18 - Gynecology and Obstetrics

Chapter 244. Approach to the Gynecologic Patient

Introduction

Gynecologic evaluation may be necessary to assess a specific problem such as pelvic pain, vaginal bleeding, or vaginal discharge (see also Ch. 253). Women also need routine gynecologic evaluations, which may be provided by a gynecologist, an internist, or a family practitioner; evaluations are recommended every year for all women who are sexually active or > 18 yr. Many women expect their gynecologist to provide general as well as gynecologic health care. Obstetric evaluation focuses on issues related to pregnancy (see Ch. 261).

General Gynecologic Evaluation

Most women, particularly those seeking general preventive care, require a complete history and physical examination as well as a gynecologic evaluation.

History

Gynecologic history consists of a description of the problem prompting the visit (chief complaint, history of present illness); menstrual, obstetric, and sexual history; and history of gynecologic symptoms, disorders, and treatments.

Current symptoms are explored using open-ended questions followed by specific questions about the following:

• Pelvic pain (location, duration, character, quality, triggering and relieving factors)

• Abnormal vaginal bleeding (quantity, duration, relation to the menstrual cycle)

• Vaginal discharge (color, odor, consistency), irritation, or both

Patients of reproductive age are asked about symptoms of pregnancy (eg, morning sickness, breast tenderness, delayed menses).

Menstrual history includes the following:

• Age at menarche

• Number of days of menses

• Length and regularity of the interval between cycles

• Start date of the last menstrual period (LMP)

• Dates of the preceding period (previous menstrual period, or PMP)

• Color and volume of flow

• Any symptoms that occur with menses (eg, cramping, loose stools)

Usually, menstrual fluid is medium or dark red, and flow lasts for 5 (± 2) days, with 21 to 35 days between menses; average blood loss is 30 mL (range, 13 to 80 mL), with the most bleeding on the 2nd day. A saturated pad or tampon absorbs 5 to 15 mL. Cramping is common on the day before and on the first day of menses. Vaginal bleeding that is painless, scant, and dark, is abnormally brief or prolonged, or occurs at irregular intervals suggests absence of ovulation (anovulation).

Obstetric history (see p. 2606) includes dates and outcomes of all pregnancies and previous ectopic or molar pregnancies.

Sexual history should be obtained in a professional and nonjudgmental way and includes the following:

• Frequency of sexual activity

• Number and sex of partners

• Use of contraception

• Participation in unsafe sex

• Effects of sexual activity (eg, pleasure, orgasm, dyspareunia)

Past gynecologic history includes questions about previous gynecologic symptoms (eg, pain), signs (eg, vaginal bleeding, discharge), and known diagnoses, as well the results of any testing.

Screening for domestic violence should be routine. Methods include self-administered questionnaires and a directed interview by a staff member or physician. In patients who do not admit to experiencing abuse, findings that suggest past abuse include the following:

• Inconsistent explanations for injuries

• Delay in seeking treatment for injuries

• Unusual somatic complaints

• Psychiatric symptoms

• Frequent emergency department visits

• Head and neck injuries

• Prior delivery of a low-birth-weight infant

Physical Examination

The examiner should explain the examination, which includes breasts (see p. 2552), abdomen, and pelvis, to the patient.

For the pelvic examination, the patient lies supine on an examination table with her legs in stirrups and is usually draped. A chaperone may be required, particularly when the examiner is male, and may also provide assistance. The pubic area and hair are inspected for lesions, folliculitis, and lice. The perineum is inspected for redness, swelling, excoriations, abnormal pigmentation, and lesions (eg, ulcers, pustules, nodules, warts, tumors). Structural abnormalities due to congenital malformations or female genital mutilation are noted. A vaginal opening that is < 3 cm may indicate infibulation, a severe form of genital mutilation (see p. 3067).

Next, the introitus is palpated between the thumb and index finger for cysts or abscesses in Bartholin's glands. While spreading the labia and asking the patient to bear down, the examiner checks the vaginal opening for signs of pelvic relaxation: an anterior bulge (suggesting cystocele), a posterior bulge (suggesting rectocele), and displacement of the cervix toward the introitus (suggesting prolapsed uterus —see p. 2531).

Before speculum and bimanual examination, the patient is asked to relax her legs and hips and breathe deeply.

Speculum examination: The speculum is sometimes kept warm with a heating pad and may be moistened or lubricated before insertion, particularly when the vagina is dry. If a Papanicolaou (Pap) test or cervical culture is planned, the speculum is rinsed with warm water; lubricant should not be used. A gloved finger is inserted into the vagina to determine the position of the cervix. Then, the speculum is inserted with the blades nearly in the vertical plane (at about 1 and 7 o'clock) while widening the vagina by pressing 2 fingers on the posterior vaginal wall (perineal body). The speculum is fully inserted toward the cervix, then rotated so that the handle is down, and gently opened; it is pulled back as needed to visualize the cervix. When the cervix is seen, the blades are positioned so that the posterior blade is deeper than the cervix (in the posterior fornix) and the anterior blade is allowed to rise gently and rest anterior to the cervix (in the anterior fornix). The examiner should take care to open the anterior blade slowly and gently and not to pinch the labia or perineum as the speculum is opened. Normally, the cervix is pink and shiny, and there is no discharge.

A specimen for the Pap test is taken from the endocervix and external cervix with a brush and plastic spatula or with a cervical sampler that can simultaneously collect cells from the cervical canal and the transition zone; the specimen is rinsed in a liquid, producing a cell suspension to be analyzed for cancerous cells and human papillomavirus. Specimens for detection of sexually transmitted diseases (STDs) are taken from the endocervix. The speculum is withdrawn, taking care not to pinch the labia with the speculum blades.

Bimanual examination: The index and middle fingers of the dominant hand are inserted into the vagina to just below the cervix. The other hand is placed just above the pubic symphysis and gently presses down to determine the size, position, and consistency of the uterus and, if possible, the ovaries. Normally, the uterus is about 6 cm by 4 cm and tilts anteriorly (anteversion), but it may tilt posteriorly (retroversion) to various degrees. The uterus may also be bent at an angle anteriorly (anteflexion) or posteriorly (retroflexion). The uterus is movable and smooth; irregularity suggests uterine fibroids (leiomyomas). Normally, the ovaries are about 2 cm by 3 cm in young women and are not palpable in postmenopausal women. With ovarian palpation, mild nausea and tenderness are normal. Significant pain when the cervix is gently moved from side to side (cervical motion tenderness) suggests pelvic inflammation.

Rectal examination: After bimanual palpation, the examiner palpates the rectovaginal septum by inserting the index finger in the vagina and the middle finger in the rectum.

Children: The examination should be adjusted according to children's psychosexual development and is usually limited to inspection of the external genitals. Young children can be examined on their mother's lap. Older children can be examined in the knee-chest position or on their side with one knee drawn up to their chest. Vaginal discharge can be collected, examined, and cultured.

Sometimes a small catheter attached to a syringe of saline is used to obtain washings from the vagina. If cervical examination is required, a fiberoptic vaginoscope, cystoscope, or flexible hysteroscope with saline lavage should be used.

In children, pelvic masses may be palpable in the abdomen.

Testing

Testing is guided by the symptoms present.

Pregnancy testing: Most women who are of reproductive age and have gynecologic symptoms are tested for pregnancy (see p. 2623). Urine assays of the β subunit of human chorionic gonadotropin (β-hCG) are specific and highly sensitive; they become positive within about 1 wk of conception. Serum assays are specific and even more sensitive.

Pap testing: Specimens of cervical cells taken for the Pap test are examined for signs of cervical cancer; the examination may also detect uterine cancer and human papillomavirus. Pap tests are done routinely for most of a woman's life (see p. 2580).

Microscopic examination of vaginal secretions: This examination helps identify vaginal infections

(eg, trichomoniasis, bacterial vaginosis, yeast infection—see Ch. 253).

Microbiologic testing: Culture or molecular methods (eg, PCR) are used to analyze specimens for specific STD organisms (eg, *Neisseria gonorrhoeae, Chlamydia trachomatis*) if patients have symptoms or risk factors; in some practices, such analysis is always done.

Cervical mucus inspection: Bedside inspection of a cervical mucus specimen by a trained examiner can provide information about the menstrual cycle and hormone states; this information may help in assessment of infertility and time of ovulation. The specimen is placed on a slide, allowed to dry, and assessed for degree of microscopic crystallization (ferning—see p. 2501), which reflects levels of circulating estrogens. Just before ovulation, cervical mucus is clear and copious with abundant ferning because estrogen levels are high. Just after ovulation, cervical mucus is thick and ferns little.

Imaging tests: Imaging of suspected masses and other lesions usually involves ultrasonography, which may be done in the office; both transvaginal and transabdominal probes are used. MRI is highly specific but expensive. CT is usually less desirable because it is somewhat less accurate, involves significant radiation exposure, and often requires a radiopaque agent.

Laparoscopy: This surgical procedure can detect structural abnormalities too small to be detected by imaging, as well as abnormalities on the surfaces of internal organs (eg, endometriosis, inflammation, scarring). It is also used to sample tissue.

Culdocentesis: Culdocentesis, now rarely used, is needle puncture of the posterior vaginal fornix to obtain fluid from the cul-de-sac (which is posterior to the uterus) for culture and for tests to detect blood from a ruptured ectopic pregnancy or ovarian cyst.

Endometrial aspiration: This procedure is done if women > 35 have unexplained vaginal bleeding. A thin, flexible, plastic suction curette is inserted through the cervix to the level of the uterine fundus; dilation is often not required. Suction is applied to the device, which is turned 360° and moved up and down a few times to sample different parts of the endometrial cavity. Sometimes the uterus must be stabilized with a cervical tenaculum.

Other tests: Pituitary and hypothalamic hormones (see p. 757) and ovarian hormones (see p. 2499) may be measured when infertility is evaluated or when abnormalities are suspected.

Pelvic Mass

(See also Chs. 250 and 256.)

A pelvic mass may be detected during routine gynecologic examination.

Etiology

Pelvic masses may originate from gynecologic organs (cervix, uterus, uterine adnexa) or from other pelvic organs (intestine, bladder, ureters, skeletal muscle, bone).

Type of mass tends to vary by age group.

In **infants,** in utero maternal hormones may stimulate development of adnexal cysts during the first few months of life. This effect is rare.

At **puberty,** menstrual fluid may accumulate and form a vaginal mass (hematocolpos) because outflow is obstructed. The cause is usually an imperforate hymen; other causes include congenital malformations of the uterus, cervix, or vagina.

In **women of reproductive age,** the most common cause of symmetric uterine enlargement is pregnancy, which may be unsuspected. Another common cause is fibroids, which may extend outward. Common adnexal masses include graafian follicles (usually 5 to 8 cm) that develop normally but do not

release an egg (called functional ovarian cysts). These cysts often resolve spontaneously within a few months. Adnexal masses may also result from ectopic pregnancy, ovarian or fallopian tube cancers, benign tumors (eg, benign cystic teratomas), or hydrosalpinges. Endometriosis can cause single or multiple masses anywhere in the pelvis, usually on the ovaries.

In **postmenopausal women,** masses are more likely to be cancerous. Many benign ovarian masses (eg, endometriomas, myomas) depend on ovarian hormone secretion and thus become less common after menopause.

Evaluation

History: General medical and complete gynecologic histories are obtained. Vaginal bleeding and pelvic pain suggest ectopic pregnancy or, rarely, gestational trophoblastic disease. Dysmenorrhea suggests endometriosis or uterine fibroids. In young girls, precocious puberty may indicate a masculinizing or feminizing ovarian tumor. In women, virilization may indicate a masculinizing ovarian tumor; menometrorrhagia or postmenopausal bleeding may indicate a feminizing ovarian tumor.

