct himself or herself with patients?” Among relevant tools of ethics for answering this question are ethical principles, because they help the physician to interpret and implement his or her general moral obligation to protect and promote the interests of the patient, which has been the traditional moral foundation of the physician–patient relationship.

Principle of Beneficence

The principle of beneficence requires one to act in a way that is expected reliably to produce the greater balance of goods over harms in the lives of others. To put this principle into clinical practice requires a reliable account of the goods and harms relevant to the care of the patient and of how those goods and harms should be reasonably balanced against each other when not all of them can be achieved in a particular clinical situation, such as a request for an elective cesarean delivery. In medicine, the principle of beneficence requires the physician to act in a way that is expected to produce reliably the greater balance of clinical goods over harms for the patient.

Beneficence-based clinical judgment has an ancient pedigree, with its first expression found in the Hippocratic Oath and accompanying texts. It makes an important claim: to interpret reliably the interests of the patient from medicine's perspective. This perspective is provided by accumulated scientific research, clinical experience, and reasoned responses to uncertainty. It is thus not the function of the individual clinical perspective of a particular physician and therefore should not be based merely on the clinical impression or intuition of an individual physician.

On the basis of this rigorous clinical perspective, which should be evidence based as often as possible, beneficence-based clinical judgment identifies the goods that can be achieved for the patient in clinical practice based on the competencies of medicine. The goods that medicine is competent to seek for patients are the prevention and management of disease, injury, handicap, and unnecessary pain and suffering and the prevention of premature or unnecessary death. Pain and suffering become unnecessary when they do not result in achieving the other goods of medical care, for example, allowing a woman to labor without effective analgesia.

There is an inherent risk of paternalism in beneficence-based clinical judgment. By this we mean that beneficence-based clinical judgment, if it is *mistakenly* considered to be the sole source of moral responsibility and, therefore, moral authority in medical care, invites the unwary physician to conclude that beneficence-based judgments can be imposed on the patient in violation of her autonomy. Paternalism is a dehumanizing response to the patient and, therefore, should be avoided in the practice of obstetrics and gynecology.

The preventive ethics response to this inherent paternalism is for the physician to explain the diagnostic, therapeutic, and prognostic reasoning that leads to the clinical judgment about what is in the interest of the patient so that the patient can assess that judgment for herself. This general rule can be put into clinical practice in the following way. The physician should disclose and explain to the patient the major factors of this reasoning process, including matters of uncertainty. (Note that this does not require that the patient be provided with a complete medical education.) The physician should then explain how and why other clinicians might reasonably differ from this clinical judgment. The physician should then present a well-reasoned response to this critique. The outcome of this process is that beneficence-based clinical judgments take on a rigor that they sometimes lack, and the process of their formulation includes explaining them to the patient. It should be apparent that beneficence-based clinical judgment frequently will result in the identification of a continuum of clinical strategies that protect and promote the patient's interests, such as the choice of a particular method of contraception. Awareness of this feature of beneficence-based clinical judgment provides an important preventive ethics antidote to paternalism by increasing the likelihood that one or more of these medically reasonable, evidence-based alternatives will be acceptable to the patient. This feature of beneficence-based clinical judgment also provides a preventive ethics antidote to “gag” rules that restrict physician's communications with the managed care patient. All beneficence-based alternatives must be identified and explained to all patients, regardless of how the physician is paid, especially those that are well

established in evidence-based obstetrics and gynecology.

The process of explaining beneficence-based clinical judgment enhances the patient's ability to understand and deal effectively with the technical aspects of medical care, an important consideration in obstetric-gynecologic practice (e.g., prophylactic oophorectomy at the time of hysterectomy or the nature and limits of obstetric ultrasonography). Data suggest the need for such enhancement. The Louis Harris survey prepared for the President's Commission on Ethics in Medicine presents an important finding: “The vast majority of physicians report that they address most aspects of the condition and treatment with their patients as a matter of course. This is substantiated by the large majority of the public, who report that their physicians usually discuss these matters with them.” This survey also reports a “large and reliable difference of approximately 15 to 25 percentage points” between the proportion of physicians who report themselves as discussing some aspects of medical care and the proportion of the public who report that their physicians discuss such matters as diagnosis and prognosis, nature and purpose of treatment, pros and cons of the treatment, and side effects. The process of disclosure described above, if adopted as a standard of care, could well close these significant gaps in the care of female and pregnant patients, especially in the managed care setting.

One advantage for the physician in carrying out this approach to communicating with the patient would be, we believe, to increase the likelihood of compliance. This is an especially pertinent consideration in gynecologic practice, in which the patient often must monitor herself for clinical changes (e.g., a woman at risk for ectopic pregnancy) and take an active role in preventive medicine (e.g., breast self-examination) as well as in obstetric practice (e.g., self-observation for unusual weight gain or bleeding). Another advantage would be to provide the patient with a better-informed opportunity to make a decision about whether to seek a second opinion. The approach outlined above should make such a decision less threatening to her physician, who already has shared with the patient the limitations on clinical judgment. A final advantage may be a reduction in the percentage (20%) of physicians who reportedly dismiss patients who disagree with them and in the high percentage (36%) of patients who report that they have stopped using physicians who disagree with them, as reported in the same Louis Harris survey.

Principle of Respect for Autonomy

In contrast to the principle of beneficence, there has been increasing emphasis in the literature of ethics in medicine on the principle of respect for autonomy. This principle requires one always to acknowledge and carry out the value-based preferences of others, unless there is compelling ethical justification for not doing so, (e.g., prescribing antibiotics for viral respiratory infections). The female or pregnant patient increasingly brings to her medical care her own perspective on what is in her interest. The principle of respect for autonomy translates this into autonomy-based clinical judgment. Because each patient's perspective on her interests is a function of her values and beliefs, it is impossible to specify the goods and harms of autonomy-based clinical judgment in advance. Indeed, it would be inappropriate for the physician to do so, because the definition of her goods and harms and their balancing are the prerogative of the patient. Not surprisingly, autonomy-based clinical judgment is strongly antipaternalistic in nature.

To understand the moral demands of this principle, we need an operationalized concept of autonomy to make it relevant to clinical practice. To do this, we identify the following three sequential autonomy-based behaviors on the part of the patient: (a) absorbing and retaining information about her condition and alternative diagnostic and therapeutic responses to it, (b) understanding that information (i.e., evaluating and rank ordering those responses and appreciating that she could experience the risks of treatment), and (c) expressing a value-based preference. The physician has a role to play in each of these. They are, respectively, (a) to recognize the capacity of each patient to deal with medical information (and not to underestimate that capacity), provide information (i.e., disclose and explain all medically reasonable alternatives, supported in beneficence-based clinical judgment), and recognize the validity of the values and beliefs of the patient, (b) not to interfere with but, when necessary, to assist the patient in her evaluation and ranking of diagnostic and therapeutic alternatives for managing her condition, and (c) to elicit and implement the patient's value-based preference.

The legal obligations of the physician regarding informed consent were established in a series of cases during the 20th century. In 1914, *Schloendorff v. The Society of The New York Hospital* established the concept of simple consent, that is whether the patient says “yes” or “no” to medical intervention. To this day in the medical and bioethics literature, this decision is quoted: “Every human being of adult years and sound mind has the right to determine what shall be done with his body, and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages.” The legal requirement of consent further evolved to include disclosure of information sufficient to enable patients to make informed decisions about whether to say “yes” or “no” to medical intervention. There are two legal standards for such disclosure. The professional community standard defines adequate disclosure in the context of what the relevantly trained and experienced physician tells patients. The reasonable person standard, which has been adopted by most states, goes further and requires the physician to disclose “material” information, what the lay person of average sophistication should not be expected to know. This second standard has emerged as the ethical standard, and we therefore urge obstetrician-gynecologists to adopt it. On this standard the physician should disclose to the patient her or the fetus's diagnosis (including a differential diagnosis when that is all that is known), the medically reasonable alternatives to diagnose and manage the patient's condition, and the short-term and long-term benefits and risks of each alternative.

A particularly important dimension of informed consent in practice involves what have come to be known as “advance directives.” Spurred by the famous case of Karen Quinlan in New Jersey in 1976, all states have enacted advance directive legislation.

The basic idea of an advance directive is that a patient, when autonomous, can make decisions regarding her medical management in advance of a time during which she becomes incapable of making health care decisions. The ethical dimensions of autonomy that are relevant here are the following:

1. A patient may exercise her autonomy now in the form of a request for or refusal of life-prolonging interventions.
2. Autonomy-based request or refusal, expressed in the past and left unchanged, remains in effect for any future time during which the patient loses autonomy.
3. That past autonomy-based request or refusal should, therefore, translate into physician obligations at the time the patient becomes unable to participate in the informed consent process.
4. In particular, refusal of life-prolonging medical intervention should translate into the withholding or withdrawal of such interventions, including artificial nutrition and hydration.

The living will is an instrument that permits the patient to make a direct decision, usually to refuse life-prolonging medical intervention in the future. The living will becomes effective when the patient is a “qualified patient,” usually terminally or irreversibly ill, and is not able to participate in the informed consent process as judged by her physician. Court review is not required. Obviously, terminally or irreversibly ill patients who are able to participate in the informed consent process retain their autonomy to make their own decisions. Some states prescribe the wording of the living will and others do not. The physician should become familiar with the legal requirements in his or her own jurisdiction. A living will, to be useful and effective, should be as explicit as possible. The legal basis for the living will is the legal right of self-determination, the right of any competent adult to determine what shall be done to her body. A number of state courts have made it clear that this right extends to the refusal of both hydration and nutrition. The reader should become familiar with hospital policies on advance directives, which should reflect applicable law.

The concept of a durable power of attorney is that any autonomous adult, in the event that that person later becomes unable to participate in the informed consent process, can assign decision-making authority to another person. The advantage of the durable power of attorney for health care is that it applies only when the patient has lost decision-making capacity, as judged by her physician. Court review is not required. It does *not*, as does the living will, require that the patient be terminally or irreversibly ill. However, unlike the living will, the durable power of attorney does not necessarily provide explicit direction, only the explicit assignment of decision-making authority to an identified individual or “agent.” Obviously, any patient who assigns durable power of attorney for health care to someone else has an interest in communicating her values, beliefs, and preferences to that person. The physician can play a facilitating role in this process. Indeed, in order to protect the patient's autonomy, the physician should play an active role in encouraging this communication process so that there will be minimal doubt about whether the person holding durable power of attorney is faithfully representing the wishes of the patient.

The main clinical advantages of these two forms of advance directives are that they encourage patients to think carefully in advance about their request for or refusal of medical intervention and that these directives, therefore, help to prevent ethical conflicts and crises in the management, especially of terminally or irreversibly ill, patients who have decision-making capacity. Unfortunately, the use of advance directives is not as widespread as it should be. The reader is encouraged to think of advance directives as powerful, practical strategies for preventive ethics for end-of-life care and to encourage patients to consider them carefully, especially patients with gynecologic disease—particularly gynecologic cancers—that could become or are life threatening.

INTERACTION OF BENEFICENCE AND RESPECT FOR AUTONOMY IN GYNECOLOGIC JUDGMENT AND PRACTICE

Beneficence-based and autonomy-based clinical judgments in gynecologic practice are usually in harmony (Fig. 58.1). A woman may have an adnexal mass of 10 cm. The gynecologist would explain this diagnostic finding and the potential for malignancy and torsion of the mass, as well as the unlikelihood of spontaneous resolution. In beneficence-based clinical judgment, surgical management provides a clear-cut greater balance of medical goods over harms for the patient, whereas nonsurgical management provides a clear-cut greater balance of medical harms over goods for the patient. Beneficence-based clinical judgment requires a careful explanation of these matters to the patient, with no restriction from managed care gag rules, and supports a definitive recommendation for surgical management. Respect for the patient's autonomy also requires explanation of these matters, but it goes further and obligates the physician to elicit the patient's value-based priorities for the management of the newly diagnosed condition, which almost always coincides with beneficence-based clinical judgment.

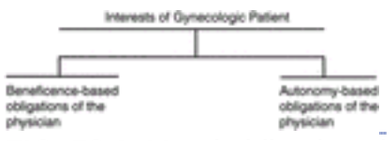

FIG. 58.1. Moral obligations in gynecologic care.

Synergy between beneficence and respect for autonomy occurs when the physician's management plan is carried out in conjunction with the patient's informed consent.

Sometimes, beneficence-based and autonomy-based clinical judgments are in conflict. In situations of conflict, neither beneficence nor respect for autonomy in and of itself should be viewed as a “trump,” to borrow a term from the game of bridge. That is, beneficence does not always override respect for autonomy, nor vice versa. Instead, both principles should be understood as theoretically equally weighted. Thus, their differences must be negotiated in clinical judgment and practice. The competing demands of both principles must be balanced and negotiated in the specific clinical case to determine which management strategies protect and promote the patient's interests. In the technical language of ethics, we are treating these principles as *prima facie* or potentially overridable in nature.

The process of negotiating conflict between the two principles is a function of the following several factors involved in gynecologic clinical judgment: Subject matter, probability of net medical benefit, availability of reasonable alternatives, and the ability of the patient to participate in the informed consent process (Fig. 58.2).


FIG. 58.2. Factors that influence the relative weight of beneficence-based and autonomy-based obligations to the gynecologic patient.