Examination: During the general examination, the examiner should look for signs of nongynecologic (eg, GI, endocrine) disorders and for ascites. A complete gynecologic examination is done. Distinguishing uterine from adnexal masses may be difficult. Endometriomas are usually nonmobile cul-de-sac masses. Adnexal cancers, benign tumors (eg, benign cystic teratomas), and adnexal masses due to ectopic pregnancy are mobile. Hydrosalpinges are usually fluctuant, tender, nonmobile, and sometimes bilateral. In young girls, pelvic organ masses may be palpable in the abdomen because the pelvis is too small to contain a large mass.

Testing: If the presence or origin (gynecologic vs nongynecologic) of a mass cannot be determined clinically, an imaging test can usually do so. Usually, pelvic ultrasonography is done first. If it does not clearly delineate size, location, and consistency of the mass, another imaging test (eg, CT, MRI) may. Ovarian masses with radiographic characteristics of cancer (eg, a solid component, surface excrescences, irregular shape) require needle aspiration or biopsy. Tumor markers may help in the diagnosis of specific tumors (see p. 1058).

Women of reproductive age are tested for pregnancy; if the test is positive, imaging is not always necessary (see p. 2608) unless ectopic pregnancy is suspected. In women of reproductive age, simple, thin-walled cystic adnexal masses that are 5 to 8 cm (usually graafian follicular cysts) do not require further investigation unless they persist for > 3 menstrual cycles.

Pelvic Pain

Pelvic pain is discomfort in the lower abdomen; it is a common complaint in women. It is considered separately from perineal pain, which occurs in the external genitals and nearby perineal skin.

Etiology

Pelvic pain may originate in reproductive organs (cervix, uterus, uterine adnexa) or other organs. Sometimes the cause is unknown.

Gynecologic disorders: Some gynecologic disorders (see Table 244-1) cause cyclic pain (ie, pain recurring during the same phase of the menstrual cycle). In others, pain is a discrete event unrelated to menstrual cycles. Whether onset of pain is sudden or gradual helps discriminate between the two.

[**Table 244-1.** Some Gynecologic Causes of Pelvic Pain]

Overall, the most common gynecologic causes of pelvic pain include

• Dysmenorrhea

• Ovulation (mittelschmerz)

• Endometriosis

Nongynecologic disorders: These disorders (see p. 105) may be

• GI (eg, gastroenteritis, inflammatory bowel disease, appendicitis, diverticulitis, tumors, constipation, intestinal obstruction, perirectal abscess, irritable bowel syndrome)

• Urinary (eg, cystitis, interstitial cystitis, pyelonephritis, calculi)

• Musculoskeletal (eg, diastasis of the pubic symphysis due to previous vaginal deliveries, abdominal muscle strains)

• Psychogenic (eg, somatization; effects of previous physical, psychologic, or sexual abuse)

The most common is difficult to specify.

Evaluation

Evaluation must be expeditious because some causes of pelvic pain (eg, ectopic pregnancy, adnexal torsion) require immediate treatment. Pregnancy should be excluded in women of childbearing age regardless of stated history.

History: History of present illness should include gynecologic history (gravity, parity, menstrual history, history of sexually transmitted disease) and onset, duration, location, and character of pain. Severity of pain and its relationship to the menstrual cycle are noted. Important associated symptoms include vaginal bleeding or discharge and symptoms of hemodynamic instability (eg, dizziness, light-headedness, syncope or near-syncope).

Review of systems should seek symptoms suggesting possible causes, including morning sickness, breast swelling or tenderness, or missed menses (pregnancy); fever and chills (infection); abdominal pain, nausea, vomiting, or change in stool habits (GI disorders); and urinary frequency, urgency, or dysuria (urinary disorders).

Past medical history should note history of infertility, ectopic pregnancy, pelvic inflammatory disease, urolithiasis, diverticulitis, and any GI or GU cancers. Any previous abdominal or pelvic surgery should be noted.

Physical examination: The physical examination begins with review of vital signs for signs of instability (eg, fever, hypotension) and focuses on abdominal and pelvic examinations.

The abdomen is palpated for tenderness, masses, and peritoneal signs. Rectal examination is done to check for tenderness, masses, and occult blood. Location of pain and any associated findings may provide clues to the cause (see Table 244-2).

Pelvic examination includes inspection of external genitals, speculum examination, and bimanual examination. The cervix is inspected for discharge, uterine prolapse, and cervical stenosis or lesions. Bimanual examination should assess cervical motion tenderness, adnexal masses or tenderness, and uterine enlargement or tenderness.

Red flags: The following findings are of particular concern:

• Syncope or hemorrhagic shock (eg, tachycardia, hypotension)

• Peritoneal signs (rebound, rigidity, guarding)

• Postmenopausal vaginal bleeding

• Fever or chills

• Sudden severe pain with nausea, vomiting, diaphoresis, or agitation

Interpretation of findings: Acuity and severity of pain and its relationship to menstrual cycles can suggest the most likely causes (see Table 244-1). Quality and location of pain and associated findings also provide clues (see Table 244-2):

Testing: All patients should have

• Urinalysis

• Urine pregnancy test

If a patient is pregnant, ectopic pregnancy is assumed until excluded by ultrasonography or, if ultrasonography is unclear, by other tests (see p. 2609). If a suspected pregnancy may be < 5 wk, a serum pregnancy test should be done; a urine pregnancy test may not be sensitive enough to rule out pregnancy that early in gestation.

Other testing depends on which disorders are clinically suspected. If a patient cannot be adequately examined (eg, because of pain or inability to cooperate) or if a mass is suspected, pelvic ultrasonography is done. If the cause of severe or persistent pain remains unidentified, laparoscopy is done.

Pelvic ultrasonography using a vaginal probe can be a useful adjunct to pelvic examination; it can better define a mass or help diagnose a pregnancy after 5 wk gestation. For example, free pelvic fluid and a positive pregnancy test plus no evidence of an intrauterine pregnancy help confirm ectopic pregnancy.

Treatment

The underlying disorder is treated when possible.

[**Table 244-2.** Some Clues to Diagnosis of Pelvic Pain]

Pain is initially treated with oral NSAIDs. Patients who do not respond well to one NSAID may respond to another. If NSAIDs are ineffective, other analgesics or hypnosis may be tried. Musculoskeletal pain may also require rest, heat, physical therapy, or, for fibromyalgia, injection of tender points.

For patients with intractable pain due to dysmenorrhea or another disorder, uterosacral nerve ablation or presacral neurectomy can be tried. If all measures are ineffective, hysterectomy can be done, but it may be ineffective or even worsen the pain.

Geriatrics Essentials

Pelvic pain symptoms in elderly women may be vague. Careful review of systems with attention to bowel and bladder function is essential.

A sexual history should be obtained; clinicians often do not realize that many women remain sexually active throughout their life. Whether a woman's partner is living should be determined before inquiring about sexual activity. In elderly women, vaginal irritation, itching, urinary symptoms, or bleeding may occur secondary to sexual intercourse. Such problems often resolve after a few days of pelvic rest.

Acute loss of appetite, weight loss, dyspepsia, or a sudden change in bowel habits may be signs of ovarian or uterine cancer and requires thorough clinical evaluation.

Key Points

- Pelvic pain is common and may have a gynecologic or nongynecologic cause.
- Pregnancy should be ruled out in women of childbearing age.
- Quality, severity, and location of pain and its relationship to the menstrual cycle can suggest the most likely causes.
- Dysmenorrhea is a common cause of pelvic pain but is a diagnosis of exclusion.

Vaginal Bleeding

Abnormal vaginal bleeding includes

- Menses that are prolonged (menorrhagia), excessive (menorrhagia or hypermenorrhea), or too frequent (polymenorrhea)
- Bleeding that is unrelated to menses, occurring irregularly between menses (metrorrhagia)
- Postmenopausal bleeding (ie, > 6 mo after the last normal menses)

Vaginal bleeding may occur during early pregnancy (see p. 2612) or late pregnancy (see p. 2620).

Pathophysiology

Most abnormal vaginal bleeding involves

- Hormonal abnormalities in the hypothalamic-pituitary-ovarian axis (most common)
- Structural, inflammatory, or other gynecologic disorders (eg, tumors)
- Bleeding disorders (uncommon)

With hormonal causes, ovulation does not occur or occurs infrequently. During an anovulatory cycle, the corpus luteum does not form, and thus the normal cyclical secretion of progesterone does not occur. Without progesterone, estrogen causes the endometrium to continue to proliferate, eventually outgrowing its blood supply. The endometrium then sloughs and bleeds incompletely, irregularly, and sometimes profusely or for a long time.

Etiology

Causes in adults (see Table 244-3) and children (see Table 244-4) vary.

Overall, the most common specific causes in adult women who are not known to be pregnant are

- Complications of an early, undiagnosed pregnancy
- Anovulatory bleeding
- Submucous myoma
- Midcycle bleeding associated with ovulation
- Breakthrough bleeding while women are taking oral contraceptives

Evaluation

Unrecognized pregnancy must be suspected and diagnosed in women of childbearing age because some causes of bleeding during pregnancy (eg, ectopic pregnancy) are life threatening.

History: History of present illness should include quantity (eg, by number of pads used per day or hour) and duration of bleeding, as well as the relationship of bleeding to menses and intercourse. Menstrual history should be obtained; it should include date of last normal menstrual period, age at menarche and menopause (when appropriate), cycle length and regularity, and quantity and duration of typical menstrual bleeding. Previous episodes of abnormal bleeding, including frequency, duration, quantity, and pattern (cyclicity) of bleeding, should be identified.

Review of systems should seek symptoms of possible causes, including missed menses, breast swelling, and nausea (pregnancy-related bleeding); abdominal pain, light-headedness, and syncope (ectopic pregnancy or ruptured ovarian cyst); chronic pain and weight loss (cancer); and easy bruising, excessive bleeding due to toothbrushing, minor lacerations, or venipuncture (a bleeding disorder).

Past medical history should identify disorders known to cause bleeding, including a recent spontaneous or therapeutic abortion and structural disorders (eg, uterine fibroids, ovarian cysts). Clinicians should identify risk factors for endometrial cancer, including obesity, diabetes, hypertension, prolonged unopposed estrogen use (ie, without progesterone), and polycystic ovary syndrome. Drug history should include specific questions about hormone use.

Physical examination: Vital signs are reviewed for signs of hypovolemia (eg, tachycardia, tachypnea, hypotension).

During the general examination, clinicians should look for signs of anemia (eg, conjunctival pallor) and evidence of possible causes of bleeding, including the following:

• Warm and moist or dry skin, eye abnormalities, tremor, abnormal reflexes, or goiter (a thyroid disorder)

[Table 244-3. Some Causes of Abnormal Vaginal Bleeding in Adult Women]

• Hepatomegaly, jaundice, asterixis, or splenomegaly (a liver disorder)

• Nipple discharge (hyperprolactinemia)

• Low body mass index and loss of subcutaneous fat (possibly anovulation)

• High body mass index and excess subcutaneous fat (androgen or estrogen excess or polycystic ovary syndrome)

• Hirsutism, acne, obesity, and enlarged ovaries (polycystic ovary syndrome)

• Easy bruising, petechiae, purpura, or mucosal (eg, gingival) bleeding (a bleeding disorder)

• In children, breast development and presence of pubic and axillary hair (puberty)

The abdomen is examined for distention, tenderness, and masses (particularly an enlarged uterus). If the uterus is enlarged, auscultation for fetal heart sounds is done.

A complete gynecologic examination is done unless abdominal examination suggests a late-stage pregnancy; then, digital pelvic examination is contraindicated until placental position is determined. In all other cases, speculum examination helps identify lesions of the urethra, vagina, and cervix. Bimanual examination is done to evaluate uterine size and ovarian enlargement. If no blood is present in the vagina, rectal examination is done to determine whether bleeding is GI in origin.

[Table 244-4. Common Causes of Vaginal Bleeding in Children]

Red flags: The following findings are of particular concern:

• Hemorrhagic shock (tachycardia, hypotension)

• Premenarchal and postmenopausal vaginal bleeding

• Vaginal bleeding in pregnant patients

Interpretation of findings: Significant hypovolemia or hemorrhagic shock is unlikely except with ruptured ectopic pregnancy or, rarely, ovarian cyst (particularly when a tender pelvic mass is present).

In children, breast development and pubic or axillary hair suggest precocious puberty and premature menses. In those without such findings, the possibility of sexual abuse should be investigated unless an explanatory lesion or foreign body is obvious.

In women of reproductive age, examination may detect a causative gynecologic lesion or other findings suggesting a cause. If younger patients taking hormone therapy have no apparent abnormalities during examination and bleeding is spotty, bleeding is probably related to the hormone therapy. If the problem is excessive menstrual bleeding only, a uterine disorder or bleeding diathesis should be considered. Inherited bleeding disorders may initially manifest as heavy menstrual bleeding beginning at menarche or during adolescence.

In postmenopausal women, gynecologic cancer should be suspected.

Dysfunctional uterine bleeding, the most common cause during reproductive years, is a diagnosis of exclusion after other causes are ruled out; testing is usually required.

Testing: All women of reproductive age require

• A urine pregnancy test

During early pregnancy (before 5 wk), a urine pregnancy test may not be sensitive enough. Urine contaminated with blood may lead to false results. A qualitative serum β subunit of human chorionic gonadotropin (β-hCG) test should be done if the urine test is negative and pregnancy is suspected. Vaginal bleeding during pregnancy requires a specific approach (see pp. 2612 and 2620).

Blood tests include CBC if bleeding is unusually heavy (eg, > 1 pad or tampon/h) or has lasted at least several days or if findings suggest anemia or hypovolemia. If anemia is identified and is not obviously due to iron deficiency (eg, based on microcytic, hypochromic RBC indices), iron studies are done.

Thyroid-stimulating hormone and prolactin levels are usually measured, even when galactorrhea is absent.

If a bleeding disorder is suspected, von Willebrand's factor, platelet count, PT, and PTT are determined.

If polycystic ovary syndrome is suspected, testosterone and dehydroepiandrosterone sulfate (DHEAS) levels are measured.

Imaging includes transvaginal ultrasonography if women have any of the following:

• Age > 35

• Risk factors for endometrial cancer

• Bleeding that continues despite use of empiric hormonal therapy

Focal thickening of the endometrium that is detected during screening ultrasonography may require hysteroscopy or saline-infusion sonohysterography to identify small intrauterine masses (eg, endometrial

polyps, submucous myomas).

Other testing includes endometrial sampling if examination and ultrasonography are inconclusive in women who are > 35, who have risk factors for cancer, or who have endometrial thickening > 4 mm. Sampling can be done by aspiration or, if the cervical canal requires dilation, by D & C.

Treatment

Hemorrhagic shock is treated. Women with iron deficiency anemia may require supplemental oral iron.

Definitive treatment of vaginal bleeding is directed at the cause. Hormones, usually oral contraceptives, are used to treat dysfunctional uterine bleeding.

Geriatrics Essentials

Postmenopausal bleeding (bleeding > 6 mo after menopause) is abnormal in most women and requires further evaluation to exclude cancer unless it clearly results from withdrawal of exogenous hormones.

In women not taking exogenous hormones, the most common cause of postmenopausal bleeding is endometrial and vaginal atrophy. In some older women, physical examination of the vagina can be difficult because lack of estrogen leads to increased friability of the vaginal mucosa, vaginal stenosis, and sometimes adhesions in the vagina. For these patients, a pediatric speculum may be more comfortable.

Key Points

- Pregnancy must be excluded in women of reproductive age even when history does not suggest it.
- Dysfunctional uterine bleeding is the most common cause of abnormal vaginal bleeding during the reproductive years.
- Vaginitis, foreign bodies, trauma, and sexual abuse are common causes of vaginal bleeding before menarche.
- Postmenopausal vaginal bleeding needs further evaluation to exclude cancer as the cause.

Vaginal Itching and Discharge

Vaginal itching (pruritus), discharge, or both result from infectious or noninfectious inflammation of the vaginal mucosa (vaginitis), often with inflammation of the vulva (vulvovaginitis). Symptoms may also include irritation, burning, erythema, and sometimes dysuria and dyspareunia. Symptoms of vaginitis are one of the most common gynecologic complaints.

Pathophysiology

Some vaginal discharge is normal, particularly when estrogen levels are high a few days before ovulation. Estrogen levels are also high during the first 2 wk of life (because maternal estrogens are transferred before birth), during the few months before menarche and during pregnancy (when estrogen production increases), and with use of drugs that contain estrogen or that increase estrogen production (eg, some fertility drugs). However, irritation, burning, and pruritus are never normal.

Normally in women of reproductive age, *Lactobacillus* sp is the predominant constituent of normal vaginal flora. Colonization by these bacteria keeps vaginal pH in the normal range (3.8 to 4.2), thereby preventing overgrowth of pathogenic bacteria. Also, high estrogen levels maintain vaginal thickness, bolstering local defenses.

Factors that predispose to overgrowth of bacterial vaginal pathogens include

- Use of antibiotics (which may decrease lactobacilli)

• Alkaline vaginal pH due to menstrual blood, semen, or a decrease in lactobacilli

• Poor hygiene

• Frequent douching

• Pregnancy

• Diabetes mellitus

Etiology

The most common causes vary by patient age (see Table 244-5 and Geriatrics Essentials on p. 2497).

Children: Vaginitis usually involves infection with GI tract flora (nonspecific vulvovaginitis). A common contributing factor in girls aged 2 to 6 yr is poor perineal hygiene (eg, wiping from back to front after bowel movements, not washing their hands after bowel movements). Chemicals in bubble baths or soaps may cause inflammation and pruritus of the vulva, which often recur. Foreign bodies may cause nonspecific vaginitis, often with a scant bloody discharge.

Women of reproductive age: Vaginitis is usually infectious. The most common types are

• Bacterial vaginosis

• Candidal vaginitis

• Trichomonal vaginitis (usually sexually transmitted)

Vaginitis may also result from foreign bodies (eg, a forgotten tampon). Inflammatory noninfectious vaginitis is uncommon.

Women of all ages: At any age, conditions that predispose to vaginal or vulvar infection include fistulas between the intestine and genital tract (which allow intestinal flora to seed the genital tract) and pelvic radiation or tumors (which break down tissue and thus compromise normal host defenses). Fistulas are usually obstetric in origin (due to vaginal birth trauma or a complication of episiotomy infection) but are sometimes due to inflammatory bowel disease

[**Table 244-5.** Some Causes of Vaginal Pruritus and Discharge]

or occur as a complication of pelvic surgery (eg, hysterectomy, anal surgery).

Noninfectious vulvitis accounts for up to 30% of vulvovaginitis cases. It may result from hypersensitivity or irritant reactions to various agents, including hygiene sprays or perfumes, menstrual pads, laundry soaps, bleaches, fabric softeners, and sometimes spermicides, vaginal creams or lubricants, latex condoms, vaginal contraceptive rings, and diaphragms.

Evaluation

History: History of present illness includes nature of symptoms (eg, pruritus, burning, pain, discharge), duration, and intensity. If vaginal discharge is present, patients should be asked about the color and odor of the discharge and any exacerbating and remitting factors (particularly those related to menses and intercourse). They should also be asked about use of hygiene sprays or perfumes, spermicides, vaginal creams or lubricants, latex condoms, vaginal contraceptive rings, and diaphragms.

Review of systems should seek symptoms suggesting possible causes, including fever or chills and abdominal or suprapubic pain (pelvic inflammatory disease [PID] or cystitis) and polyuria and polydipsia

(new-onset diabetes).

Past medical history should note risk factors for candidal infection (eg, recent antibiotic use, diabetes, HIV infection, other immunosuppressive disorders), fistulas (eg, Crohn's disease, GU or GI cancer, pelvic or rectal surgery, lacerations during delivery), and sexually transmitted diseases (eg, unprotected intercourse, multiple partners).

Physical examination: Physical examination focuses on the pelvic examination.

The external genitals are examined for erythema, excoriations, and swelling. A water-lubricated speculum is used to check the vaginal walls for erythema, discharge, and fistulas. The cervix is inspected for inflammation (eg, trichomoniasis) and discharge. Vaginal pH is measured, and samples of secretions are obtained for testing. A bimanual examination is done to identify cervical motion tenderness and adnexal or uterine tenderness (indicating PID).

Red flags: The following findings are of particular concern:

• Trichomonal vaginitis in children (suggesting sexual abuse)

• Fecal discharge (suggesting a fistula, even if not seen)

Interpretation of findings: Often, the history and physical examination help suggest a diagnosis (see Table 244-5), although there can be much overlap.

In **children,** a vaginal discharge suggests a foreign body in the vagina. If no foreign body is present and children have trichomonal vaginitis, sexual abuse is likely. If they have unexplained vaginal discharge, cervicitis, which may be due to a sexually transmitted disease, should be considered. Nonspecific vulvovaginitis is a diagnosis of exclusion.

In **women of reproductive age,** discharge due to vaginitis must be distinguished from normal discharge. Normal vaginal discharge is commonly milky white or mucoid, odorless, and nonirritating; it can result in vaginal wetness that dampens underwear.

Bacterial vaginosis produces a thin, gray discharge with a fishy odor. A trichomonal infection produces a frothy, yellow-green vaginal discharge and causes vulvovaginal soreness. Candidal vaginitis produces a white discharge that resembles cottage cheese, often increasing the week before menses; symptoms worsen after sexual intercourse.

Contact irritant or allergic reactions cause significant irritation and inflammation with comparatively minimal discharge.

Discharge due to cervicitis (eg, due to PID) can resemble that of vaginitis. Abdominal pain, cervical motion tenderness, or cervical inflammation suggests PID.

In **women of all ages,** vaginal pruritus and discharge may result from skin disorders (eg, psoriasis, tinea versicolor), which can usually be differentiated by history and skin findings.

Discharge that is watery, bloody, or both may result from vulvar, vaginal, or cervical cancer; cancers can be differentiated from vaginitis by examination and Papanicolaou (Pap) tests.

In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry.

Testing: All patients require the following in-office testing:

• pH

• Wet mount

• K hydroxide (KOH) preparation

Testing for gonorrhea and chlamydial infections is typically done unless a noninfectious cause (eg, allergy, foreign body) is obvious.

Vaginal secretions are tested using pH paper with 0.2 intervals from pH 4.0 to 6.0. Then, a cotton swab is used to place secretions on 2 slides; secretions are diluted with 0.9% NaCl on one slide (saline wet mount) and with 10% KOH on the other (KOH preparation).

The KOH preparation is sniffed (whiff test) for a fishy odor, which results from amines produced in trichomonal vaginitis and bacterial vaginosis. The slide is examined using a microscope; KOH dissolves most cellular material except yeast hyphae, making identification easier.