When the subject matter is primarily technical in nature, such as the selection of an effective antibiotic regimen or intraoperative surgical technique, clinical judgment is justifiably beneficence based. This is because technical matters largely concern the evidence-based determination of medical goods and harms for aggregates of patients with a particular diagnosis and treatment plan. Such decisions are justifiably within the gynecologist's purview. The individual values and beliefs of a particular patient cannot readily be taken into account in this process. In contrast, when the patient's basic values and beliefs are at stake, such as the workup or treatment of infertility or elective abortion, clinical judgment is justifiably autonomy based. This is because particular diagnostic or treatment interventions can directly and adversely affect the basic values and beliefs of a particular patient, a matter that only an individual patient can decide. Such decisions are justifiably within the patient's purview.

When the probability of net medical benefit for the patient of diagnostic or therapeutic medical intervention is high, such as chemotherapy for some forms of gestational trophoblastic disease or surgical correction of a prolapsed uterus, beneficence-based clinical judgment is dominant. This is because, in such circumstances, the net benefit is clear-cut. The gynecologist is, therefore, justified in recommending interventions that have a high probability of net medical benefit. By contrast, when that probability is low, such as with experimental therapy for advanced ovarian malignancy or prophylactic oophorectomy at age 40 to 45 years, clinical judgment is justifiably autonomy based. This is because, when there is no clear-cut benefit and significant risks of intervention exist, the patient is in the best position to determine which trade-off makes the most sense. The gynecologist is, therefore, justified in offering these alternatives but not in recommending one as indisputably the best.

When there is no reasonable alternative to manage the patient's condition (e.g., removal of a ruptured ectopic pregnancy or screening for cervical cancer by Pap smears), clinical judgment is appropriately beneficence based, because there is no other alternative that to any degree protects and promotes the interests of the patient. The gynecologist is, therefore, justified in strongly recommending the intervention in question. By contrast, when there are reasonable alternatives, such as surgery versus radiotherapy for stage Ia cervical cancer or a method of contraception versus tubal ligation, clinical judgment is appropriately autonomy based. This is because reasonable alternatives all promote the patient's interests to a significant degree, and no one alternative can exclude any other as unreasonable. The gynecologist is justified in presenting or offering the reasonable alternatives.

When the ability to implement the informed consent process is low, as for a patient with severe or profound mental retardation or in a life-threatening emergency without time for consent, clinical judgment is justifiably beneficence based. This is because it is impossible to determine the patient's relevant values and beliefs because of either significant irreversible cognitive impairment or urgent lack of time. The gynecologist is, therefore, justified in basing clinical decision making primarily on beneficence. By contrast, when the ability of the patient to participate in the informed consent process is not low, as in a speaker of a foreign language or the existence of a legally valid advance directive, then clinical judgment is justifiably autonomy based. This is because the ability of the patient to participate in the informed consent process is presumed in the absence of compelling reasons to the contrary.

As a rule, the result of the informed consent process should be implemented. When the patient refuses to accept any of the alternatives supported in beneficence-based clinical judgment, the physician is ethically and legally obligated to engage in what is known as “informed refusal.” This legal and ethical obligation arises from the 1980 case of *Truman v. Thomas* from California. Dr. Thomas had delivered several of Mrs. Truman's babies and, during the delivery of her last child, recommended that she have a Pap smear. She refused to have this test until she could pay for it and did not accept Dr. Thomas's offer to perform it without charge. Mrs. Truman next visited Dr. Thomas with advanced cervical cancer, from which she died. During the malpractice action brought by her survivors, Dr. Thomas stated that, although they were of clinical concern to him in the management of Mrs. Truman, he did not tell Mrs. Truman of the risks of having detectable presymptomatic changes in her cervix indicative of cervical cancer or that he was concerned that she could die from such disease. The California Supreme Court ruled that, because risks were of clinical salience to Dr. Thomas—they were the motivation for his offering the Pap smear—he should have informed Mrs. Thomas about these risks so that her refusal would be informed. This case changed practice and introduced the concept of informed refusal into medical law and ethics.

The ethical and legal obligation of the physician in the matter of informed refusal is very clear and not difficult to fulfill. The patient should be informed in straightforward, but not harsh or hostile, terms the medical risks that she is taking in her refusal of a diagnostic or therapeutic intervention supported in beneficence-based clinical judgment. The risks to be disclosed are those that are salient in clinical judgment. If they are important to the physician, that is, motivating the offer or recommendation of the diagnostic test or therapy, they are salient and should be disclosed. This discussion should be documented thoroughly in the patient's chart. This is all that the law requires. Good ethical practice suggests strongly that this disclosure should be followed by a recommendation that the patient reconsider her refusal. As a matter of good ethical practice, the physician should respond, in the end, to adamant refusal by offering a trial of respect for the patient's refusal, asking her to return for an office visit, and to reconsider her refusal once she has had some experience with it. This preventive ethics approach avoids the need to abandon the patient, keeps lines of communication open, and sends a powerful ignal of concern by the physician to the patient about the medical folly of her refusal.

Patients' demands for inappropriate management are the reverse side of this coin. We suggest the following preventive ethics strategy in response:

1. Is the intervention reliably expected to have its intended, usual anatomic or physiologic effect? If in reliable, especially evidence-based, beneficence-based clinical judgment it is not expected to do so, then the physician should not offer it. There is no obligation to offer or to perform medical interventions that are futile in this strict sense, such as providing a feeding tube for a patient with cachexia caused by cancer.
2. Is the intervention reliably expected to have some minimal clinical benefit, defined as maintaining some minimal level of ability to interact with the environment and thus grow and develop as a human being? Is the patient in a persistent or permanent vegetative state? If, in reliable beneficence-based clinical judgment, the intervention is not expected to have benefit, then the physician should offer it and then recommend against it. We suggest this approach to respect patients or surrogate decision makers who are vitalists, those who value the preservation of life at any cost. The physician should explain that this is *not* a value in medical ethics and never has been. Moreover, the intervention in question, whether it is initiated or continued, will just sustain a false hope of recovery.
3. If the patient or the patient's surrogate persists in the demand, then the physician should consult with colleagues and then the ethics committee, which should have a clear policy on response to demands by patients or their surrogates for futile intervention.

INTERACTION OF BENEFICENCE AND RESPECT FOR AUTONOMY IN OBSTETRIC CLINICAL JUDGMENT AND PRACTICE

The ethical principles of beneficence and respect for autonomy play a more complex role in obstetric clinical judgment and practice (Fig. 58.3). There are obviously beneficence-based and autonomy-based obligations to the pregnant patient. The physician's perspective on the pregnant woman's interests provides the basis for the physician's beneficence-based obligations to her, whereas her own perspective on those interests provides the basis for the physician's autonomy-based obligations to her. Because of an insufficiently developed central nervous system, the fetus cannot meaningfully be said to possess values and beliefs. Thus, there is no basis for saying that a fetus has a perspective on its interests. There can, therefore, be no autonomy-based obligations to any fetus. Hence, the language of fetal rights has no meaning and therefore no application to the fetus in obstetric clinical judgment and practice, despite its popularity in public and political discourse in the United States and other countries. Obviously, the physician has a perspective on the fetus's health-related interests, and the physician can have beneficence-based obligations to the fetus, *but only when the fetus is a patient.* Because of its importance for obstetric clinical judgment and practice, the topic of the fetus as a patient requires detailed consideration.

FIG. 58.3. Moral obligations in obstetric care.

Two Senses of the Concept of the Fetus as a Patient

The concept of the fetus as a patient is essential to obstetric clinical judgment and practice. Developments in fetal diagnosis and management strategies to optimize fetal outcome have become widely accepted, encouraging the development of this concept. This concept has considerable clinical significance because, when the fetus is a patient, directive counseling (i.e., recommending a form of management) for fetal benefit is appropriate, and when the fetus is not a patient, nondirective counseling (i.e., offering but not recommending a form of management for fetal benefit) is appropriate. However, these apparently straightforward roles for directive and nondirective counseling are often difficult to apply in actual perinatal practice because of uncertainty about when the fetus is a patient. One approach to resolving this uncertainty would be to argue that the fetus is or is not a patient in virtue of personhood, or some other form of independent moral status. We now show that this approach fails to resolve the uncertainty and we, therefore, defend an alternative approach that does resolve the uncertainty.

Independent Moral Status of the Fetus

One prominent approach for establishing whether or not the fetus is a patient has involved attempts to show whether or not the fetus has independent moral status. This is the first sense of the concept of the fetus as a patient. Independent moral status for the fetus means that one or more characteristics that the fetus possesses in and of itself and, therefore, independently of the pregnant woman or any other factor, generate and therefore ground obligations to the fetus on the part of the pregnant woman and her physician.

A striking variety of characteristics have been nominated for this role, such as moment of conception, implantation, central nervous system development, quickening, and the moment of birth. It should come as no surprise that, given the variability of proposed characteristics, there is considerable variation among ethical arguments about when the fetus acquires independent moral status. Some take the view that the fetus has independent moral status from the moment of conception or implantation. Others believe that independent moral status is acquired in degrees, thus resulting in “graded” moral status. Still others hold, at least by implication, that the fetus never has independent moral status so long as it is in utero.

Despite ever-expanding theologic and philosophic literature on this subject, there has been no closure on a single authoritative account of the independent moral status of the fetus. This is an unsurprising outcome because, given the absence of a single method that would be authoritative for all of the markedly diverse theologic and philosophic schools of thought involved in this endless debate, closure is impossible. For closure ever to be possible, debates about such a final authority within and between theologic and philosophic traditions would have to be resolved in a way satisfactory to all, an inconceivable intellectual and cultural event.

We propose to abandon these futile attempts to understand the fetus as a patient in terms of independent moral status of the fetus and turn to an alternative approach that makes it possible to identify ethically distinct senses of the fetus as a patient and their clinical implications for directive and nondirective counseling. In its first sense, that of the independent moral status of the fetus, the fetus as a patient has no stable or clinically applicable meaning. We, therefore, consider a second sense of the concept of the fetus as a patient.

Dependent Moral Status of the Fetus

Our analysis of this second sense of the concept of the fetus as a patient begins with the recognition that being a patient does not require that one possess independent moral status. Rather, being a patient means that one can benefit from the applications of the clinical skills of the physician. Put more precisely, a human being without independent moral status is properly regarded as a patient when the following two conditions are met: that a human being (a) is presented to the physician, and (b) there exist clinical interventions that are reliably expected to be efficacious, in that they are reliably expected to result in a greater balance of clinical goods over harms for the human being in question. This is the second sense of the concept of the fetus as a patient, what we call the dependent moral status of the fetus.

The authors have argued elsewhere that beneficence-based obligations to the fetus exist when the fetus is reliably expected *later* to achieve independent moral status as a child and person. That is, the fetus is a patient when the fetus is presented for medical interventions, whether diagnostic or therapeutic, that reasonably can be expected to result in a greater balance of goods over harms for the child and person the fetus can *later* become during early childhood. The ethical significance of the concept of the fetus as a patient, therefore, depends on links that can be established between the fetus and its later achieving independent moral status.

Viable Fetal Patient

One such link is viability. Viability is not, however, an intrinsic property of the fetus because viability must be understood in terms of both biologic and technologic factors. It is only by virtue of both factors that a viable fetus can exist ex utero and thus achieve independent moral status. Moreover, these two factors do not exist as a function of the autonomy of the pregnant woman. When a fetus is viable, that is, when it is of sufficient maturity that it can survive into the neonatal period and achieve independent moral status given the availability of the requisite technologic support, and when it is presented to the physician, the fetus is a patient.

Viability exists as a function of biomedical and technologic capacities, which are different in different parts of the world. As a consequence, there is no worldwide, uniform gestational age to define viability. In the United States, we believe that viability occurs at approximately 24 weeks of gestational age.

When the fetus is a patient, directive counseling for fetal benefit is ethically justified. In clinical practice, directive counseling for fetal benefit involves one or more of the following: recommending against termination of pregnancy, recommending against nonaggressive management, or recommending aggressive management. Aggressive obstetric management includes interventions such as fetal surveillance, tocolysis, cesarean delivery, and delivery in a tertiary care center when indicated. Nonaggressive obstetric management excludes such interventions. Directive counseling for fetal benefit, however, must take account of the presence and severity of fetal anomalies, extreme prematurity, and obligations to the pregnant woman.

It is very important to appreciate in obstetric clinical judgment and practice that the strength of directive counseling for fetal benefit varies according to the presence and severity of anomalies. As a rule, the more severe the fetal anomaly, the less directive counseling should be for fetal benefit. In particular, when lethal anomalies such as anencephaly can be diagnosed with certainty, there are no beneficence-based obligations to provide aggressive management. Such fetuses are dying patients, and the counseling, therefore, should be nondirective in recommending between nonaggressive management and termination of pregnancy, but directive in recommending against aggressive management for the sake of maternal benefit. By contrast, third-trimester abortion for Down syndrome or achondroplasia is not ethically justifiable, because the future child has a high probability of growing and developing as a human being.