The saline wet mount is examined using a microscope as soon as possible to detect motile trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation.

If clinical criteria and in-office test results are inconclusive, the discharge may be cultured for fungi and trichomonads.

Treatment

Any specific cause is treated.

The vulva should be kept as clean as possible. Soaps and unnecessary topical preparations (eg, feminine hygiene sprays) should be avoided. Intermittent use of ice packs or warm sitz baths (with or without baking soda) may reduce soreness and pruritus. If chronic vulvar inflammation is due to being bedbound or incontinent, better vulvar hygiene may help.

If symptoms are moderate or severe or do not respond to other measures, drugs may be needed. For pruritus, topical corticosteroids (eg, 1% hydrocortisone bid prn) can be applied to the vulva but not into the vagina. Oral antihistamines lessen pruritus and cause drowsiness, helping patients sleep.

Prepubertal girls should be taught good perineal hygiene (eg, wiping front to back after bowel movements and voiding, washing their hands, avoiding fingering the perineum).

Geriatrics Essentials

In postmenopausal women, a marked decrease in estrogen causes vaginal thinning, increasing vulnerability to infection and inflammation (atrophic vaginitis). Other common causes of decreased estrogen in older women include oophorectomy, pelvic radiation, and certain chemotherapy drugs.

In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry.

Poor hygiene (eg, in patients who are incontinent or bedbound) can lead to chronic vulvar inflammation due to chemical irritation by urine or feces.

Bacterial vaginosis, candidal vaginitis, and trichomonal vaginitis are uncommon among postmenopausal women but may occur in those with risk factors.

Key Points

• Vaginal complaints are often nonspecific.

• Causes vary depending on the patient's age.

• Most patients require measurement of vaginal pH, microscopic examination of secretions, and, if needed, culture for sexually transmitted organisms.

Chapter 245. Female Reproductive Endocrinology

Introduction

Hormonal communication between the hypothalamus, anterior pituitary gland, and ovaries regulates the female reproductive system. The hypothalamus secretes a small peptide, gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone. GnRH regulates release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from specialized cells (gonadotropes) in the anterior pituitary gland (see Fig. 245-1 and p. 758). These hormones are released in short bursts (pulses) every 1 to 4 h. LH and FSH promote ovulation and stimulate secretion of the sex hormones estradiol (an estrogen) and progesterone from the ovaries.

Estrogen and progesterone circulate in the bloodstream almost entirely bound to plasma proteins. Only unbound estrogen and progesterone appear to be biologically active. They stimulate the target organs of the reproductive system (eg, breasts, uterus, vagina). They usually inhibit but, in certain situations (eg, around the time of ovulation), may stimulate gonadotropin secretion.

Puberty

Puberty is the sequence of events in which a child acquires adult physical characteristics

[**Fig. 245-1.** The CNS-hypothalamic-pituitary-gonadal target organ axis.]

and capacity for reproduction. Circulating LH and FSH levels are elevated at birth but fall to low levels within a few months and remain low until puberty. Until puberty, few qualitative changes occur in reproductive target organs.

Over the last 150 yr, the age at which puberty begins has been decreasing, primarily because of improved health and nutrition, but this trend has stabilized. Puberty often occurs earlier than average in moderately obese girls and later than average in severely under-weight and undernourished girls. Such observations suggest that a critical body weight is necessary for puberty. Puberty occurs earlier in girls whose mothers matured earlier and, for unknown reasons, in girls who live in urban areas or who are blind.

Physical changes of puberty occur sequentially during adolescence (Fig. 245-2). Breast budding (see Fig. 245-3) and onset of the growth spurt are usually the first changes recognized. Then, pubic and axillary hair appears (see Fig. 245-4), and the growth spurt peaks. Menarche (the first menstrual period) occurs about 2 yr after breast budding. The growth spurt peaks early in puberty; it is limited after menarche. Body habitus changes; the pelvis and hips widen. Body fat increases and accumulates in the hips and thighs.

Mechanisms initiating puberty are unclear. Central influences may inhibit release of GnRH during childhood, then initiate its release to induce puberty in early adolescence. Early in puberty, hypothalamic GnRH release becomes less sensitive to inhibition by estrogen and progesterone. The resulting increased release of GnRH promotes LH and FSH secretion, which stimulates production of sex hormones, primarily estrogen. Estrogen stimulates development of secondary sexual characteristics. Pubic and axillary hair growth may be stimulated by the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate; production of these androgens increases several years before puberty in a process called adrenarche.

Ovarian Follicular Development

A female is born with a finite number of egg precursors (germ cells). Germ cells begin

[**Fig. 245-2.** Puberty—when female sexual characteristics develop.]

[Fig. 245-3. Diagrammatic representation of Tanner stages I to V of human breast maturation.]

[Fig. 245-4. Diagrammatic representation of Tanner stages I to V for development of pubic hair in girls.]

as primordial oogonia that proliferate markedly by mitosis through the 4th mo of gestation. During the 3rd mo, some oogonia begin to undergo meiosis, which reduces the number of chromosomes by one half. By the 7th mo, all viable germ cells develop a surrounding layer of granulosa cells, forming a primordial follicle, and are arrested in meiotic prophase; these cells are primary oocytes. Beginning after the 4th mo of gestation, oogonia (and later oocytes) are lost spontaneously in a process called atresia; eventually, 99.9% are lost. In older mothers, the long time that surviving oocytes spend arrested in meiotic prophase may account for the increased incidence of genetically abnormal pregnancies.

During each menstrual cycle, 3 to 30 follicles are recruited for accelerated growth. Usually in each cycle, only one follicle is selected for ovulation. This dominant follicle releases its oocyte at ovulation and promotes atresia of the other recruited follicles.

Menstrual Cycle

Menstruation is the periodic discharge of blood and sloughed endometrium (collectively called menses or menstrual flow) through the vagina; menstruation occurs throughout a woman's reproductive life in the absence of pregnancy. Menopause is the permanent cessation of menses (see p. 2518).

Average duration of menses is 5 (± 2) days. Blood loss per cycle averages 30 mL (normal range, 13 to 80 mL) and is usually greatest on the 2nd day. A saturated pad or tampon absorbs 5 to 15 mL. Menstrual blood does not usually clot (unless bleeding is very heavy), probably because fibrinolysin and other factors inhibit clotting.

The median menstrual cycle length is 28 days (usual range, about 25 to 36 days). Generally, variation is maximal and intermenstrual intervals are longest in the years immediately after menarche and immediately before menopause, when ovulation occurs less regularly. The menstrual cycle begins and ends with the first day of menses (day 1).

The menstrual cycle can be divided into follicular (preovulatory), ovulatory, and luteal (postovulatory) phases (see
Fig. 245-5).

Follicular phase: This phase varies in length more than other phases do. In the first half of the follicular phase (early follicular phase), the primary event is growth of recruited follicles. At this time, the gonadotropes in the anterior pituitary contain little LH and FSH, and estrogen and progesterone production is low. As a result, overall FSH secretion increases slightly, stimulating growth of recruited follicles. Also, circulating LH levels increase slowly, beginning 1 to 2 days after the increase in FSH. The recruited ovarian follicles soon increase production of

[Fig. 245-5. The idealized cyclic changes in pituitary gonadotropins, estradiol (E_2), progesterone (P), and uterine endometrium during the normal menstrual cycle.]

estradiol; estradiol stimulates LH and FSH synthesis but inhibits their secretion.

During the 2nd half of the follicular phase (late follicular phase), the follicle selected for ovulation matures and accumulates hormone-secreting granulosa cells; its antrum enlarges with follicular fluid, reaching 18 to 20 mm before ovulation. FSH levels decrease; LH levels are affected less. FSH and LH levels diverge partly because estradiol inhibits FSH secretion more than LH secretion. Also, developing follicles produce the hormone inhibin, which inhibits FSH secretion but not LH secretion. Other contributing factors may include disparate half-lives (20 to 30 min for LH; 2 to 3 h for FSH) and unknown factors. Levels of estrogen, particularly estradiol, increase exponentially.

Ovulatory phase: Ovulation (ovum release) occurs. Estradiol levels usually peak as the ovulatory phase begins. Progesterone levels also begin to increase. Stored LH is released in massive amounts (LH

surge), usually over 36 to 48 h, with a smaller increase in FSH. The LH surge occurs because at this time, high levels of estradiol trigger LH secretion by gonadotropes (positive feedback). The LH surge is also stimulated by GnRH and progesterone. During the LH surge, estradiol levels decrease, but progesterone levels continue to increase. The LH surge stimulates enzymes that initiate breakdown of the follicle wall and release of the now mature ovum within about 16 to 32 h. The LH surge also triggers completion of the first meiotic division of the oocyte within about 36 h.

Luteal phase: The follicle is transformed into a corpus luteum. The length of this phase is the most constant, averaging 14 days, after which the corpus luteum degenerates. The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg/day 6 to 8 days after ovulation. Progesterone stimulates development of the secretory endometrium, which is necessary for embryonic implantation. Because progesterone is thermogenic, basal body temperature increases by 0.5°C for the duration of this phase. Because levels of circulating estradiol, progesterone, and inhibin are high during most of the luteal phase, LH and FSH levels decrease. Estradiol and progesterone levels decrease late in this phase.

If implantation occurs, the corpus luteum does not degenerate but remains, supported by human chorionic gonadotropin that is produced by the developing embryo.

Cyclic Changes in Other Reproductive Organs

Endometrium: The endometrium, which consists of glands and stroma, has a basal layer, an intermediate spongiosa layer, and a layer of compact epithelial cells that line the uterine cavity. Together, the spongiosa and epithelial layers form the functionalis, a transient layer that is sloughed during menses. After menstruation, the endometrium is typically < 2 mm thick with dense stroma and narrow, straight, tubular glands lined with low columnar epithelium. As estradiol levels increase, the intact basal layer regenerates the endometrium to a maximum thickness of 11 mm late in the follicular phase. The mucosa thickens and the glands lengthen and coil, becoming tortuous. During the luteal phase, progesterone stimulates the glands to dilate, fill with glycogen, and become secretory, while stromal vascularity increases. As estradiol and progesterone levels decrease late in the luteal phase, the stroma becomes edematous, and the endometrium and its blood vessels necrose, leading to bleeding and menstrual flow.

Because histologic changes are specific to the phase of the menstrual cycle, the cycle phase or tissue response to sex hormones can be determined accurately by endometrial biopsy. The endometrium can also be seen using transvaginal ultrasonography; late in the follicular phase, it characteristically has a tri-laminar pattern, with hyperechoic basal and luminal layers and an intervening hypoechoic layer. After ovulation, the endometrium appears homogeneously echogenic.

Cervix: During the follicular phase, increasing estradiol levels increase cervical vascularity and edema and cervical mucus quantity, elasticity, and NaCl concentration. The external os opens slightly and fills with mucus at ovulation. During the luteal phase, increasing progesterone levels make the cervical mucus thicker and less elastic. Menstrual cycle phase can sometimes be identified by microscopic examination of cervical mucus dried on a glass slide; ferning (palm leaf arborization of mucus) indicates increased NaCl in cervical mucus. Ferning becomes prominent just before ovulation, when estrogen levels are high; it is minimal or absent during the luteal phase.

Vagina: Early in the follicular phase, when estradiol levels are low, the vaginal epithelium is thin and pale. Later in the follicular phase, as estradiol levels increase, squamous cells mature and become cornified, causing epithelial thickening. During the luteal phase, the number of precornified intermediate cells increases, and the number of leukocytes and amount of cellular debris increase as mature squamous cells are shed.

Chapter 246. Menstrual Abnormalities

Introduction

(For a description of the menstrual cycle, see p. 2499.)

Menstrual abnormalities include amenorrhea, dysfunctional uterine bleeding, dysmenorrhea, and premenstrual syndrome. Irregular or absent menses and nonmenstrual vaginal bleeding have many causes, but in women of reproductive age, pregnancy should always be suspected. Abnormal vaginal bleeding in nonpregnant women (see p. 2490) is evaluated differently from vaginal bleeding in pregnant women (see pp. 2612 and 2620).

Amenorrhea

Amenorrhea (the absence of menstruation) can be primary or secondary.

Primary amenorrhea is failure of menses to occur by any of the following:

- Age 16 or 2 yr after the onset of puberty
- About age 14 in girls who have not gone through puberty (eg, growth spurt, development of secondary sexual characteristics)

Secondary amenorrhea is cessation of menses after they have begun; evaluation for amenorrhea is usually done if menses are absent for > 6 mo.

Pathophysiology

Normally, the hypothalamus generates pulses of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to produce gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH])—see p. 2499). Gonadotropins stimulate the ovaries to produce estrogen (mainly estradiol), androgens (mainly testosterone), and progesterone. Estrogen stimulates the endometrium, causing it to proliferate. After ovulation, the corpus luteum produces progesterone, which causes the endometrium to become secretory and prepares it for egg implantation. If pregnancy does not occur, estrogen and progesterone production decreases, and the endometrium breaks down and is sloughed during menses.

When part of this system malfunctions, ovulatory dysfunction occurs; the cycle of gonadotropin-stimulated estrogen production and cyclic endometrial changes is disrupted, and menstrual flow does not occur, resulting in anovulatory amenorrhea. Most amenorrhea, particularly secondary amenorrhea, is anovulatory.

However, amenorrhea can occur when ovulation is normal, as occurs when genital anatomic abnormalities (eg, congenital anomalies causing outflow obstruction, intrauterine adhesions [Asherman's syndrome]) prevent normal menstrual flow despite normal hormonal stimulation.

Etiology

Amenorrhea is usually classified as anovulatory (see Table 246-1) or ovulatory (see Table 246-2). Each type has many causes, but overall, the most common causes of amenorrhea include

- Pregnancy (the most common cause in women of reproductive age)
- Constitutional delay of puberty
- Functional hypothalamic anovulation (eg, due to excessive exercise, eating disorders, or stress)

• Use or abuse of drugs (eg, oral contraceptives, depoprogesterone, antidepressants, antipsychotics)

• Breastfeeding

• Polycystic ovary syndrome

Contraceptives can cause the endometrium to thin, sometimes resulting in amenorrhea. Antidepressants and antipsychotics can elevate prolactin.

Some disorders can cause ovulatory or anovulatory amenorrhea. Congenital anatomic abnormalities cause only primary amenorrhea.

Anovulatory amenorrhea: The most common causes (see Table 246-1) involve a disruption of the hypothalamic-pituitary-ovarian axis. Thus, causes include

• Hypothalamic dysfunction (particularly functional hypothalamic anovulation)

• Pituitary dysfunction

• Premature ovarian failure

• Endocrine disorders that cause androgen excess (particularly polycystic ovary syndrome)

[**Table 246-1.** Some Causes of Anovulatory Amenorrhea]

Anovulatory amenorrhea is usually secondary but may be primary if ovulation never begins—eg, because of a genetic disorder. If ovulation never begins, puberty and development of secondary sexual characteristics are abnormal.

Ovulatory amenorrhea: The most common causes (see Table 246-2) include

• Chromosomal abnormalities

• Other congenital anatomic genital abnormalities that obstruct menstrual flow

Obstructive abnormalities are usually accompanied by normal hormonal function. Such obstruction may result in hematocolpos (accumulation of menstrual blood in the vagina), which can cause the vagina to bulge, or in hematometra (accumulation of blood in the uterus), which can cause uterine distention or a mass. Because ovarian function is normal, external genital organs and other secondary sexual characteristics develop normally. Some congenital disorders (eg, those accompanied by vaginal aplasia or a vaginal septum) also cause urinary tract and skeletal abnormalities.

Some acquired anatomic abnormalities, such as endometrial scarring after instrumentation

[**Table 246-2.** Some Causes of Ovulatory Amenorrhea]

or postpartum hemorrhage (Asherman's syndrome), cause secondary ovulatory amenorrhea.

Evaluation

Girls are evaluated if

• They have no signs of puberty (eg, breast development, growth spurt) by age 13 1/2.

• Pubic hair is absent at age 14.

• Menarche has not occurred by age 16 or by 2 yr after the onset of puberty (development of secondary

sexual characteristics).

Women of reproductive age should have a pregnancy test after missing one menses. They are evaluated for amenorrhea if

• They are not pregnant and have missed menstrual cycles for ≥ 3 mo.

• They have < 9 menses a year.

• They have a sudden change in menstrual pattern.

History: History of present illness includes whether menses have ever occurred (to distinguish primary from secondary amenorrhea) and, if so, how old patients were at menarche, whether periods have ever been regular, and when the last normal menstrual period occurred. History should also include duration and flow of menses; presence or absence of cyclic breast tenderness and mood changes; and growth, development, and age at thelarche (development of breasts at puberty).

Review of systems should cover symptoms suggesting possible causes, including galactorrhea, headaches, and visual field defects (pituitary disorders); fatigue, weight gain, and cold intolerance (hypothyroidism); palpitations, nervousness, tremor, and heat intolerance (hyperthyroidism); acne, hirsutism, and deepening of the voice (androgen excess); and, for patients with secondary amenorrhea, hot flushes, vaginal dryness, sleep disturbance, fragility fractures, and decreased libido (estrogen deficiency). Patients with primary amenorrhea are asked about symptoms of puberty (eg, breast development, growth spurt, presence of axillary and pubic hair) to help determine whether ovulation has occurred.

Past medical history should note risk factors for functional hypothalamic anovulation, such as stress; chronic illness; a recent change in weight, diet, or exercise intensity; and, in patients with secondary amenorrhea, risk factors for Asherman's syndrome (eg, D & C, endometritis, obstetric injury, uterine surgery).

Drug history should include specific questions about use of drugs that affect dopamine (eg, antihypertensives, antipsychotics, opioids, tricyclic antidepressants) and sex hormones that can cause virilization (eg, androgens, estrogens, high-dose progestins).

Family history should include height of family members and any cases of delayed puberty or genetic disorders in family members.

Physical examination: Clinicians should note vital signs and body composition and build, including height and weight, and should calculate body mass index (BMI). Secondary sexual characteristics are evaluated; breast and pubic hair development are staged using Tanner's method. If axillary and pubic hair is present, adrenarche has occurred.

With the patient seated, clinicians should check for breast secretion by applying pressure to all sections of the breast, beginning at the base and moving toward the nipple. Galactorrhea (breast milk secretion not temporally associated with childbirth) may be observed; it can be distinguished from other types of nipple discharge by finding fat globules in the fluid using a low-power microscope.

Pelvic examination is done to detect anatomic genital abnormalities; a bulging hymen may be caused by hematocolpos, which suggests genital outflow obstruction. Pelvic examination findings also help determine whether estrogen is adequate. In postpubertal females, thin, pale vaginal mucosa without rugae and pH > 6.0 indicate estrogen deficiency. The presence of cervical mucus with spinnbarkeit (a stringy, stretchy quality) usually indicates adequate estrogen.

General examination focuses on evidence of virilization, including hirsutism, temporal balding, acne, voice deepening, increased muscle mass, clitoromegaly (clitoral enlargement), and defeminization (a decrease in previously normal secondary sexual characteristics, such as decreased breast size and vaginal atrophy). Hypertrichosis (excessive growth of hair on the extremities, head, and back), which is common

in some families, is differentiated from true hirsutism, which is characterized by excess hair on the upper lip and chin and between the breasts. Skin discoloration (eg, yellow of jaundice or carotenemia, black patches of acanthosis nigricans) should be noted.

Red flags: The following findings are of particular concern:

• Delayed puberty

• Virilization

• Visual field defects

Interpretation of findings: Pregnancy should not be excluded by history; a pregnancy test is required.

In primary amenorrhea, the presence of normal secondary sexual characteristics usually reflects normal hormonal function; amenorrhea is usually ovulatory and typically due to a congenital anatomic genital tract obstruction. Primary amenorrhea accompanied by abnormal secondary sexual characteristics is usually anovulatory (eg, due to a genetic disorder).

In secondary amenorrhea, clinical findings sometimes suggest a mechanism (see Table 246-3).

• Galactorrhea suggests hyperprolactinemia (eg, pituitary dysfunction, use of certain drugs); if visual field defects and headaches are also present, pituitary tumors should be considered.

• Symptoms and signs of estrogen deficiency (eg, hot flushes, night sweats, vaginal dryness or atrophy) suggest premature ovarian failure.

• Virilization suggests androgen excess (eg, polycystic ovary syndrome, androgen-secreting tumor, Cushing's syndrome, use of certain drugs). If patients have a high BMI, acanthosis nigricans, or both, polycystic ovary syndrome is likely.

Testing: History and physical examination help direct testing.

If girls have secondary sexual characteristics, a pregnancy test should be done to exclude pregnancy and gestational trophoblastic disease as a cause of amenorrhea. Women of reproductive

[**Table 246-3.** Findings Suggesting Possible Causes of Amenorrhea]

age should have a pregnancy test after missing one menses.

The approach to primary amenorrhea (see Fig. 246-1) differs from that to secondary amenorrhea (see Fig. 246-2), although no specific general approaches or algorithms are universally accepted.

If symptoms or signs suggest a specific disorder, specific tests may be indicated regardless of what an algorithm recommends. For example, patients with abdominal striae, moon facies, a buffalo hump, truncal obesity, and thin extremities should be tested for Cushing's syndrome (see p. 797). Patients

[**Fig. 246-1.** Evaluation of primary amenorrhea.]

[**Fig. 246-2.** Evaluation of secondary amenorrhea.]

with headaches and visual field defects or evidence of pituitary dysfunction require brain MRI.

If clinical evaluation suggests a chronic disease, liver and kidney function tests are done, and ESR is determined.

Often, testing includes measurement of hormone levels; total serum testosterone or dehydroepiandrosterone sulfate (DHEAS) levels are measured only if signs of virilization are present. Certain hormone levels should be remeasured to confirm the results. For example, if serum prolactin is high, it should be remeasured; if serum FSH is high, it should be remeasured monthly at least twice. Amenorrhea with high FSH levels (hypergonadotropic hypogonadism) suggests ovarian dysfunction; amenorrhea with low FSH levels (hypogonadotropic hypogonadism) suggests hypothalamic or pituitary dysfunction.

If patients have secondary amenorrhea without virilization and have normal prolactin and FSH levels and normal thyroid function, a trial of estrogen and a progestin to try to stimulate withdrawal bleeding can be done (progesterone challenge test). The trial begins by giving medroxyprogesterone 5 to 10 mg po once/day or another progestin for 7 to 10 days.

- If bleeding occurs, amenorrhea is probably not caused by an endometrial lesion (eg, Asherman's syndrome) or outflow tract obstruction, and the cause is probably hypothalamic-pituitary dysfunction, ovarian failure, or estrogen excess.