The strength of directive counseling for fetal benefit in cases of extreme prematurity of viable fetuses does not vary. In particular, this is the case for what we term just-viable fetuses, those with a gestational age of 24 to 26 weeks, for which there are significant rates of survival but high rates of mortality and morbidity. These rates of morbidity and mortality can be increased by nonaggressive obstetric management, whereas aggressive obstetric management may influence outcome favorably. Thus, it appears that there are substantial beneficence-based obligations to just-viable fetuses to provide aggressive obstetric management. This even more the case in pregnancies beyond 26 weeks of gestational age. Therefore, directive counseling for fetal benefit is justified in all cases of extreme prematurity of viable fetuses, considered by itself. Of course, such directive counseling is appropriate only when it is based on documented efficacy of aggressive obstetric management for each

fetal indication. For example, such efficacy has not been demonstrated for routine cesarean delivery to manage extreme prematurity.

Any directive counseling for fetal benefit must occur in the context of balancing beneficence-based obligations to the fetus against beneficence-based and autonomy-based obligations to the pregnant woman (see Fig. 58.3). Any such balancing must take into account that a pregnant woman is obligated only to take reasonable risks of medical interventions that are reliably expected to benefit the viable fetus or child later. A unique feature of obstetric ethics is that the pregnant woman's autonomy influences whether, in a particular case, the viable fetus ought to be regarded as having been presented to the physician.

Obviously, any strategy for directive counseling for fetal benefit that takes account of obligations to the pregnant woman must be open to the possibility of conflict between the physician's recommendation and a pregnant woman's autonomous decision to the contrary. Such conflict is best managed preventively through the informed consent process as an ongoing dialogue throughout a woman's pregnancy, augmented as necessary by negotiation and respectful persuasion.

Previable Fetal Patient

The only possible link between the previable fetus and the child it can become is the pregnant woman's autonomy. This is because technologic factors cannot result in the previable fetus becoming a child. The link, therefore, between a fetus and the child it can become when the fetus is previable can be established only by the pregnant woman's decision to confer the status of patient on her previable fetus. The previable fetus, therefore, has no claim to the status of patient independently of the pregnant woman's autonomy. The pregnant woman is free to withhold, confer upon or, having once conferred, withdraw the status of patient from her previable fetus according to her own values and beliefs. The previable fetus is presented to the physician solely as a function of the pregnant woman's autonomy.

Counseling the pregnant woman regarding the management of her pregnancy when the fetus is previable should be nondirective in terms of continuing the pregnancy or having an abortion if she refuses to confer the status of patient on her fetus. If she does confer such status in a settled way, at that point beneficence-based obligations to her fetus come into existence, and directive counseling for fetal benefit becomes appropriate. Just as for viable fetuses, such counseling must take account of the presence and severity of fetal anomalies, extreme prematurity, and obligations owed to the pregnant woman.

For pregnancies in which the woman is uncertain about whether to confer such status, the authors propose that the fetus be *provisionally* regarded as a patient. This justifies directive counseling against behavior that can harm a fetus in significant and irreversible ways, such as substance abuse, especially alcohol, until the woman settles on whether to confer the status of patient on the fetus.

In particular, nondirective counseling is appropriate in cases of what we term *near-viable fetuses*, those that are 22 to 23 weeks of gestational age, for which there are anecdotal reports of survival. In our view, aggressive obstetric and neonatal management should be regarded as clinical investigation (i.e., a form of medical experimentation), not a standard of care. There is no obligation on the part of a pregnant woman to confer the status of patient on a near-viable fetus, because the efficacy of aggressive obstetric and neonatal management has yet to be proven.

In Vitro Embryo Patient

A subset of previable fetuses as patients concerns the in vitro embryo. It might seem that the in vitro embryo is a patient because such an embryo is presented to the physician. However, for beneficence-based obligations to a human being to exist, medical interventions must be reliably expected to be efficacious.

Recall that, in terms of beneficence, whether the fetus is a patient depends on links that can be established between the fetus and its eventual independent moral status. Therefore, the reasonableness of medical interventions on the in vitro embryo depends on whether that embryo later becomes viable. Otherwise, no benefit of such intervention can meaningfully be said to result. An in vitro embryo, therefore, becomes viable only when it survives in vitro cell division, transfer, implantation, and subsequent gestation to such time that it becomes viable. The process of achieving viability occurs only in vivo and is, therefore, entirely dependent on the woman's decision regarding the status of the fetus as a patient, should assisted conception successfully result in the gestation of the previable fetus. Whether an in vitro embryo will become a viable fetus, and whether medical intervention on such an embryo will benefit the fetus, are both functions of the pregnant woman's autonomous decision to withhold, confer upon or, having once conferred, withdraw the moral status of patient from the previable fetus that might result from assisted conception.

It, therefore, is appropriate to regard the in vitro embryo as a previable fetus rather than as a viable fetus. As a consequence, any in vitro embryo should be regarded as a patient only when the woman into whose reproductive tract the embryo will be transferred confers that status. Thus, counseling about preimplantation diagnosis should be nondirective. Preimplantation diagnostic counseling should be nondirective because the woman may elect not to implant abnormal embryos. These embryos are not patients, so there is no basis for directive counseling. Information should be presented about prognosis for a successful pregnancy and the possibility of confronting a decision about selective reduction, depending on the number of embryos transferred. Counseling about how many in vitro embryos should be transferred should be rigorously evidence based.

When to Offer, Recommend, and Perform Cesarean Section

When to offer, recommend, and perform cesarean delivery is a common clinical ethical challenge in day-to-day obstetric practice, a challenge that will only increase with the growing influence of managed care and widespread quality assurance in hospitals. In this section we provide an ethically justified and clinically comprehensive algorithm for offering, recommending, and performing cesarean delivery, with particular reference to managed care, based on the ethical principles of beneficence and respect for autonomy and the concept of a fiduciary (Fig. 58.4 and Fig. 58.5).

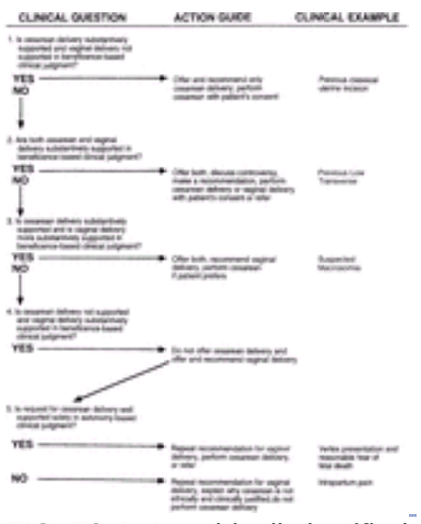

FIG. 58.4. An ethically justified, clinically comprehensive algorithm for offering, recommending, and performing cesarean delivery. (From Chervenak FA, McCullough LB. Identification and management of ethical conflict in the patient–gynecologist relationship. J Reprod Med 1993;38:553–557, with permission.)

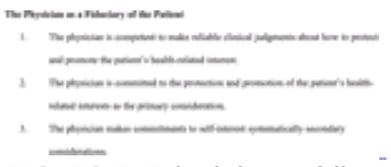

FIG. 58.5. Principles guiding the physician acting as patient fiduciary.

Our algorithm has five questions that define five clinical categories and begins by asking, “Is cesarean delivery substantively supported and vaginal delivery not supported in beneficence-based clinical judgment?” For example, when there is a previous classic incision in the uterus, cesarean is clearly preferable to vaginal delivery because cesarean prevents the fetal and maternal risk of a ruptured classic incision in up to 12% of cases. Vaginal delivery in these circumstances would result in a substantial increase in maternal and fetal morbidity and mortality. Because vaginal delivery involves unnecessary and preventable harms that are both quantitatively and qualitatively important, and cesarean prevents these harms, no well-founded beneficence-based clinical judgment could support offering vaginal

delivery to a woman with a previous classic uterine incision. Only cesarean delivery should be offered and recommended to such patients. With the patient's consent, it should then be performed.

The second question concerns those clinical circumstances, such as previous low transverse uterine incisions, in which there is scientific controversy as to whether elective cesarean delivery is the better alternative. There are competing well-founded beneficence-based clinical judgments regarding how to balance the fetal benefit of preventing harm against the maternal risks associated with cesarean delivery. Whenever multiple management strategies are supported substantively in beneficence-based clinical judgment, all should be offered to the pregnant woman so that she can exercise her autonomy meaningfully. Such disclosure empowers the woman to emphasize her own perspective in balancing maternal and fetal risks. Not offering all management options substantively supported in beneficence-based clinical judgment is an unjustified form of paternalism. It is ethically appropriate to offer and perform either cesarean or a trial of vaginal delivery. A physician is justified in making a recommendation based on his or her evaluation of the controversy.

The third question concerns clinical circumstances when cesarean delivery is substantively supported in beneficence-based clinical judgment, but attempted vaginal delivery is supported more substantively. Attempted vaginal delivery is the better alternative but not the only one, as in the case of suspected macrosomia in the absence of certain factors such as diabetes. Clinical and sonographic prediction of macrosomia is not precise. Although cesarean is supported substantively in beneficence-based clinical judgment, trial of labor is supported more substantively. To avoid unjustified paternalism, both cesarean and a trial of vaginal delivery should be offered. Because a trial of vaginal delivery is the better option, it should be recommended. In addition, a cesarean is also supported substantively in beneficence-based clinical judgment, so it is justified to perform a cesarean if that is the patient's preference.

In the authors' view, in most remaining cases the woman should not routinely be offered cesarean delivery, because beneficence-based clinical judgment supports that vaginal delivery is appropriate and cesarean delivery is not appropriate (the fourth question). Cesarean delivery involves a quantitative increase of risks of unnecessary and preventable maternal morbidity and mortality, risks that are decreased by vaginal delivery. The qualitative nature of the unnecessary and preventable risks of cesarean delivery looms large in this beneficence-based calculus. As a consequence, it is not ethically justified to offer cesarean delivery, and only vaginal delivery should be offered and recommended routinely. If evidence accumulates that vaginal delivery poses a long-term risk to some women's health, such as damage to the pelvic floor, then it would be justified to offer and discuss cesarean delivery as a reasonable alternative. That is, this patient population should be managed under question three, even question two, depending on the strength of the evidence.

In rare cases (question five), patients request cesarean delivery not indicated on beneficence-based grounds, raising the challenging concept that autonomy-based indications in limited and rare circumstances can be well supported. For example, one of us (FAC) approved a cesarean delivery for a patient who expressed a legitimate fear of spontaneous fetal death and for whom there were no maternal contraindications to cesarean. She understood and accepted the maternal morbidity and mortality associated with cesarean delivery. An effort was made to dissuade the patient, but she considered and rejected it. A patient's preference that is based on deeply held values that are reaffirmed after a serious attempt to change her decision meets the test for being well supported in autonomy-based clinical judgment.

We can now answer a question that Feldman and Freiman asked more than 10 years ago: “If an informed patient opts for prophylactic cesarean section at term, can it be denied?” If such a request is well supported in autonomy-based clinical judgment, which will be rare, it should be carried out by the physician, or an appropriate referral should be made. Feldman and Freiman also suggested that patients should be informed of the “very real risks associated with the passive anticipation of vaginal delivery after fetal maturity has been reached.” However, we conclude that this obligation does not exist, because an affirmative answer makes the incorrect assumption that cesarean delivery is supported in beneficence-based clinical judgment.

Well-supported requests for cesarean delivery contrast with those that are not well supported in autonomy-based clinical judgment (i.e., when the goals expressed in the patient's preference for cesarean can be achieved without delivering by cesarean). For example, a woman who is in pain during labor may request cesarean delivery for relief of the pain. However, this goal can be achieved by administration of analgesia, whereas cesarean delivery for pain relief will result in more pain and unnecessary risk of morbidity and mortality. The preference is internally inconsistent and, therefore, not well supported in autonomy-based clinical judgment.

On the basis of our algorithm, there are four ethical indications for cesarean delivery as follows: (a) when it is the only reasonable alternative in beneficence-based clinical judgment, (b) when it is the more substantively supported in beneficence-based clinical judgment, (c) when it is substantively supported in beneficence-based clinical judgment and the patient prefers it, and (d) when it is well supported in autonomy-based clinical judgment, a purely autonomy-based but rare indication.

This algorithm underscores the importance of the professional integrity of the physician's role in the informed consent process. In some clinical situations, such as a previous low transverse uterine incision, there are advantages of elective repeat cesarean delivery for the physician, including time saved, convenience, and possibly increased remuneration. It is a clear and unacceptable violation of the professional integrity of the physician's role in the informed consent process for the physician to distort this process in pursuit of such personal, not professional, advantages.

One business strategy of managed care models is to impose shared economic risk on the physician and sometimes on the patient, with a view toward influencing both to use resources with economic efficiency. Strategies such as capitation for covered lives will put the economic interests of obstetricians and other physicians at risk every time they use a costly surgical intervention such as cesarean delivery. On the basis of our algorithm, the response of the physician always should be to offer a cesarean delivery when it is substantively supported in beneficence-based clinical judgment (i.e., when question one, two, or three in our algorithm of Figure 58.4 is answered in the affirmative). Gag rules, in contrast, are inconsistent with good ethical practice.

We believe the doctor and the patient should be insulated from shared economic risk when the first clinical question is answered in the affirmative because vaginal delivery would fall below standard of care, and managed care providers, like physicians, are fiduciaries of patients. As such, physicians are obligated ethically not to practice below standard of care, which is established by beneficence-based clinical judgment. Physicians who recommend cesarean delivery in response to clinical question two should negotiate payment plans that insulate them from risk when no one else is available to deliver breech-presenting infants vaginally. This is because economic attempts to resolve genuine clinical controversies in any specialty are scientifically arbitrary and, therefore, inconsistent with the integrity of medicine as a profession.