- If bleeding does not occur, an estrogen (eg, conjugated equine estrogen 1.25 mg, estradiol 2 mg) once/day is given for 21 days, followed by medroxyprogesterone 10 mg po once/day or another progestin for 7 to 10 days. Absence of bleeding suggests an endometrial lesion or outflow tract obstruction.

However, because this trial takes weeks and results can be inaccurate, diagnosis of some serious disorders may be delayed significantly; thus, brain MRI should be considered before or during the trial.

Mildly elevated levels of testosterone or DHEAS suggest polycystic ovary syndrome, but levels can be elevated in women with hypothalamic or pituitary dysfunction and are sometimes normal in hirsute women with polycystic ovary syndrome. The cause of elevated levels can sometimes be determined by measuring serum LH. In polycystic ovary syndrome, circulating LH levels are often increased, increasing the ratio of LH to FSH.

Treatment

Treatment is directed at the underlying disorder; with such treatment, menses sometimes resume. For example, most abnormalities obstructing the genital outflow tract are surgically repaired.

If a Y chromosome is present, bilateral oophorectomy is recommended because risk of ovarian germ cell cancer is increased.

Problems associated with amenorrhea may also require treatment, including

- Inducing ovulation if pregnancy is desired

- Treating symptoms and long-term effects of estrogen deficiency (eg, osteoporosis)

- Treating symptoms of estrogen excess (eg, prolonged bleeding, persistent or marked breast tenderness)

- Minimizing hirsutism and long-term effects of androgen excess (eg, cardiovascular disorders, hypertension)

Key Points

- Pregnancy must always be excluded by testing.

- Primary amenorrhea is evaluated differently from secondary amenorrhea.

- Primary amenorrhea with normal secondary sexual characteristics suggests congenital anatomic genital

tract obstruction; pelvic ultrasonography is indicated.

- Primary amenorrhea without normal secondary sexual characteristics is usually anovulatory (eg, due to a genetic disorder).

- Virilization suggests androgen excess (eg, due to polycystic ovary syndrome, an androgen-secreting tumor, Cushing's syndrome, or use of certain drugs).

- Symptoms and signs of estrogen deficiency (eg, hot flushes, night sweats, vaginal dryness or atrophy) suggest premature ovarian failure.

- Galactorrhea suggests hyperprolactinemia (eg, due to pituitary dysfunction or use of certain drugs).

Dysfunctional Uterine Bleeding

(Functional Uterine Bleeding)

Dysfunctional uterine bleeding is abnormal uterine bleeding that, after examination and ultrasonography, cannot be attributed to the usual causes (structural gynecologic abnormalities, cancer, inflammation, systemic disorders, pregnancy, complications of pregnancy, use of oral contraceptives or certain drugs). Treatment is usually with hormonal therapy, such as oral contraceptives.

Dysfunctional uterine bleeding (DUB), the most common cause of abnormal uterine bleeding, occurs most often in women > 45 (> 50% of cases) and in adolescents (20% of cases).

About 90% of cases are anovulatory; 10% are ovulatory.

Pathophysiology

During an anovulatory cycle, the corpus luteum does not form. Thus, the normal cyclical secretion of progesterone does not occur, and estrogen stimulates the endometrium unopposed. Without progesterone, the endometrium continues to proliferate, eventually outgrowing its blood supply; it then sloughs and bleeds incompletely, irregularly, and sometimes profusely or for a long time. When this abnormal process occurs repeatedly, the endometrium can become hyperplastic, sometimes with atypical or cancerous cells.

In ovulatory DUB, progesterone secretion is prolonged; irregular shedding of the endometrium results, probably because estrogen levels remain low, near the threshold for bleeding (as occurs during menses). In obese women, ovulatory DUB can occur if estrogen levels are high, resulting in amenorrhea alternating with irregular or prolonged bleeding.

Complications: Chronic bleeding may cause iron deficiency anemia. If DUB is due to chronic anovulation, infertility may also be present.

Etiology

Anovulatory DUB can result from any disorder or condition that causes anovulation (see Table 246-1). Anovulation is most often secondary to polycystic ovary syndrome or is idiopathic (sometimes occurring when gonadotropin levels are normal); sometimes anovulation results from hypothyroidism. During perimenopause, DUB may be an early sign of ovarian failure; follicles are still developing but, despite increasing levels of follicle-stimulating hormone (FSH), do not produce enough estrogen to trigger ovulation. About 20% of women with endometriosis (see p. 2538) have anovulatory DUB due to unknown mechanisms.

Ovulatory DUB may occur in polycystic ovary syndrome (because progesterone secretion is prolonged) or in endometriosis, which does not affect ovulation. Other causes are a short follicular phase and luteal phase dysfunction (due to inadequate progesterone stimulation of the endometrium); a rapid decrease in

estrogen before ovulation can cause spotting.

Symptoms and Signs

Compared with typical menses, bleeding may occur more frequently (< 21 days apart—polymenorrhea), last longer or involve more blood loss (> 7 days or > 80 mL—menorrhagia, or hypermenorrhea), or occur frequently and irregularly between menses (metrorrhagia).

Ovulatory DUB tends to cause excessive bleeding during regular menstrual cycles. Women may have other symptoms of ovulation, such as premenstrual symptoms, breast tenderness, midcycle cramping pain (mittelschmerz), a change in basal body temperature with ovulation (see p. 2595), and sometimes dysmenorrhea. Anovulatory DUB occurs at unpredictable times and in unpredictable patterns and is not accompanied by cyclic changes in basal body temperature.

Diagnosis

• Exclusion of other potential causes

• CBC, pregnancy test, and hormone measurement (thyroid-stimulating hormone, prolactin)

• Usually transvaginal ultrasonography and endometrial sampling

Women should be evaluated for DUB when the amount or timing of vaginal bleeding is inconsistent with normal menses. DUB is a diagnosis of exclusion; other conditions that can cause similar bleeding must be excluded (see p. 2490). Pregnancy should be excluded, even in young adolescents and perimenopausal women. Coagulation disorders should be considered, particularly in adolescents who have anemia or require hospitalization for bleeding. Regular cycles with prolonged or excessive bleeding (possible ovulatory DUB) suggest structural abnormalities.

Laboratory testing: Several tests are typically done:

• A urine pregnancy test

• CBC

• TSH, prolactin, and progesterone levels

All women of reproductive age should have a pregnancy test. CBC is routinely done. However, Hct may be normal in women who report heavy bleeding, or anemia may be severe in women who regularly have heavy periods.

Thyroid-stimulating hormone levels are usually measured, and prolactin levels are measured, even when galactorrhea is absent, because thyroid disorders and hyperprolactinemia are common causes of abnormal bleeding. To determine whether bleeding is anovulatory or ovulatory, some clinicians measure serum progesterone levels during the luteal phase (after day 14 of a normal menstrual cycle or after basal body temperature increases, as occurs during this phase). A level of ≥ 3 ng/mL (≥ 9.75 nmol/L) suggests that ovulation has occurred.

Other tests are done depending on results of the history and physical examination and include the following:

• Coagulation tests if women have risk factors or bruising or hemorrhage

• Liver function tests if a liver disorder is suspected

• Testosterone and dehydroepiandrosterone sulfate (DHEAS) levels if polycystic ovary syndrome is suspected

- Follicle-stimulating hormone (FSH) and estradiol levels if premature ovarian failure is possible
- A cervical cytology test (eg, Papanicolaou [Pap] test) if results are out-of-date
- Testing for *Neisseria gonorrhea* and *Chlamydia* sp if pelvic inflammatory disease or cervicitis is suspected

If all clinically indicated tests are normal, the diagnosis is DUB.

Additional testing: Transvaginal ultrasonography is done if women have any of the following:

- Age ≥ 35 or, if unopposed estrogen exposure is prolonged, younger
- Risk factors for endometrial cancer (eg, obesity, diabetes, hypertension, polycystic ovary syndrome, other conditions associated with prolonged unopposed estrogen)
- Bleeding that continues despite use of empiric hormonal therapy

These criteria include almost all women with DUB.

Transvaginal ultrasonography can detect structural abnormalities, including most masses and focal thickening of the endometrium. If focal thickening is detected, hysteroscopy or saline-infusion sonohysterography may be needed to identify smaller intrauterine masses (eg, endometrial polyps, submucous myomas).

Endometrial sampling is usually recommended to rule out hyperplasia or cancer in women with any of the following:

- Criteria indicating need for transvaginal ultrasonography
- Bleeding that is persistent, irregular, or heavy
- Irregular cycles that suggest chronic anovulatory bleeding
- Endometrial thickness > 4 mm or focal or irregular areas
- Inconclusive ultrasonography findings

Directed biopsy (with hysteroscopy) may be done to visualize the endometrial cavity directly and target the abnormal tissue.

Treatment

- Control of bleeding, usually with hormone therapy
- In women with endometrial hyperplasia, prevention of endometrial cancer

Bleeding: Patients with very heavy bleeding (which is uncommon) are stabilized hemo-dynamically with IV crystalloid fluid, blood products, and other measures as needed. If bleeding persists, a bladder catheter is inserted into the uterus and inflated with 30 mL of water to tamponade the bleeding. Once patients are stable, hormonal therapy is used to control bleeding.

For anovulatory DUB with very heavy bleeding, conjugated estrogens 25 mg IV q 4 to 6 h for a total of 4 doses may be used. Immediately afterward, women are given a combination (estrogen/progestin) oral contraceptive, which may be continued until bleeding abates. Otherwise, anovulatory DUB is usually treated with combination oral contraceptives (see p. 2584). Depending on the severity of bleeding, an oral contraceptive can be given bid or tid for 5 to 6 days, then once/day. After acute bleeding is controlled, a combination oral contraceptive is given continually for about 3 mo to prevent recurrence.

Other options include a levonorgestrel-releasing intrauterine device (IUD), depot medroxyprogesterone acetate injections, and cyclic use of a progestin (eg, medroxyprogesterone acetate 5 to 10 mg po once/day, norethindrone 5 mg po once/day for 10 to 14 days/mo). These treatments may be indicated when estrogen is contraindicated or when spontaneous cyclic menses do not resume after 3 mo of oral contraceptive therapy.

If pregnancy is desired and bleeding is not heavy, ovulation induction with clomiphene (50 mg po on days 5 through 9 of the menstrual cycle) can be tried.

Endometrial ablation (eg, using freezing or burning) may help control bleeding (in 60 to 80%). If this treatment does not control bleeding, bleeding is usually caused by adenomyosis and is thus not DUB.

Hysteroscopy with D & C may be therapeutic as well as diagnostic; it may be the treatment of choice when anovulatory bleeding is severe or when hormone therapy is ineffective. Structural causes such as polyps or fibroids may be identified or removed during hysteroscopy. This procedure may decrease bleeding but, in some women, causes amenorrhea due to endometrial scarring (Asherman's syndrome).

For ovulatory DUB, oral contraceptives are usually effective. Other options include NSAIDs given during menses, ovarian suppression with depot leuprolide, depot medroxyprogesterone acetate, and a levonorgestrel-releasing IUD.

Endometrial hyperplasia: In postmenopausal women, atypical adenomatous endometrial hyperplasia is usually treated with hysterectomy. In premenopausal women, it is treated with medroxyprogesterone acetate 20 to 40 mg po once/day for 3 to 6 mo.

If repeat endometrial sampling indicates resolution of hyperplasia, women may be given cyclic medroxyprogesterone acetate (5 to 10 mg po once/day for 10 to 14 days each month) or, if pregnancy is desired, clomiphene. If sampling shows persistent or progressive atypical hyperplasia, hysterectomy is necessary.