Payment for cesarean delivery in response to question three is ethically complex. Managed care organizations (MCOs) want the lowest possible rate of cesareans, yet an ethically more important consideration is that physicians have fiduciary obligations to be advocates for their patients. For example, some women are justifiably averse to a trial of vaginal delivery after low transverse cesarean delivery and cannot be persuaded to change their decision. Such factors justifiably influence the definition of the lowest acceptable rate of cesarean delivery. The imposition of shared economic risk is an ethically acceptable strategy only when physicians take the leading role in defining an acceptable cesarean delivery rate for this clinical circumstance. To do otherwise violates the integrity of medicine as a profession.

For cesarean delivery and other procedures that are performed in the clinical circumstances of question five (see Fig. 58.4), physicians should negotiate payment arrangements that require the patient to bear all the economic risk, because the indication for the procedure is solely autonomy based. Managed care plans and other payers have an ethical obligation as fiduciaries to provide care that is consistent with well-formed beneficence-based clinical judgment. Claims on resources that are based solely on autonomy and not on beneficence are, in principle, limited. It follows that patients have, at best, disputable claims on such resources when the indication for their use is purely autonomy based. In general, when the only justification for a procedure or other use of resources is autonomy based, physicians are justified in negotiating payment arrangements that shift some, or even all, economic risk to the patient.

Shared economic risk should have no effect on offering and recommending procedures that are substantively supported in beneficence-based clinical judgment. This aspect of the informed consent process should be kept immune from shared economic risk by managed care companies. The physician's role as the fiduciary of the patient in advocating ethically defensible degrees of shared economic risk cannot be overemphasized. In our view, the degree of shared economic risk should be nonexistent for clinical questions one through four and imposed entirely on patients who want cesarean delivery for question five (see Fig. 58.4).

MANAGED CARE AND THE VIRTUES OF THE OBSTETRICIAN-GYNECOLOGIST

In the previous sections we have made reference to managed care. In this section we provide a more detailed analysis of the ethics of managed care, with particular reference to the virtues of the obstetrician-gynecologist. The practice of obstetrics and gynecology is coming under managed care, which involves a set of strategies used by both private and public payers to control the cost of medical care. Two main business tools are used to achieve this goal, creating (a) conflicts of interest in how physicians are paid, diplomatically called *sharing economic risk*, and (b) increasingly strict control of clinical judgment and practice through such means as practice guidelines, critical pathways, physician report cards, and retrospective chart review. These business tools generate ethical challenges to obstetrician-gynecologists that seriously threaten the virtues that define the fiduciary character of medicine as a profession.

The physician-fiduciary, as a primary consideration, is expected as a matter of routine and habit to fulfill obligations to protect and promote patients' interests rather than pursue one's own interests. Virtues are those traits and habits of character that routinely focus the concern and behavior of an individual on the interests of others and thereby habitually blunt the motivation to act on self-interest as the physician's primary consideration. We believe that four virtues constitute the physician–patient relationship based on the physician as fiduciary.

The first virtue is *self-effacement.* This requires the physician not to act on the basis of potential differences between the patient and the physician such as race, religion, national origin, education, gender, manners, socioeconomic status, hygiene, or proficiency in speaking English. Self-effacement prevents biases and prejudices arising from these differences that could adversely impact on the plan of care for the patient.

The second virtue is *self-sacrifice.* This requires physicians to accept reasonable risks to themselves. As one example, physicians manifest this virtue in their willingness to care for patients with infectious diseases such as tuberculosis, hepatitis, and human immunodeficiency virus infection, all of which are a potential threat to the physician's health. In both fee-for-service and managed care, this virtue of self-sacrifice obligates the physician to turn away from economic self-interest and focus on the patient's need for relief when the two are in conflict.

The third virtue, *compassion*, motivates the physician to recognize and seek to alleviate the stress, discomfort, pain, and suffering associated with the patient's disease and illness. Self-effacement, self-sacrifice, and compassion provide the basis for a powerful ethical response to the business tool of conflicts of interest by the physician.

This response is strengthened by the fourth virtue, *integrity.* This virtue imposes an intellectual discipline on the physician's clinical judgments about the patient's problems and how to address them. Integrity prescribes rigor in the formation of clinical judgment. Clinical judgment is rigorous when it is based on the best available scientific information or, when such information is lacking, consensus clinical judgment and on careful thought processes of an individual physician that can withstand peer review. In settings that lack such quality control mechanisms, physicians confront a powerful incentive to make the pursuit of remuneration via fee-for-service the primary consideration. Integrity is thus an antidote to the pitfalls of bias, subjective clinical impressions, and unexamined clinical common sense that can undermine evidence-based practice. Integrity provides the basis for the physician's ethical response to the business tool of control of clinical judgment and practice.

None of these four virtues is absolute in its ethical demands. The task of medical ethics is to identify both the application and the limits of these four virtues. The concept of legitimate self-interest provides the basis for these limits. Legitimate self-interest includes protecting the conditions for practicing medicine well, fulfilling obligations to persons in the physician's life other than the patient, and protecting activities outside the practice of medicine that the physician finds deeply fulfilling.

Managed Care and the Physician as Fiduciary

Fee-for-service unconstrained by fiduciary obligations could and did lead to harm to patients from nonindicated over-utilization of resources. It is a violation of the standard of care to subject patients to unnecessary active intervention in order to achieve personal economic gain.

Managed care unconstrained by fiduciary obligations puts patients at risk of harm by denying access to the standard of care. This will occur if patients are subjected to unnecessary risk from withholding appropriate care and intervention in order to achieve economic efficiency. A primary goal of managed care is to achieve this economic efficiency through price competitiveness in order to retain and grow market share.

Financial incentives to the physician and supervision of clinician decision making with strict controls of utilization of services are the business tools managed care uses. Forms of payment by managed care plans, such as capitation and withhold, deliberately impose an economic conflict of interest on the physician. Every time the physician uses a resource, such as consultation, diagnostic testing, or surgical procedures, the physician pays an economic penalty. The ethical challenge occurs when the patient's interests are subordinated to the pursuit of financial rewards and thereby harmed by this under-utilization. This conflict of interest becomes actual when a physician signs such a payment contract.

The physician's decision in signing contracts is subject to considerations of legitimate self-interest. For example, failure to sign a contract with a plan that has captured 20% of one's patients will result in a significant loss of income that the physician may not be able to replace through other contracts. Because there is usually an excess of physician supply in large markets, physicians as suppliers who fail to sign contracts in a buyer's market do so at their economic peril. Therefore, rational calculation of one's legitimate concern to protect income from significant reduction may strongly incline a physician to sign virtually every contract presented as a matter of prudent protection of legitimate self-interest.

However, the virtue of self-sacrifice prohibits the physician from making the avoidance of such financial risk the *primary* consideration. Avoiding financial risk as one's *primary* consideration involves an ethically pathologic process that leads naturally and quickly to the abandonment of self-effacement (economically driven managed care for some patients but not for others), compassion (patients' health-related concerns do not matter but are only a means to maximize revenues), and integrity (the standard of care is sacrificed to maximize revenues). Importantly, physicians are not sanctioned by society to engage in the destruction of medicine as a fiduciary profession.

Adhering to the demands of the virtues provides the antidote to this unacceptable sequence of ethical failure. Physicians should negotiate changes in payment contracts to make economic conflicts of interest as manageable as possible. It is not realistic to call for elimination of conflict of interest, as some have done. It is important to recall that fee-for-service involves conflicts of interest that also cannot be eliminated.

Physicians should not assume that MCOs are unwilling to negotiate contracts to reduce the severity of economic conflicts of interest. Physicians should, therefore, make a good faith effort to negotiate these matters. If the MCO refuses to negotiate and the economic risk of not signing the contract is significant, then the physician should voluntarily accept the ethical responsibility to be alert to and manage these conflicts of interest well. First, integrity requires that the physician avoid the self-deception of underestimating any potential influence on clinical judgment and practice by the conflict of interest. Second, once these contracts are signed, the virtues add an important dimension to total quality management: diligent monitoring of conflicts of interest to prevent them from resulting in substandard care should be among the physician's “accountabilities.” Third, the realities of managed care mean that, for the near term at least, increasing financial sacrifice may be required to protect the integrity of medicine as a fiduciary profession. Fourth, in group practice, there should be a fair sharing of economic self-sacrifice. In particular, individual efforts to tune the system to one's economic advantage in a group, for example, avoiding the care of high-risk pregnancies, and to the disadvantage of colleagues should be avoided.

The second business tool of managed care, increasingly strict control of clinical judgment and practice, is a heterogeneous phenomenon. Some managed care plans are poorly capitalized and poorly managed. They compete by price, with little or no attention given to the quality of their services. A “bottom line” mentality dominates, with economic savings and net revenue maximization the overriding values. These poorly managed companies have little or no understanding of or interest in the fiduciary nature of medicine, so their controls of clinical judgment and practice are driven almost entirely by economic considerations.

Physicians subject to management controls by such companies face the very difficult challenge of trying to get such companies to constrain their economic interests by their fiduciary obligations, a daunting task but not, we believe, an impossible task. The concerns of ethics, especially to protect the integrity of the fiduciary enterprise, may be swept aside frequently when they are not ignored altogether. Nonetheless, physicians in such MCOs are the ultimate bulwark on which patients and society must be able to rely to protect patients from management's unbridled pursuit of economic self-interest. Physicians, therefore, should strenuously resist and seek to change management controls driven solely by economic considerations. Evidence-based medicine is a powerful tool for achieving this goal. If physicians refused to cooperate with such poorly managed companies, systematic dissociation would result in a loss of market share or, more optimistically, better management.

Antitrust legislation needs to be changed to permit group responses to this kind of MCO. We realize that this may not be a politically realistic proposal. Antitrust legislation may legally prevent physicians from banding together to deal with this problem. Thus, regulatory relief through state and federal governments becomes an ethically justified strategy to stop the abuse of these plans.

There is a contrast that provides a cause for optimism. Well-managed and well-capitalized plans can be as much concerned with quality as with economic efficiency. The trend of some large Fortune 500 employers to require National Committee on Quality Assurance certification will reinforce the importance of quality. The virtues, as we have shown above, have an important role to play in the definition of quality. The concept of quality should be expanded beyond the usual measures of morbidity, mortality, and customer satisfaction to include monitoring for and managing threats to the fiduciary character of medicine.

One approach to doing so concerns the development and use of practice guidelines, an important form of evidence-based medicine. It appears that well-managed plans will rely increasingly on this as their primary business tool rather than the strategy of creating conflicts of interest with its disruptive and demoralizing effects. Nonetheless, practice guidelines pose a number of ethical concerns.

First, guidelines have the potential to impede economic efficiency, an important value of all MCOs. Economically inefficient plans are threatened with significant loss of market share or even extinction through local market competition by MCOs competing solely by price.

Second, every step of a guideline absorbs monetary resources that would otherwise be available for, among other purposes, physician remuneration, or return to investors in the case of for-profit plans. An interest in job security and maximizing income could, therefore, subtly enter into physicians' judgments about the value of

deleting, adding, or altering diagnostic and therapeutic steps to a guideline. As a consequence, uncertainty about whether a particular step of a guideline adds clinical value may lead to the elimination of that step if doing so increases economic efficiency. This subtle form of conflict of interest should be monitored closely so that the virtues of integrity and self-sacrifice are not unduly threatened.

Third, curtailment of steps in a guideline also might result in physicians concentrating only on the clinical care for which they have direct and immediate answers. The failure to pursue unanswered questions may result in less complete care and failure to develop new clinical competencies, a long-term negative effect on the standard of care.

The integrity of medicine as a fiduciary enterprise justifies, indeed requires, practice guidelines that acknowledge the heterogeneity of patients' conditions and the natural history of diseases and their management, to avoid inadvertent and preventable harm to patients' interests. In defense of such guidelines, which must be as scientifically rigorous as possible—integrity requires this, too—physicians will be obligated by the virtue of integrity to take the unpopular and, at times, antibusiness position of defending economic inefficiency as the necessary price of protecting medicine as a fiduciary profession. Failure to do so amounts to willful failure of the physician's fiduciary responsibilities.

Being a physician-controlled MCO provides no immunity against the ethical challenges of the business tools of managed care. These new physician-owned provider entities will not provide a solution in and of themselves to the ethical threats of conflict of interest and control of clinical judgment and practice. The virtue-based arguments we made will apply to these new entities, without exception.

There is no conclusive evidence that preserving medicine as a fiduciary profession is impossible, even given the enormous economic power of MCOs. Ethics teaches us that business and economic power are not absolute and should always be called to account for their consequences. Society has not given MCOs the moral authority or permission to destroy the fiduciary character of medicine as a consequence of the pursuit of economic interest and power. Nor has society given physicians moral authority or permission to cooperate willfully with this destruction. Quite the opposite, society counts on physicians, because ultimately society can count on no one else to preserve and advocate for the fiduciary character of the medical profession.

CONCLUSION

In this chapter we have provided a general ethical framework for both gynecologic and obstetric clinical judgment and practice. Implementing this framework on a daily basis is essential to creating and sustaining the physician–patient relationship in obstetrics and gynecology. This framework emphasizes preventive ethics, an appreciation that the potential for ethical conflict is built into clinical practice and the use of such clinical tools as informed consent and negotiation to prevent such conflict from occurring. We have provided guidelines for preventing conflict about futile management in gynecologic practice and about cesarean delivery in obstetric practice. We have also shown how the virtues provide a basis for a powerful and effective preventive ethics response to the business tools of managed practice.

SUMMARY POINTS

- In clinical decision making, the obstetrician-gynecologist should take account of both beneficence-based and autonomy-based obligations to the patient.
- The obstetrician-gynecologist should discuss the need for advance directives (living will and durable power of attorney) with patients with gynecologic diseases that could become or are life-threatening.
- The viable fetus is a patient, while the previable fetus is a patient as a function of the pregnant woman's decision to confer this status.
- Offering, recommending, and performing cesarean delivery should be based on the obstetrician-gynecologist's beneficence-based and autonomy-based obligations to the pregnant woman and fetal patient.
- The professional virtues of self-effacement, self-sacrifice, compassion, and integrity are essential for the obstetrician-gynecologist to fulfill fiduciary obligations to patients.
- Obstetrician-gynecologists should resist managed care that is driven solely by economic considerations and cooperate with managed care that is based on evidence-based processes and outcomes.

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Chapter 59

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Evidence-Based Approach to Obstetrics and Gynecology

THE RATIONALE FOR EVIDENCE-BASED MEDICINE
THE PRACTICE OF EVIDENCE-BASED MEDICINE
A MODEL FOR THE PRACTICE OF EVIDENCE-BASED MEDICINE
PUTTING EVIDENCE-BASED MEDICINE INTO PRACTICE
USING EVIDENCE-BASED MEDICAL SUMMARIES
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PRACTICING EVIDENCE-BASED MEDICINE INDEPENDENTLY
Task 1. Ask an Answerable Question
Task 2. Search for Evidence
Sources of Evidence
Task 3. Appraise the Evidence
Assessing Importance and Validity
Types of Epidemiologic Studies
Task 4: Apply the Evidence
REFERENCES

> The aim of medicine in the broadest sense is to provide for every human being from conception to death, the greatest fullness of health and length of life that is allowed by his genetic constitution and by the accidents of life.
>
> MacFarlane Burnett

> Excellent medical practice should be inspired by love and guided by science. Both are essential. If a clinician practices scientific medicine without compassion, he or she becomes an automaton. On the other hand, if a clinician is compassionate but unscientific, he or she may be as dangerous as a well-intended parent feeding chicken noodle soup to a child with meningitis. Evidence-based medicine is not only well-intended, it is well-directed.
>
> David A. Grimes

THE RATIONALE FOR EVIDENCE-BASED MEDICINE

Silverman has chronicled a tragic but instructive story of how the goal of medicine to provide health can be thwarted despite the best of intentions. From 1942 to 1954, more than 10,000 children worldwide were blinded because of a relatively minor change in health care practice. In an effort to improve the survival of premature infants, clinicians exposed newborns to high concentrations of oxygen with the unintended but disastrous consequence of retrolental fibroplasia.

The practice of administering high concentrations of oxygen in the first few days of life was initiated largely on the basis of theoretical considerations and was promulgated in pediatric teaching and research centers. As stated by Silverman, “the retrolental fibroplasia catastrophe would not have been extensive if pediatric leaders had insisted that scientific rules of evidence must be satisfied before any new technique in management of premature infants was used in teaching centers” ([1]).

Silverman also cites Eugene Braunwald, who has likened the dissemination of medical techniques before proper evaluation “to a genie who has escaped from a bottle—it is virtually impossible to undo the confusion resulting from such unrestrained therapeutic exuberance” ([1]). Once the use of high-concentration oxygen therapy for premature infants was established, stopping the practice took more than a decade of effort.

The example cited has parallels throughout the history of medicine. The practice of medicine into the 16th century was based largely on the teachings of the Greek physician Galen (A.D. 138–201) whose pronouncements were embraced without apparent question for centuries. The 17th century saw some questioning of the authority on which medical practice was based. A glimpse of the state of medicine at that time illustrates why such questioning was needed. As King Charles II of England lay dying in 1685, he was cared for by a dozen or more physicians who administered “an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beetroot, chamomile, fennel seed, linseed, cinnamon, cardamom seed, saffron, cochineal and aloes.” When these measures did not succeed, the king's physicians forced “a mixture of Raleigh's antidote, pearl julep, and ammonia” down his throat ([2]).

Not until the 19th and 20th centuries, however, did the questioning of traditional medical authorities lead to major advances. A great leap forward occurred in 1865, when Claude Bernard, a French physiologist, described experimental reasoning in his text *An Introduction to the Study of Experimental Medicine.* This was followed in 1937 with a classic text by A. Bradford Hill describing the use of statistical methods for clinical research.

Randomized controlled trials conducted in the early to mid-20th century clearly indicated the value of basing medical practice on observation and experiment. Perhaps the most dramatic example of randomized controlled trials in that period was the United Kingdom's Medical Research Council's trial of using streptomycin to treat tuberculosis. Streptomycin became available in 1946, but it was in short supply. The Medical Research Council used a portion of existing supplies to test the drug's effectiveness in treating tuberculosis; those patients receiving streptomycin had a clear survival advantage compared to those treated with bed rest.

Once the value of scientific inquiry as the basis for clinical practice had been established, Cochrane argued for an ongoing assessment of the effectiveness of available treatments and services, in part as a matter of social justice. He was concerned that the limited resources for health care in the United Kingdom's National Health Service be efficiently used for effective treatments, thereby enhancing the likelihood that effective treatments would be more widely available. In his classic text, *Effectiveness and Efficiency: Random Reflections on Health Services*, published in 1971 (Cambridge University Press), Cochrane outlined criteria for the evaluation of effectiveness and efficiency in clinical practice. His efforts, along with those of his colleagues at the U.K. Medical Research Council who had conducted early randomized controlled trials, contributed heavily to what is today termed “evidenced-based medicine.”

The need for evidence-based medicine is as apparent in obstetrics and gynecology as it is in other disciplines. Our history includes bloodletting as standard treatment for eclampsia into the 20th century and the persistence of the practice of routine episiotomy to the present despite the lack of evidence supporting the practice. The rapid incorporation of unproven technologies into widespread use has had a major effect on the practice of obstetrics and gynecology. Conversely, some therapies, such as corticosteroid therapy for women at risk of giving birth prematurely, have been underused despite compelling evidence of their effectiveness.

THE PRACTICE OF EVIDENCE-BASED MEDICINE

Clinical epidemiologists at McMaster University participating in the Evidence-based Medicine Working Group have defined evidence-based medicine as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” ([3]). The terms “conscientious” and “judicious” emphasize the need for individualized care. “Conscientious use” requires that evidence be applied consistently when individual circumstances warrant, and “judicious use” requires integration of clinical expertise and evidence to balance risks and benefits of tests and treatments for the individual—based on the individual's circumstance and preferences. By this definition, evidence-based medicine is practiced when clinical expertise is integrated with the best available evidence from a systematic search of the relevant literature. The Working Group further explained that evidence-based medicine “de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making and stresses the examination of evidence from clinical research” ([4]).

Many clinicians took offense from this latter assertion, claiming that evidence-based medicine advocates not only downplay clinical expertise and pathophysiology, but are promoting cookbook medicine, in which all that is required for optimal clinical decisions is a knowledge of the medical literature. Evidence-based medicine advocates deny that they ever intended this and went on to explain: “Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date to the detriment of patients” ([3]).

As also noted by Sackett and colleagues, evidence-based medicine is not “cookbook” medicine, “cost-cutting” medicine, or restricted to evaluation of randomized trials and meta-analyses ([3]). Evidence-based medicine cannot be “cookbook” because it integrates clinical expertise, patient choice, and external evidence. Successful

integration requires the individualization of therapy; the obstetrician-gynecologist must decide whether information obtained from relevant literature pertains to the individual patient, and the obstetrician-gynecologist and patient must determine which evidence-based therapeutic options are preferable.

Evidence-based medicine is not “cost-cutting” medicine because its focus is not on costs, but on effectiveness and efficiency. The most effective therapy for an individual may also be the most expensive therapy; thus, the practice of evidence-based medicine could lead to increased, not decreased costs. Finally, evidence-based medicine uses proper randomized controlled trials and well-conducted meta-analyses when available. However, the best available evidence in medicine, including obstetrics and gynecology, often comes from observational studies.

Grimes has identified five barriers to technology assessment that apply to evidence-based medicine in general:

1. the unchallenged acceptance of authority
2. the acceptance of new technology without critical appraisal
3. the tendency to let existing dogma prevail
4. pedantry in medical education
5. the practice of medicine by uncontrolled clinical impressions or “the last disaster we encountered or hear about” ([5]).

Haynes and Haines went on to identify some additional barriers as well as possible solutions, shown in Table 59.1.

TABLE 59.1. *Barriers and solutions to the practice of evidence-based medicine*

We will focus on the use of information and abstraction services in this chapter, as these provide valuable, practical resources for practitioners attempting to discern the current best evidence for clinical care decisions.

Debate continues about the extent to which new technologies or treatments should be assessed before being incorporated into practice and where the burden of proof for effectiveness should lie. Should promising new interventions be assumed to be effective until there is evidence they are not, or should they be assumed to be ineffective until there is evidence they are effective? Philosophically, the practitioner of evidence-based medicine will, in most cases, lean toward the latter approach.

A MODEL FOR THE PRACTICE OF EVIDENCE-BASED MEDICINE

The concepts of evidence-based decision making have continued to evolve. Haynes and colleagues proposed the model in Figure 59.1.

FIG. 59.1. An updated model for evidence-based clinical decisions. (From Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP Journal Club* 2002;Mar-Apr [*in press*]).

Depending on the circumstances, one component may play a greater role than others in decision making, but ideally, all components are brought into play. The clinical expertise component ensures that the best available evidence is applied to the individual clinical circumstances and in concert with the wishes and likely actions of the patient. This model obviously precludes “the mindless application of rules and guidelines” ([6]).

The discussion of evidence-based medicine is incomplete without recognizing the existence of substantial “gray zones” in clinical practice. As with other medical disciplines, the practice of obstetrics and gynecology includes some clinical questions that can be informed by compelling evidence and many others for which adequate evidence is lacking. As noted by Naylor, “Evidence-based medicine offers little help in the many gray zones of practice where the evidence about risk–benefit ratios of competing clinical options is incomplete or contradictory.” Alternatively, “[w]hat is black and white in the abstract may rapidly become gray in practice, as clinicians seek to meet their individual patients' needs.” ([7]). The latter circumstance is a gray zone potentially embraced by the model of evidence-based medicine presented here. Clinical expertise is required to ensure that evidence is applied in the best interest of individuals—even though it means practicing in a “gray zone.” The former circumstance is clearly a constraint on the practice of evidence-based medicine.

Clinicians frequently and readily make decisions in the absence of compelling evidence. McDonald has argued that such decisions are made by principles, axioms, and ad hoc rules or “heuristics” that should be explicit. Formal characterization of the rules of medical decision making in the absence of evidence or in the presence of inconsistent evidence would provide both clinicians and their patients a better understanding of how medical uncertainty is dealt with.

PUTTING EVIDENCE-BASED MEDICINE INTO PRACTICE

Information to guide medical decision making is proliferating, whereas discretionary time for most clinicians is shrinking. The practice of evidence-based medicine initially required the obstetrician-gynecologist to understand and apply principles of clinical epidemiology, to efficiently search the literature, and to critically appraise the literature in solving clinical problems and making the best possible medical decisions. In recent years, the burden of searching and appraisal has been substantially reduced, for common clinical topics, at least, by the evolution of increasingly robust, evidence-based resources, in which evidence on a given problem is searched for exhaustively, assessed rigorously, and updated frequently. These are especially strong in the area of therapeutic interventions, for example, the Cochrane Library, available on CD and the Internet (http://www.update-software.com/cochrane). The busy obstetrician-gynecologist has three choices in evaluating available evidence and incorporating that evidence into practice:

1. practicing evidence-based medicine independently
2. using evidence-based medical summaries developed by others
3. using evidence-based practice protocols developed by others.

Depending on the topic, time, and evidence-based resources available, the consummate evidence-based practitioner should be able to pursue whichever route seems most likely to be satisfactory to deal with the problem at hand. The latter two approaches are addressed briefly here. The first approach is discussed in detail, as it includes the basic skills needed when no credible evidence-based resource is readily available.