More benign cystic or adenomatous hyperplasia can usually be treated with high-dose cyclic progesterone therapy (eg, cyclic medroxyprogesterone acetate); sampling is repeated after about 3 mo.

Dysmenorrhea

Dysmenorrhea is uterine pain around the time of menses. Pain may occur with menses or precede menses by 1 to 3 days. Pain tends to peak 24 h after onset of menses and subside after 2 to 3 days. It is usually sharp but may be cramping, throbbing, or a dull, constant ache; it may radiate to the legs. Headache, nausea, constipation or diarrhea, lower back pain, and urinary frequency are common; vomiting occurs occasionally. Symptoms of premenstrual syndrome may occur during part or all of menses. Sometimes endometrial clots or casts are expelled.

Etiology

Dysmenorrhea can be

• Primary (more common)

• Secondary (due to pelvic abnormalities)

Primary dysmenorrhea: Symptoms cannot be explained by structural gynecologic disorders. Pain is thought to result from uterine contractions and ischemia, probably mediated by prostaglandins and other inflammatory mediators produced in secretory endometrium and possibly associated with prolonged uterine contractions and decreased blood flow to the myometrium. Contributing factors may include passage of menstrual tissue through the cervix, a narrow cervical os, a malpositioned uterus, lack of exercise, and anxiety about menses. It occurs almost invariably in ovulatory cycles. Risk factors for severe symptoms include earlier age at menarche, long or heavy menstrual periods, smoking, and a

family history of dysmenorrhea.

Primary dysmenorrhea usually starts during adolescence and tends to lessen with age and after pregnancy.

Secondary dysmenorrhea: Symptoms are due to pelvic abnormalities. Common causes include

• Endometriosis (the most common cause)

• Uterine adenomyosis

• Fibroids

Less common causes include congenital malformations, ovarian cysts and tumors, pelvic inflammatory disease, pelvic congestion, and copper intrauterine devices (IUDs).

In a few women, pain occurs when the uterus attempts to expel tissue through an extremely tight cervical os (secondary to conization, loop electrosurgical excision procedure [LEEP], cryocautery, or thermocautery). Pain occasionally results from a pedunculated submucosal fibroid or an endometrial polyp extruding through the cervix.

Secondary dysmenorrhea usually begins during adulthood unless caused by congenital malformations.

Evaluation

History: History of present illness should cover complete menstrual history, including age at onset of menses, duration and amount of flow, time between menses, variability of timing, and relation of menses to symptoms. Clinicians should also ask about the age at which symptoms began, their nature and severity, factors that relieve or worsen symptoms, degree of disruption of daily life, and presence of pelvic pain unrelated to menses.

Review of systems should include accompanying symptoms such as cyclic nausea, vomiting, bloating, diarrhea, and fatigue. Sexual history should include effect of contraceptives on pain and prior or current history of sexual abuse.

Past medical history should identify known causes, including endometriosis, uterine adenomyosis, or fibroids. Method of contraception should be ascertained, specifically asking about IUD use.

Physical examination: Pelvic examination focuses on detecting causes of secondary dysmenorrhea. The vagina, vulva, and cervix are inspected for lesions and for masses protruding through the cervical os. Structures are palpated to check for a tight cervical os, prolapsed polyp or fibroid, uterine masses, adnexal masses, thickening of the rectovaginal septum, induration of the cul-de-sac, and nodularity of the uterosacral ligament.

Red flags: The following findings are of particular concern:

• New or sudden-onset pain

• Unremitting pain

• Fever

• Vaginal discharge

Interpretation of findings: Red flag findings suggest a cause of pelvic pain other than dysmenorrhea.

Primary dysmenorrhea is suspected if symptoms begin soon after menarche or during adolescence.

Secondary dysmenorrhea is suspected if symptoms begin after adolescence or in patients with known causes, including uterine adenomyosis, fibroids, a tight cervical os, a mass protruding from the cervical os, or, particularly, endometriosis.

Endometriosis is considered in patients with adnexal masses, thickening of the rectovaginal septum, induration of the cul-de-sac, nodularity of the uterosacral ligament, or, occasionally, nonspecific vaginal, vulvar, or cervical lesions.

Testing: Testing aims to exclude structural gynecologic disorders. Most patients should have

• Pregnancy testing

• Pelvic ultrasonography

Intrauterine and ectopic pregnancy are ruled out by pregnancy testing. If pelvic inflammatory disease is suspected, cervical cultures are done.

Pelvic ultrasonography is highly sensitive for pelvic masses such as fibroids, endometriosis, and uterine adenomyosis.

If these tests are inconclusive and symptoms persist, other tests are done. Hysterosalpingography or sonohysterography can be used to identify endometrial polyps, submucous fibroids, or congenital abnormalities. MRI may be used to identify other abnormalities, including congenital abnormalities, or to further define previously identified abnormalities if surgery is planned. If results of all other tests are inconclusive, hysteroscopy or laparoscopy can be done.

Treatment

Underlying disorders are treated. Symptomatic treatment begins with adequate rest and sleep and regular exercise. A low-fat diet and nutritional supplements such as ω-3 fatty acids, flaxseed, magnesium, vitamin E, zinc, and vitamin B_1 are suggested as potentially effective. Women with primary dysmenorrhea are reassured about the absence of structural gynecologic disorders.

If pain persists, drugs, typically prostaglandin inhibitors such as NSAIDs, are tried. NSAIDs are usually started 24 to 48 h before and continued until 1 or 2 days after menses begins. If the NSAID is ineffective, suppression of ovulation with a low-dose estrogen/progestin oral contraceptive is advisable. Other hormonal treatments, such as danazol, progestins (eg, levonorgestrel, etonogestrel, depot medroxyprogesterone acetate), gonadotropin-releasing hormone agonists, or a progesterone IUD, may decrease dysmenorrheal symptoms.

Periodic adjunctive use of analgesics may be needed. Hypnosis is being evaluated as treatment. Other proposed nondrug therapies, including acupuncture, acupressure, chiropractic therapy, and transcutaneous electrical nerve stimulation, have not been well studied.

For intractable pain of unknown origin, presacral neurectomy and division of the sacrouterine ligaments to interrupt uterine nerves may help.

Key Points

• Most dysmenorrhea is primary.

• Underlying structural pelvic lesions need to be excluded.

• Usually, testing begins with ultrasonography.

Polycystic Ovary Syndrome

(Hyperandrogenic Chronic Anovulation; Stein-Leventhal Syndrome)

Polycystic ovary syndrome is a clinical syndrome characterized by mild obesity, irregular menses or amenorrhea, and signs of androgen excess (eg, hirsutism, acne). In most patients, the ovaries contain multiple cysts. Diagnosis is by pregnancy testing, hormone measurement, and imaging to exclude a virilizing tumor. Treatment is symptomatic.

Polycystic ovary syndrome occurs in 5 to 10% of women and involves anovulation or ovulatory dysfunction and androgen excess of unclear etiology. It is usually defined as a clinical syndrome, not by the presence of ovarian cysts. Ovaries may be enlarged with smooth, thickened capsules or may be normal in size. Typically, ovaries contain many 2- to 6-mm follicular cysts and sometimes larger cysts containing atretic cells. Estrogen levels are elevated, increasing risk of endometrial hyperplasia and, eventually, endometrial cancer. Androgen levels are often elevated, increasing risk of metabolic syndrome (see p. 64) and causing hirsutism. Over the long term, androgen excess increases risk of cardiovascular disorders, including hypertension.

Symptoms and Signs

Symptoms typically begin during puberty and worsen with time. The typical symptoms are mild obesity, hirsutism, and irregular menses or amenorrhea. Some women have other signs of virilization, such as acne and temporal balding. Areas of thickened, darkened skin (acanthosis nigricans) may appear in the axillae, on the nape of the neck, and in skinfolds; the cause is high insulin levels due to insulin resistance.

Diagnosis

• Clinical criteria

• Serum testosterone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone levels

• Pelvic ultrasonography

Ovulatory dysfunction is usually present at puberty, resulting in primary amenorrhea; thus, this syndrome is unlikely if regular menses occurred for a time after menarche. Examination usually detects abundant cervical mucus, reflecting high estrogen levels. The diagnosis is suspected if women have at least 2 typical symptoms.

Testing includes pregnancy testing, pelvic ultrasonography, and measurement of serum total testosterone, follicle-stimulating hormone (FSH), prolactin, and thyroid-stimulating hormone (TSH). Serum free testosterone level is more sensitive than total testosterone but is technically more difficult to measure (see p. 2342).

The diagnosis requires at least 2 of the following 3 criteria:

• Ovulatory dysfunction causing menstrual irregularity

• Clinical or biochemical evidence of hyperandrogenism

• More than 10 follicles per ovary (detected by pelvic ultrasonography), usually occurring in the periphery and resembling a string of pearls

In women meeting criteria, serum cortisol is measured to exclude Cushing's syndrome, and early-morning serum 17-hydroxyprogesterone is measured to exclude adrenal virilism. Serum dehydroepiandrosterone sulfate (DHEAS) is measured. If DHEAS is abnormal, women are evaluated as for amenorrhea (see p. 2504). Adult women with polycystic ovary syndrome are evaluated for metabolic syndrome by measuring BP and usually serum glucose.

Treatment

• Intermittent progestins or oral contraceptives

• Management of hirsutism and, in adult women, long-term effects of androgen excess

• Infertility treatments in women who desire pregnancy

To reduce the risk of endometrial hyperplasia and cancer in women who do not desire pregnancy, clinicians can use an intermittent progestin (eg, medroxyprogesterone 5 to 10 mg po once/day for 10 to 14 days q 1 to 2 mo) or oral contraceptives. These treatments also reduce circulating androgens.

For hirsutism (see p. 728), physical measures (eg, bleaching, electrolysis, plucking, waxing, depilation) can be used. Eflornithine cream 13.9% bid may help remove unwanted facial hair. In adult women who do not desire pregnancy, hormonal therapy that decreases androgen levels or spironolactone can be tried.

Weight loss is encouraged. It may help induce ovulation, increase insulin sensitivity, and reduce acanthosis nigricans and hirsutism.

Metformin 500 to 1000 mg bid is used to help increase insulin sensitivity if weight loss is unsuccessful or menses do not resume. Metformin can also reduce free testosterone levels. When metformin is used, serum glucose should be measured, and kidney and liver function tests should be done periodically. Because metformin may induce ovulation, contraception is needed if pregnancy is not desired.

For women who desire pregnancy, infertility treatments (eg, clomiphene, metformin) are used (see p. 2595). Weight loss may also be helpful. Hormonal therapy that may have contraceptive effects is avoided.

Premature Ovarian Failure

(Premature Menopause; Hypergonadotropic Hypogonadism)

In premature ovarian failure, ovaries do not produce enough estrogen despite high levels of circulating gonadotropins (especially follicle-stimulating hormone) in women < 40.

Etiology

Premature ovarian failure has various causes (see Table 246-4). Genetic disorders that confer a Y chromosome, which are usually evident by age 35, increase risk of ovarian cancer.

Symptoms and Signs

Typically, amenorrhea or irregular bleeding and symptoms or signs of estrogen deficiency (eg, osteoporosis, atrophic vaginitis, decreased libido) are present.

Diagnosis

• FSH and estradiol levels

• Sometimes karyotype analysis

Diagnosis is suspected in women < 40 with typical symptoms. A pregnancy test is done, and serum follicle-stimulating hormone (FSH) and estradiol levels are measured weekly for 2 to 4 wk; if FSH levels are high (> 20 mIU/mL, but usually > 30 mIU/mL) and estradiol levels are low (usually < 20 pg/mL), ovarian failure is confirmed. Then, further tests are done based on which cause is suspected. Karyotype is determined if women with confirmed ovarian failure are < 35.