USING EVIDENCE-BASED MEDICAL SUMMARIES

Evidence-based medical summaries go beyond traditional review articles, which have been shown to have little scientific merit. Several levels of summaries now exist, with increasing levels of integration around specific clinical topics. At the top level are resources such as *Clinical Evidence* from the British Medical Journal Publishing Group (http://www.evidence.org/), in which systematic reviews and best available individual studies are summarized for specific clinical topics, including pregnancy and

childbirth and women's health. Below this level, several sources of summaries of studies and systematic reviews exist. For example, there are a number of journals of secondary publication of structured abstracts and clinical commentaries that have been selected based on explicit criteria intended to select valid and clinically important articles. Such criteria eliminate 98% of the clinical literature. Examples of these journals are *ACP Journal Club, Evidence-Based Medicine, Evidence-Based Obstetrics and Gynecology, Evidence-Based Nursing*, and *Evidence-Based Mental Health. Evidence-Based Obstetrics and Gynecology* is published quarterly (http://www.harcourt-international.com/journals/ebog), and covers reproductive endocrinology, infertility, maternal–fetal medicine (including general obstetrics), gynecologic oncology, urogynecology, and general gynecology. *ACP Journal Club, Evidence-Based Medicine*, and *Evidence-Based Nursing* also include broad coverage of women's health issues, but at a less specialized level, and can be accessed electronically (as http://www.acpjc.org/, http://ebm.bmjjournals.com/; http://ebn.bmjjournals.com/, respectively). *ACP Journal Club, Clinical Evidence*, the Cochrane Library, and the Database of Abstracts of Reviews of Evidence, along with MEDLINE and other bibliographic databases, can all be searched individually or simultaneously through Ovid's Evidence-Based Medicine Reviews service, available at most medical and many major hospital libraries, and often available by remote Internet access (e.g., from home and clinic), according to library policy. Of these, the most helpful source of reviews of evidence concerning interventions currently available is the Cochrane Library. This library is described further under “Task 2: Search the Evidence” later in the chapter. A limited number of reviews on topics including diagnostic tests, prognosis, and etiology are available from the other sources listed previously.

Systematic reviews, in contrast to narrative reviews, are intended to answer specific clinical questions in depth. Systematic reviews use explicit methods to assemble relevant studies, critically appraise those studies, and synthesize the studies to address a clinical question. Methods for systematic reviews have been developed to limit systematic error (bias) and random error (chance); the value of a systematic review depends largely on how faithfully these methods have been followed.

When the quantitative results of individual studies in a systematic review are combined using statistical methods, the review is called a meta-analysis. Meta-analysis is increasingly used to summarize the obstetric and gynecologic literature. A properly done meta-analysis can provide a wealth of information for clinical decision making; a poorly conducted meta-analysis can be misleading. Criteria for evaluating the quality of a meta-analysis have been described (Table 59.2).

1. Is the purpose of the study (i.e., the hypothesis) clearly identified and is it an overview of a randomized trial of the treatment you are interested in?
2. Does it include a methods section that describes an active, comprehensive effort to include all relevant studies in the analysis?
3. Were explicit inclusion and exclusion criteria used to specify studies eligible for the meta-analysis?
4. Was there an assessment of publication bias (i.e., bias resulting from reporting only those results that are statistically significant, which tends to overestimate the effect under study)?
5. Was a blinded assessment of individual study quality conducted appropriately and systematically?
6. Were the pooled data appropriate for testing the hypothesis?
7. Were multiple raters used to assess coding? If so, were they blinded and were measures of interrater reliability provided?
8. Were the selection and coding of data based on sound clinical principles or convenience?
9. Was documentation provided that explained how the data were coded and analyzed?
10. Was the comparability of cases and controls assessed?
11. Was heterogeneity testing conducted to assess consistency of results from study to study and reported appropriately?
12. Were results reported in sufficient detail to enable replication of results by the reviewer?
13. Were alternative explanations for observed results considered in the discussion?
14. Were the conclusions generalized appropriately and did they stay within the domain of the literature review?
15. Were guidelines provided for future research?

Source: Thacker SB, Peterson HB, Stroup DF. Meta-analysis for the obstetrician-gynecologist. *Am J Obstet Gynecol* 1996;174:1403–1407, and Sackett DL, Richardson WS, Rosenberg W, et al. *Evidence-based medicine: how to practice and teach EBM*. New York: Churchill Livingstone, 1997: 97.

TABLE 59.2. *Questions to ask in evaluating a published meta-analysis*

Obstetricians-gynecologists using meta-analyses for decision making should be fully aware that the value of the meta-analysis is constrained by the value of the individual studies being synthesized. The use of meta-analysis may inappropriately confer a cloak of respectability around a collection of poor quality studies. A collection of studies of poor quality is nothing more than that. A properly executed and reported review, however, should make the limitations of the studies it summarizes apparent to the careful reader, and provide an accurate assessment of the state of knowledge, even if the knowledge is not as advanced as the user might prefer.

Whether meta-analysis should be restricted to randomized controlled trials has been debated. Proper randomized trials provide better evidence about health care interventions than observational studies. A major purpose of meta-analysis is to increase statistical power. Pooling of data from randomized controlled trials is likely to provide a more precise estimate of a treatment effect than individual trials alone. Pooling observational studies to increase statistical power may introduce bias that is difficult to interpret. Most authorities believe that observational studies should be synthesized separately from randomized controlled trials, if they are synthesized at all.

USING EVIDENCE-BASED PRACTICE PROTOCOLS

Evidence-based practice protocols have been developed to guide clinical decision making. The stages of development of practice protocols are similar to that described for the clinician practicing evidence-based medicine independently. They are:

- defining the problem
- identifying and critically appraising available evidence
- translating the evidence into clinical policy ([8]).

Rules for developing clinical guidelines have been developed by the Institute of Medicine. The Canadian Task Force on Periodic Health Examination established a process to rate the quality of evidence for guideline development that has been adopted by others, including the U.S. Preventive Services Task Force and the American College of Obstetricians and Gynecologists (ACOG).

The general intent of practice guidelines is to “inform medical decisions and to decrease variations in care by systematically influencing clinical decisions” ([9]). However, guidelines may be influenced by the author's intent—whether it is improving quality of care, saving costs, or reducing liability. Regardless of perspective, the common denominator should be policies firmly based on evidence where evidence is available. Whether or not clear evidence is available, the basis on which policy decisions were made should be explicit.

In 1995, ACOG established an evidence-based guidelines process. Guidelines initially called *Practice Patterns* and now called *Practice Bulletins* are based on evidence that is evaluated and graded. Considerations regarding costs are also addressed.

Evidence suggests that, in general, practice guidelines have the potential to improve patient care. Weingarten has argued for careful testing of practice guidelines to determine which improve patient care ([9]). Even good guidelines will become obsolete if not kept up to date, so date of preparation is important to consider.

PRACTICING EVIDENCE-BASED MEDICINE INDEPENDENTLY

The obstetrician-gynecologist who practices evidence-based medicine independently needs to be able to accomplish four basic tasks ([10]):

1. frame the clinical problem into a researchable question
2. design and conduct a thorough search of the literature relevant to the question
3. evaluate the quality of evidence obtained from the literature search and summarize the best available evidence to address the clinical question
4. apply the best available evidence to the care of the individual patient, taking into account each patient's circumstances, values, and preferences.

Education in evidence-based medicine works best if clinical questions arise from current dilemmas in patient care. This technique keeps the level of interest high, the applicability pertinent, and the effort current. Convenient access to a computer for on-line searching is preferable and increasingly powerful, but some searching for some topics may need to take place among journals and textbooks. In this section, we follow one scenario through all four tasks of practicing evidence-based medicine.

Task 1. Ask an Answerable Question

Framing the clinical question is the first and one of the most important steps in practicing evidence-based medicine. The question should be focused and answerable. Sackett and colleagues have suggested that a well-built, answerable question has four parts: a description of the patient or problem, a statement of the intervention

being considered, a statement of the alternative to the intervention, and a description of the desired outcome ([10]). Many times the question will be obvious, such as the starting dose of a new medication, and the resource will be handy, such as a formulary book. Other times, the question will not be clear or there may be several kinds of questions that would apply to a single patient problem. To illustrate how to ask an answerable question, we will present a clinical scenario and follow it through the evidence-based medicine process. The example we have chosen is a question about treatment. Other possible topics for questions include diagnostic tests, prognosis, harm, and the evaluation of guidelines.

Example A 36-year old, gravida 2, para 1 presents to labor and delivery at 31 weeks gestation. She reports leaking fluid for approximately 4 hours. The current pregnancy has been otherwise uncomplicated. Physical examination reveals no signs of infection and confirms membrane rupture. The patient is having a few small, irregular contractions that she cannot feel; fetal heart tones are 120 beats per minute with good variability; her cervix is 2 to 3 cm dilated. For this example, we have constructed the following question, “In patients who have preterm premature rupture of the membranes, would steroid therapy to reduce the complications of prematurity, when compared with observation alone, lead to lower mortality or morbidity from premature delivery?” In our example, the description of the patient is addressed (“in patients who have preterm, premature rupture of membranes”), the intervention being considered is stated (“would steroid therapy to reduce the complications of prematurity”) as is the alternative (“when compared with observation alone”). The question concludes with a description of the desired outcome (“lead to lower mortality or morbidity from premature delivery”). Several different questions can be framed from this clinical scenario. The first question we framed was designed to select a therapy. A question about determining etiology (e.g., “In patients with a pregnancy resulting in preterm premature rupture of the membranes, is a culture for group B *Streptococcus* more likely to be positive compared to patients with rupture of the membranes at term?”) Similarly we could have asked about prevention, such as, “In patients with a history of preterm premature rupture of the membranes, does first trimester screening and treatment for bacterial vaginosis reduce the likelihood of recurrence with subsequent pregnancies relative to no screening and treatment?” Sometimes it may be difficult to identify an answerable question. In other cases there may be more questions than time to answer them. Prioritization would ensure that the most important issue for the patient or the question most likely to be encountered again in clinical practice will be answered.

Task 2. Search for Evidence

Once the question has been framed, the pertinent evidence must be searched. The first step in this task is determining the resource most likely to be helpful in the search. The best resource may differ depending on the question posed. For treatment effectiveness or safety, the most useful and scientifically sound sources will be randomized controlled trials and systematic reviews. If one expects that a sufficient number of randomized trials have been conducted to warrant a useful systematic review, a good initial step to assess questions about treatment would be to search Ovid's Evidence-Based Medicine Reviews and search the Cochrane Library, Clinical Evidence, ACP Journal Club, and MEDLINE simultaneously.

Example The use of steroids for reducing neonatal morbidity has been a recognized therapy since the 1970s and enough clinical trials have been reported that systematic reviews have been published. Thus, we chose to search the Cochrane Library, a database with systematic reviews. After locating the Cochrane Library on the Internet or loading the program from purchased disks, we identify the Cochrane Library introductory page. After clicking on the search icon, we enter the word “steroid” as a key word and the search is initiated by clicking on the search button. At the top of the page, the index lists the types of information available for our search. Under the heading, “systematic reviews,” is a subheading, “complete reviews.” By scrolling down the list under this subheading, we quickly (in less than 1 minute) identify a recent (January 1996) critical review “Corticosteroids prior to preterm delivery.” The Cochrane Library is one of the specialized databases developed by a group of individuals committed to preparing, maintaining, and disseminating systematic reviews of the effects of health care. These systematic reviews use explicitly defined methods to reduce the effects of bias. The Library includes databases of Cochrane and non-Cochrane systematic reviews plus a clinical trials database of over 150,000 entries. Although the database of systematic reviews includes unpublished reports and information not available on MEDLINE, it does not yet cover all clinical areas. Nevertheless, perinatal medicine and many topics in women's health are well represented. The Cochrane Library is available through the Internet (via Ovid's Evidence-Based Medicine Reviews or after subscribing at http://www.ovid.com/) and on CD-ROM from Update Software in Oxford, England, the BMJ Publishing Group in London.

Sources of Evidence

For some questions and clinical problems, systematic reviews or meta-analyses may not be available. In such cases, the searcher will have to identify individual studies, rate these studies for quality, and then synthesize the best available evidence. The largest available source of medical literature is the National Library of Medicine's MEDLINE, a bibliographic database covering materials from 1966 to the present. Facilitated access to millions of articles from more than 3,000 journals has led the way to specialized databases. MEDLINE can be obtained in libraries or purchased through commercial vendors; it is available on-line. Members of ACOG can access MEDLINE through ACOGNET. MEDLINE is also free on the Internet (http://www.ncbi.nlm.nih.gov/pubmed). If one intends to use MEDLINE as a standalone resource, it is generally most expedient to go directly to PubMed. Also, for clinical questions, there is a special screen that provides more evidence-based, clinically relevant searches: http://www.ncbi.nlm.nih.gov:80entrez/query/static/clinical.html — the search, for example, takes about 10 seconds and one of the references identified is the current Cochrane Review.

Example We also conduct a separate search on the MEDLINE main search screen which takes longer to locate publications under the text words “corticosteroids” and “preterm”. Because MEDLINE contains millions of articles and the Cochrane Library contains only systematic reviews, the Cochrane Library, in this case, provides the best available evidence more efficiently. ACOG has a Web site accessible to its members. In addition to MEDLINE, publications of ACOG, including evidence-based *Practice Bulletins*, are available on-line. Similarly, the American College of Physicians (ACP) has a database—directed mainly to internists—derived from structured abstracts and clinical commentaries based on a preestablished methodology that screens out poor evidence (http://www.acpjc.org/). Consensus guidelines offer another potential source of evidence. However, consensus guidelines often provide summaries of evidence without clearly stating how the evidence was obtained and evaluated. The National Institutes of Health (NIH) has a Web site that makes available its consensus guidelines and workshop proceedings (http://odp.od.nih.gov/consensus). The National Guideline Clearinghouse (http://www.guideline.gov/index.asp) includes a broader range of guidelines.
Example Through the Internet, we identify two NIH consensus reports on the use of corticosteroids to reduce morbidity from prematurity. The most recent consensus panel addresses changes in practice from single-dose therapy to multiple-dose therapy. However, the basis for the first NIH report was the Cochrane Library systematic review. A search of the National Guideline Clearinghouse on “preterm and corticosteroids” provides one relevant guideline, “Management of preterm labour” from the Singapore Ministry of Health/National Medical Research Council (Singapore Ministry of Health)/Chapter of Obstetricians and Gynaecologists, Academy of Medicine, Singapore, May 2001.

Task 3. Appraise the Evidence

Once we complete our search for the evidence, we assess both the importance and the validity of the evidence for use of corticosteroids to accelerate fetal lung maturity.

Example The Cochrane systematic review “Corticosteroids prior to preterm delivery” included 18 randomized trials that are of acceptable quality (i.e., meet specified criteria for the elimination of bias, as described in the *Cochrane Collaboration Handbook*, which is included in the Cochrane Library) and that report clinically relevant outcomes. Thus, we found strong evidence on the general subject of using corticosteroids prior to preterm delivery. Our specific question, however, dealt with the use of corticosteroids in the presence of ruptured membranes. The description of study methods in the review was sufficiently detailed to determine that women with preterm, premature rupture of the membranes were not subjects in two of the 18 studies included in the systematic review. We obtain copies of the other 16 reports and determine that five have data on the risk of neonatal respiratory distress syndrome for women with preterm, premature rupture of the membranes at 31 weeks gestation and who had corticosteroids administered without other interventions. We used SAS to calculate the relative risks. Together, these five reports provide support for use of corticosteroids among such women. The summary risk estimate of neonatal respiratory distress syndrome for women who had corticosteroids administered relative to the risk in women who did not have corticosteroids administered is 0.58 (95% confidence interval, range: 0.44–0.76) (Table 59.3). Because the 95% confidence interval does not overlap 1.0, the reduction in risk for women who had corticosteroids administered is tatistically significant.

TABLE 59.3. *Selected studies [a] of the effect of corticosteroids after prelabor rupture of the membranes on respiratory distress syndrome*

While reading the Cochrane review, we find that randomized trials with long-term infant follow-up are available to assess the likelihood of late sequelae of steroid therapy. While reviewing the NIH consensus panel report from 2000, we also note that several of these trials may have included multiple-dose therapy. The NIH consensus panel report from 2000 discusses the practices of single-dose versus multiple-dose therapy and notes that there is not adequate, unbiased evidence to support multiple doses of antenatal steroids. Evidence from randomized trials, several of which are underway, is needed to resolve ongoing questions about the benefits and risks of multiple-dose therapy. Ongoing clinical trials funded by the NIH can be accessed at http://www.clinicaltrials.gov/.

Assessing Importance and Validity

The task of appraising the evidence includes assessing both the importance and the validity of the evidence. Some clinicians choose to determine validity before evaluating importance, and others reverse the order. No matter what the order, when the first step is promising, the other must be completed.

An assessment of the importance of a study finding focuses both on the strength of the association between the factor under investigation and the study outcome and on the number of people potentially affected by the finding. Measures commonly used to assess the strength of association in epidemiologic studies are the odds ratio (OR) (Fig. 59.2) and the relative risk (RR) (Fig. 59.3). As discussed subsequently, a properly conducted randomized controlled trial provides the highest quality of evidence; the RR is the measure of association commonly used in such trials and provides a result that is easier for most clinicians to interpret, especially when the rate of events is high (when the event rates are low, the OR and RR are very close numerically).

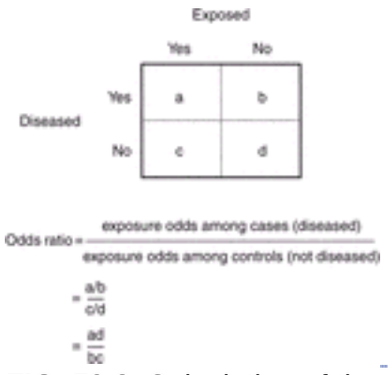

FIG. 59.2. Calculation of the odds ratio using the 2 × 2 table. The values a, b, c, and d represent the numbers of people in each of four possible combinations of exposure and disease status.

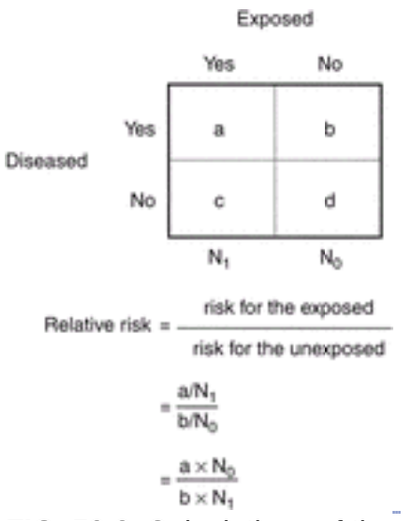

FIG. 59.3. Calculations of the relative risk using the 2 × 2 table. The values a, b, c, and d represent the numbers of people in each of four possible combinations of exposure and disease (N_1, total number exposed; N_0, total number unexposed).

The obstetrician-gynecologist assessing validity is searching for biases. Sackett and colleagues ([10]) have provided questions that may aid in an assessment of validity including those adapted for Table 59.2 and included in Table 59.4. Biases are systematic errors, either in design or analysis, that could lead to an incorrect conclusion. Biases can result from the way study participants were selected (selection bias), from the way information was collected from study participants (information bias), and from failure to adjust for factors that influence the study outcome but that are extraneous to the study's question (confounders). Biases may distort the measure of study outcomes so greatly that study data may suggest a strong association (a potentially important effect) when, in fact, no association exists. Conversely, the data may suggest no association when a strong one is present. In other words, biases may lead to a distortion of the truth.

The main questions to answer:
1. Was the assignment of patients to treatments randomized? and was the randomization list concealed?
2. Were all patients who entered the trial accounted for at its conclusion? and were they analyzed in the groups to which they were randomized?
And, some finer points to address:
1. Were patients and clinicians kept "blind" to which treatment was being received?
2. Aside from the experimental treatment, were the groups treated equally?
3. Were the groups similar at the start of the trial?

Source: Sackett DL, Richardson WS, Rosenberg W, et al. *Evidence-based medicine: how to practice and teach EBM.* New York: Churchill Livingstone, 1997:92.

TABLE 59.4. *Are the results of this single study valid?*

When a recent systematic review of randomized controlled trials (such as those available from the Cochrane Library) is available, the obstetrician-gynecologist can accept the conclusions of the reviewer, critically appraise the quality of the review by using criteria such as those in Table 59.2 and Table 59.4, or conduct an independent search and review of the evidence. When a recent systematic review is not available, the obstetrician-gynecologist must track down and critically appraise the available evidence.

The system for evaluating the quality of evidence proposed by the Canadian Task Force on Periodic Health Examination and adopted by the U.S. Preventive Services Task Force (Table 59.5) is a useful framework for assessing the relative strengths and weaknesses of different types of epidemiologic studies.

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Source: U.S. Preventive Services Task Force. *Guide to clinical preventive services,* second ed. Baltimore: Williams & Wilkins, 1996.

TABLE 59.5. *System for evaluating quality of evidence proposed by the Canadian Task Force on Periodic Health Examination*

Types of Epidemiologic Studies

A basic understanding of epidemiologic methods is necessary for intelligent appraisal of medical evidence. Brief reviews of epidemiologic methods are available, as is a series of articles in the *Journal of the American Medical Association* (free on the Internet, available at http://www.cche.net/usersguides/main.asp) specifically intended to help clinicians critically appraise the medical literature. Standard texts of clinical epidemiology are also helpful.

Most of the studies in the medical literature that will be relevant to clinical decision making in obstetrics and gynecology are epidemiologic studies. The goal of an epidemiologic study is to accurately measure the relationship between an exposure of interest (e.g., steroid therapy) and an outcome of interest (e.g., neonatal morbidity and mortality from respiratory distress syndrome). The two basic types of epidemiologic studies are experimental and observational.

In experimental studies (e.g., randomized controlled trials), the exposure is manipulated and the effect of that manipulation on the outcome is measured directly. When properly conducted, these studies provide the strongest evidence because they are least likely to be affected by bias and, thus, are most likely to obtain an accurate measure. However, randomized trials are of varying quality. A poorly conducted randomized trial may be of little or no value. The U. S. Preventive Services Task Force requires that randomized trials be “properly conducted” to be considered high-quality evidence (see Table 59.5). Other guidelines for evaluating the quality of randomized trials (The CONSORT statement, http://www.consort-statement.org/) are also available.

In observational studies (e.g., cohort, case-control, and cross-sectional studies), the exposure is observed rather than manipulated. Observational studies provide a wide range of quality of evidence. The quality of evidence from cohort (follow-up) studies, in which study participants are classified as exposed or unexposed to the factor of interest and then followed over time to see whether they develop the outcome of interest, depends on the strength of the study design and analysis. Case-control studies, in which study participants are classified as having or not having the outcome of interest (typically a disease), then assessed to determine whether they were exposed to a factor of interest in the past, have the same potential range of quality. Although prospective studies (including cohort studies) are often thought to be methodologically superior to retrospective (including case-control) studies, theoretically, a perfectly conducted cohort study will provide the same level of evidence as a perfectly conducted case-control study. In practice, however, retrospective (including case-control) studies are generally more susceptible to bias than are prospective (including cohort) studies.

Cross-sectional studies warrant special mention for the lack of evidence they typically provide. Cross-sectional studies can be regarded as a snapshot of individuals that provides information about whether the individuals have been exposed to the factor of interest and whether they have the outcome of interest at that moment. In these studies, the quality of evidence is typically very low because little information is available about whether the exposure caused the outcome. In fact, in many cross-sectional studies it is impossible to determine whether the outcome preceded the exposure.

An example concerning the use of condoms for human immunodeficiency virus (HIV) prevention may be helpful for distinguishing the four types of epidemiologic studies discussed here:

- *Randomized controlled trial:* Men at risk for acquiring HIV infection are randomized to use or nonuse of latex condoms and then followed over time to determine whether they become infected. Although, it would be unethical to assign one study group a known effective strategy for preventing a deadly disease and leaving the other group at risk, a randomized trial of a behavioral intervention to encourage men to use condoms could potentially be conducted without ethical proscriptions.
- *Cohort (follow-up) study:* Men at risk for HIV infection who choose to use latex condoms consistently and men who choose not to are followed over time to determine whether they become infected. Important differences between men who do and do not use condoms that influence the risk of acquiring HIV infection may bias the estimate of the effect of condom use.
- *Case-control study:* Men with and without HIV infection are selected for study and then asked to provide a detailed record of prior condom use. Men with HIV infection may be more or less likely than uninfected men to recall condom use accurately; differences in recall (a type of information bias) may bias study findings. In the cohort study design, men would be asked to prospectively chart condom use which would likely lead to a better measure of condom use than reliance on memory alone.
- *Cross-sectional study:* Men with and without HIV infection are asked about current or recent condom use. It is impossible, however, to determine whether the condom use preceded or followed infection with HIV.

Task 4: Apply the Evidence

Once the importance and validity of the evidence have been assessed, the evidence has to be applied to an individual patient. The smaller the number of randomized controlled trials available to assess the safety and effectiveness of treatment and the narrower the variety of clinical circumstances studied, the more the obstetrician-gynecologist will need to rely on clinical expertise to determine how the available evidence applies to a particular patient. One approach to this task is asking, “Would my patient satisfy the eligibility criteria for the trial?” ([10]) or, “Is my patient so different from those in the trial that the results don't apply to her?”

Evidence-based medicine also considers the values and preferences of each patient. The values and preferences of the patient may well tip the scale toward or away from a given treatment, particularly in instances where the balance of risks and benefits of treatment are unclear or there are competing options with similar balances of somewhat different benefits and risks.

Example Our review of the evidence indicates that single-dose corticosteroids are safe and effective to use for preterm, premature rupture of membranes. The findings applied to a broad range of gestational ages of less than 35 weeks, male and female infants, and across races. No adverse consequences for any subgroups were identified. Thus, there is good evidence that our patient is an appropriate candidate for corticosteroid therapy. Because the benefits are substantial and there are no documented risks, the patient will likely agree to steroid therapy.

SUMMARY POINTS

- Evidence-based medicine is neither “cookbook” medicine nor “cost-cutting” medicine. Rather, it is the use of the best available evidence in caring for an individual.
- The practice of evidence-based medicine brings into play three components: Clinical state and circumstance; patients' preferences and actions; and research evidence. Depending on the circumstances, one component may play a greater role than another.
- Obstetrician-gynecologists can practice evidence-based medicine by using evidence-based medical summaries, systematic reviews, or evidence-based practice protocols.
- Obstetrician-gynecologists can also learn to practice evidence-based medicine independently by becoming proficient at four tasks:
  - framing a researchable question
  - conducting a search for evidence to address the question
  - critically appraising the evidence
  - applying the evidence to the individual patient.

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Color Plate

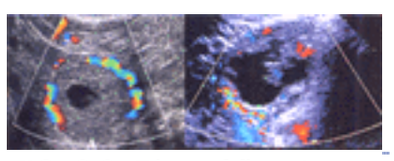

FIG. 8.2. Ring of fire. A corpus luteum **(A)** can be confused with an ectopic pregnancy **(B).** The *arrow* indicates blood flow in the embryo **(B).** (From Diana M. Strickland, RDMS, RDCS; with permission.) (This figure is printed in black and white as Figure 8.2)

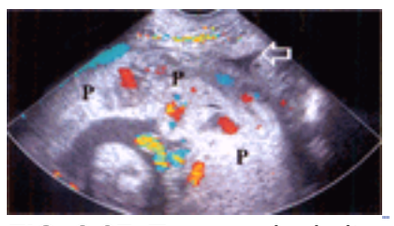

FIG. 8.27. Transvaginal ultrasonogram of a placenta previa. The placenta *(P)* covers the internal os. The tip of the transvaginal probe is in the anterior fornix. (This figure is printed in black and white as Figure 8.27)

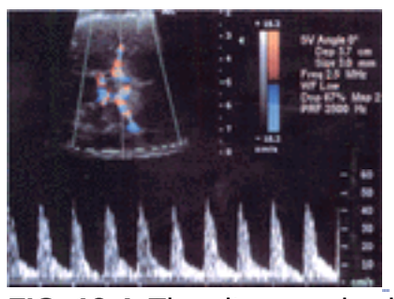

FIG. 12.4. The ultrasound color Doppler image shows the circle of Willis and the middle cerebral artery branches. Also shown is the near 0-degree angle of insonation and the middle cerebral artery flow velocity waveform. (This figure is printed in black and white as Figure 12.4)

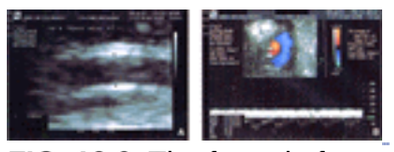

FIG. 12.9. The formula for measurement of umbilical venous flow is shown. **A:** On ultrasound, how to obtain umbilical vein diameter (note that the calipers are placed just inside the specular reflections). **B:** On ultrasound, how color is used to ensure an angle of insonation at nearly 0 degrees and how Doppler velocimetry is used to obtain a steady umbilical vein waveform velocity. (This figure is printed in black and white as Figure 12.9)

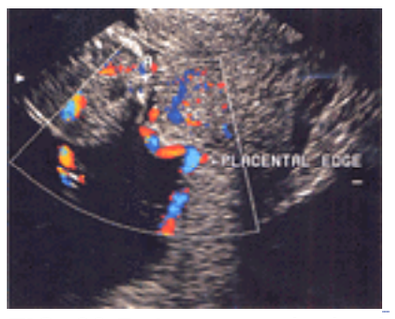

FIG. 20.5. A transvaginal color Doppler ultrasound image of a suspected vasa previa. Markers indicate the distance between the internal os and the cord insertion into the membranes away from the placental edge, a distance less than 1 cm. (This figure is printed in black and white as Figure 20.5)

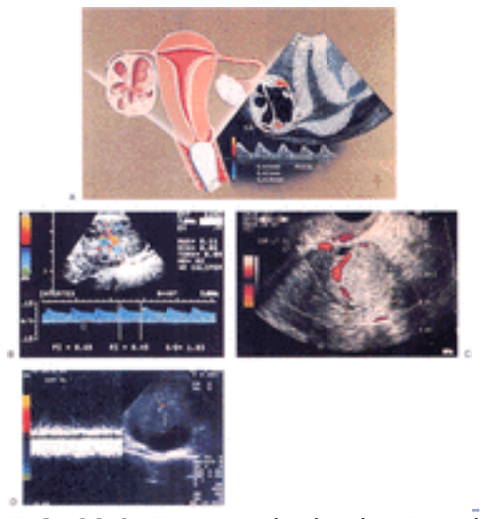

FIG. 28.3. Transvaginal color Doppler sonography (TV-CDS). **A:** Diagram showing the components of a TV-CDS, which include real-time imaging and display of vessels, with subsequent selection of sample volume for Doppler analysis by evaluation of the Doppler waveform. (Drawing by Paul Gross, MS.) **B:** TV-CDS showing low-impedance flow (resistive index = 0.45; pulsatile index = 0.60) within the wall of a corpus luteum. **C:** Amplitude color Doppler image of hemorrhagic corpus luteum showing no flow within the center of the mass, which contained organized clot. **D:** Complex mass with low-impedance arterial and increased venous flow within an irregular solid area, highly indicative of ovarian cancer. (This figure is printed in black and white as Figure 28.3)

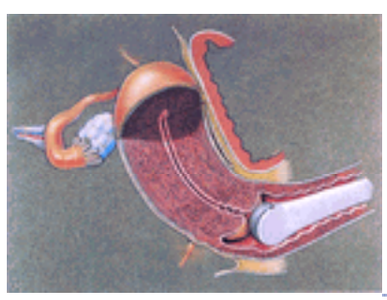

FIG. 28.5. Endometrial disorders. **A:** Diagram showing proximity of the endometrium of an anteflexed uterus to the transvaginal probe. The field of view depicting the long axis of the uterus and endometrium is shown. (Drawing by Paul Gross, MS.) (This figure is printed in black and white as Figure 28.5)

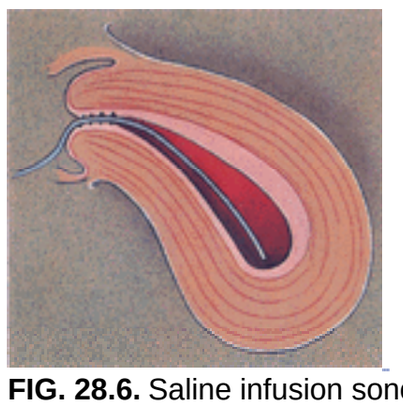

FIG. 28.6. Saline infusion sonohysterography (SIS). **A:** Diagram showing intrauterine catheter used for distension of lumen with saline for detailed evaluation of the endometrium from the inside. (Diagram by Paul Gross, MS.) (This figure is printed in black and white as Figure 28.6)

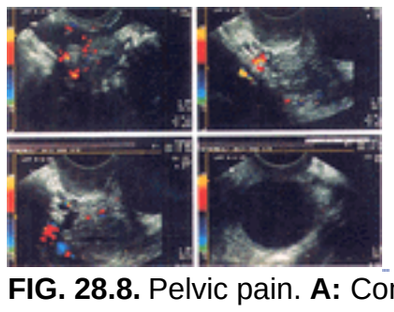

FIG. 28.8. Pelvic pain. **A:** Composite transvaginal sonogram showing enlarged left ovary (**top right and bottom left**) without flow and associated with a paraovarian cyst in left adnexa (**lower right**). The right ovary (**top left**) was normal, showing intraparenchymal flow. The left adnexa was found to be twisted three times and was surgically untwisted with good result. (This figure is printed in black and white as Figure 28.8)

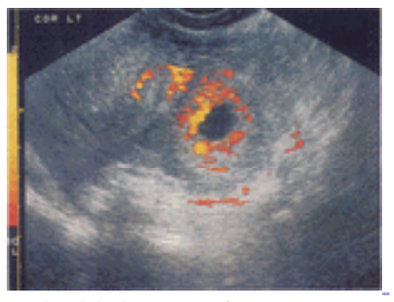

FIG. 28.9. Ectopic pregnancy. **B:** Transvaginal color Doppler sonogram showing vascularity of “tubal ring” of an unruptured ectopic pregnancy. (This figure is printed in black and white as Figure 28.9)

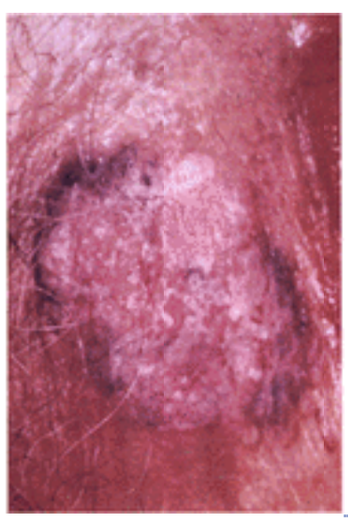

FIG. 33.3. Squamous cell hyperplasia of the vulva. Pruritic vulvar hypertrophied plaque of squamous cell hyperplasia with associated postinflammatory hyperpigmentation. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) (This figure is printed in black and white as Figure 33.3)

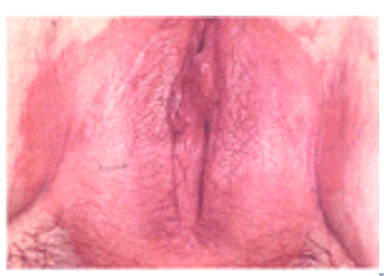

FIG. 33.6. Seborrhea. The involved vulvar skin is somewhat reddened. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) (This figure is printed in black and white as Figure 33.6)

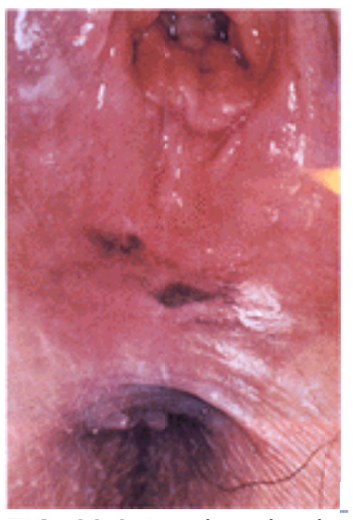

FIG. 33.9. Lentigo simplex. Several small flat pigmented lesions of lentigo simplex. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) (This figure is printed in black and white as Figure 33.9)

FIG. 33.12. Postinflammatory hypopigmentation. The white area has lost melanocytes and melanin. (From Wilkinson, Stone. *Atlas of vulvar disease.* Philadelphia: Lippincott, Williams and Wilkins, with permission.) (This figure is printed in black and white as Figure 33.12)

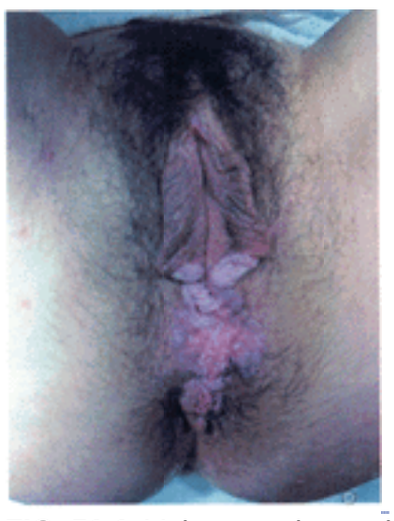

FIG. 51.1. Vulvar carcinoma in situ presenting as white or hyperpigmented lesion. (This figure is printed in black and white as Figure 51.1)

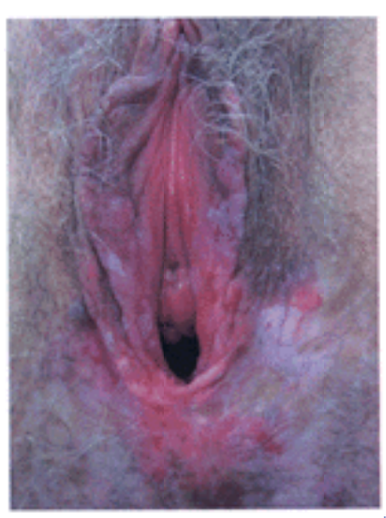

FIG. 51.2. Vulvar carcinoma in situ before application of 5% acetic acid. (This figure is printed in black and white as Figure 51.2)

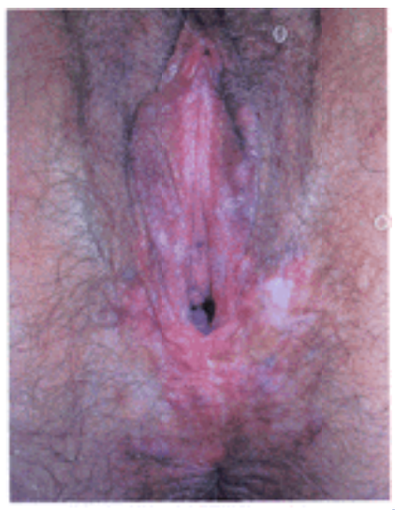

FIG. 51.3. Vulvar carcinoma in situ after application of 5% acetic acid. (This figure is printed in black and white as Figure 51.3)

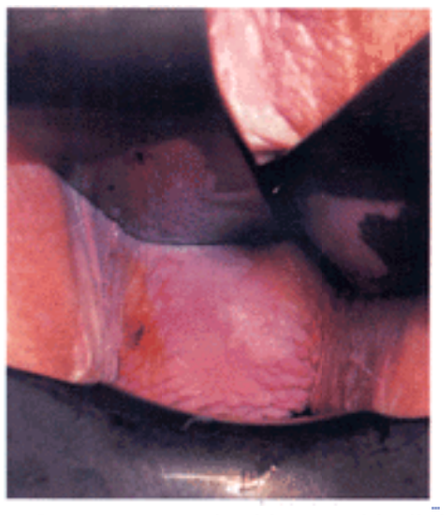

FIG. 51.15. Vaginal intraepithelial neoplasia III after application of acetic acid. Note acetowhite lesions. (This figure is printed in black and white as Figure 51.15)