Treatment

• Estrogen/progesterone therapy

Women who do not desire pregnancy are given estrogen/progesterone therapy (see p. 2519) until about age 51.

For women who desire pregnancy, in vitro fertilization of donated oocytes plus exogenous estrogen and a progestin, which enable the endometrium to support the transferred embryo (see p. 2597), can be tried. This technique is fairly successful, but even without this technique, 5 to 15% of women with diagnosed premature ovarian failure become pregnant.

Women with a Y chromosome require laparotomy or laparoscopy and excision of all gonadal tissue.

Premenstrual Syndrome

(Premenstrual Tension)

Premenstrual syndrome (PMS) is characterized by irritability, anxiety, emotional lability, depression, edema, breast pain, and headaches, occurring during

[Table 246-4. Common Causes of Premature Ovarian Failure]

the 7 to 10 days before and usually ending a few hours after onset of menses. Diagnosis is clinical, often based on the patient's daily recording of symptoms. Treatment is symptomatic and includes diet, drugs, and counseling.

Etiology

PMS appears to be caused by multiple endocrine factors (eg, hypoglycemia, other changes in carbohydrate metabolism, hyperprolactinemia, fluctuations in levels of circulating estrogen and progesterone, abnormal responses to estrogen and progesterone, excessive aldosterone or ADH). Estrogen and progesterone can cause transitory fluid retention, as can excess aldosterone or ADH.

Symptoms and Signs

Type and intensity of symptoms vary from woman to woman and from cycle to cycle. Symptoms last a few hours to ≥ 10 days, usually ending when menses begins. In perimenopausal women, symptoms may persist until after menses.

The most common symptoms are irritability, anxiety, agitation, anger, insomnia, difficulty concentrating, lethargy, depression, and severe fatigue. Fluid retention causes edema, transient weight gain, and breast fullness and pain. Pelvic heaviness or pressure and backache may occur. Some women, particularly younger ones, have dysmenorrhea when menses begins. Other nonspecific symptoms may include headache, vertigo, paresthesias of the extremities, syncope, palpitations, constipation, nausea, vomiting, and changes in appetite. Acne and neurodermatitis may also occur. Existing skin disorders may worsen, as may respiratory problems (eg, allergies, infection) and eye problems (eg, visual disturbances, conjunctivitis).

Premenstrual dysphoric disorder (PMDD): Some women have severe PMS symptoms that occur regularly and only during the 2nd half of the menstrual cycle; symptoms end with menses or shortly after. Mood is markedly depressed, and anxiety, irritability, and emotional lability are pronounced. Suicidal thoughts may be present. Interest in daily activities is greatly decreased. Symptoms are severe enough to interfere with routine daily activities or overall functioning.

Diagnosis

• For PMS, patient's reporting of symptoms

• For PMDD, clinical criteria

PMS is diagnosed based on physical symptoms (eg, bloating, weight gain, breast tenderness, swelling of

hands and feet). Women may be asked to record their symptoms daily.

If PMDD is suspected, women are asked to rate their symptoms daily for ≥ 2 cycles to determine whether severe symptoms occur regularly. For PMDD to be diagnosed, women must have ≥ 5 of the following symptoms for most of the week before menses and at least one symptom must be from the first 4:

• Feelings of sadness, hopelessness, or self-depreciation

• A tense (on edge) feeling or anxiety

• Emotional lability with frequent tearfulness

• Irritability or anger that persists, leading to increased interpersonal conflicts

• Loss of interest in daily activities, possibly causing withdrawal

• Decreased concentration

• Fatigue, lethargy, or lack of energy

• Changes in eating habits, including bingeing

• Insomnia or hyperinsomnia

• Feelings of being overwhelmed or out of control

• Physical symptoms associated with PMS

Also, the symptom pattern must have occurred for most of the previous 12 mo, and symptoms must be severe enough to interfere with daily activities and function.

Treatment

• General measures

• Sometimes SSRIs or hormonal manipulation

Treatment is symptomatic, beginning with adequate rest and sleep and regular exercise. Regular exercise may help alleviate bloating as well as irritability, anxiety, and insomnia. Dietary changes—increasing protein, decreasing sugar, and taking vitamin B complex (especially pyridoxine, a form of vitamin B_6) or Mg supplements—may help, as may counseling and avoiding stressful activities. Consuming foods high in Ca and vitamin D and, if needed, Ca and vitamin D supplements may help prevent PMS. Fluid retention may be relieved by reducing Na intake and taking a diuretic (eg, hydrochlorothiazide 25 to 50 mg po once/day in the morning) just before symptoms are expected. However, minimizing fluid retention does not relieve all symptoms and may have no effect.

SSRIs (eg, fluoxetine 20 mg po once/day) may be used to reduce anxiety, irritability, and other emotional symptoms, particularly if stress cannot be avoided. SSRIs are effective in relieving symptoms of PMDD.

For some women, hormonal manipulation is effective. Options include

• Oral contraceptives (eg, norethindrone 5 mg once/day)

• Progesterone by vaginal suppository (200 to 400 mg once/day)

• An oral progestin (eg, micronized progesterone 100 mg at bedtime) for 10 to 12 days before menses

• A long-acting progestin (eg, medroxyprogesterone 200 mg IM q 2 to 3 mo)

Rarely, for very severe or refractory symptoms, a gonadotropin-releasing hormone agonist (eg, leuprolide 3.75 mg IM, goserelin 3.6 mg sc q mo) with low-dose estrogen/progestin (eg, estradiol 0.5 mg once/day plus micronized progesterone 100 mg at bedtime) is given to minimize cyclic fluctuations.

Spironolactone, bromocriptine, and monoamine oxidase inhibitors are not useful.

Chapter 247. Menopause

Introduction

Menopause is physiologic or iatrogenic cessation of menses (amenorrhea) due to decreasing ovarian function. Manifestations may include hot flushes, atrophic vaginitis, and osteoporosis. Diagnosis is clinical: absence of menses for 1 yr. Manifestations may be treated (eg, with hormone therapy or SSRIs).

Physiologic menopause is established when menses have been absent for 1 yr. In the US, average age of physiologic menopause is 51. Perimenopause refers to the years before (duration varies greatly) and the 1 yr after the last menses. Perimenopause is usually characterized initially by an increase in frequency of menses, followed by a decrease (oligomenorrhea), but any pattern is possible; conception is possible during perimenopause. Climacteric refers to a longer phase in which women lose reproductive capacity; it begins before perimenopause.

As ovaries age, their response to the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) decreases, initially causing a shorter follicular phase (with shorter and more irregular menstrual cycles), fewer ovulations, and thus decreased progesterone production (see Fig. 245-5 on p. 2500). Eventually, follicles do not respond, producing little estradiol. Some estrogens (mainly estrone) still circulate; they are produced by peripheral tissues (eg, fat, skin) from androgens (eg, androstenedione, testosterone). However, the total estrogen level is much lower. Around menopause, androstenedione levels decrease by half, but the decrease in testosterone levels, which begins gradually in young adulthood, does not accelerate during menopause because the stroma of the postmenopausal ovary and adrenal gland continue to secrete substantial amounts. Decreased levels of ovarian inhibin and estrogen, which inhibit pituitary release of LH and FSH, result in a substantial increase in circulating LH and FSH levels.

Premature menopause (premature ovarian failure—see p. 2516) is cessation of menses due to noniatrogenic ovarian failure before age 40. Contributory factors may include smoking, living at high altitude, and undernutrition. Iatrogenic (artificial) menopause results from medical interventions (eg, oophorectomy, chemotherapy, pelvic irradiation, any intervention that impairs ovarian blood supply).

Symptoms and Signs

Perimenopausal changes in menstruation usually begin during a woman's 40s. Menstrual flow and cycle length can vary. Menses become irregular, then are skipped.

Large daily fluctuations in estrogen levels usually begin at least 1 yr before menopause and are thought to cause perimenopausal symptoms. Symptoms can last from 6 mo to over 10 yr and range from nonexistent to severe.

Vasomotor: Hot flushes (flashes) and sweating due to vasomotor instability affect 75 to 85% of women and usually begin before menses stop. Hot flushes continue for > 1 yr in most women and for > 5 yr in 50%. Women feel warm or hot and may perspire, sometimes profusely; core temperature increases. The skin, especially of the head and neck, may become red and warm. The episodic flush, which may last from 30 sec to 5 min, may be followed by chills. Flushes may manifest during the night as night sweats. The mechanism of hot flushes is unknown, but they may be triggered by cigarette smoking, hot beverages, foods containing nitrites or sulfites, spicy food, alcohol, and possibly caffeine.

Neuropsychiatric: Neuropsychiatric changes (eg, poor concentration, memory loss, depression, anxiety) may accompany menopause but are not directly related to decreased estrogen. Recurrent night sweats, which can disrupt sleep, can contribute to insomnia, fatigue, irritability, and poor concentration.

Genital: Decreased estrogen leads to vaginal and vulvar dryness and thinning, which may result in inflammation of the vaginal mucosa (atrophic vaginitis). Atrophy may cause irritation, dyspareunia, and dysuria and may increase vaginal pH. The labia minora, clitoris, uterus, and ovaries decrease in size.

Other: Although menopause is normal, health problems can occur, and for some, quality of life may decrease. Risk of osteoporosis increases because estrogen is decreased, increasing bone resorption by osteoclasts (see p. 356). The most rapid loss occurs during the first 2 yr after estrogen begins to decrease.

Diagnosis

• Clinical evaluation

• FSH levels rarely needed

Diagnosis is clinical. Menopause is likely if menses have gradually decreased in frequency and have been absent for 6 mo. Women with amenorrhea are examined to exclude pregnancy if they are < 50 and are always examined to exclude ovarian tumors (for evaluation of amenorrhea, see p. 2504). Abnormal pelvic masses are evaluated (see p. 2485). If women in their 50s have a history of irregular menses followed by cessation of menses, with or without symptoms of estrogen deficiency, and no other abnormal findings, no diagnostic testing is necessary.

FSH levels may be measured, but this test is rarely necessary. Consistently elevated levels predict menopause, sometimes many months to a year in advance.

Postmenopausal women who have risk factors for osteoporosis and all women > 65 should be screened for osteoporosis (see p. 357).

Treatment

• Avoidance of triggers and stress

• Exercise and relaxation techniques

• Possibly SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)

• Possibly hormone therapy

Discussing the physiologic causes of menopause and possible symptoms and signs with patients helps them manage the changes that occur. Treatment is symptomatic.

For hot flushes, avoiding triggers and wearing clothing in layers that can be removed as needed may help. Soy protein has been used, but its efficacy has not been confirmed. Black cohosh, other medicinal herbs, vitamin E, and acupuncture do not appear helpful. Regular exercise, stress avoidance, and relaxation techniques may improve sleep and reduce irritability; relaxation techniques can also reduce vasomotor symptoms. Paced respiration, a type of slow, deep breathing, may also help relieve hot flushes.

Nonhormonal drug treatments for hot flushes include SSRIs (eg, fluoxetine, sustained-release paroxetine, sertraline), SNRIs (eg, venlafaxine), and clonidine 0.1 mg transdermally once/day. Dose requirements for SSRIs and SNRIs vary; starting doses can be lower than those used to treat depression and increased as needed. It is not clear whether gabapentin is helpful.

OTC vaginal lubricants and moisturizers help relieve vaginal dryness. Measures to prevent and treat osteoporosis are considered (see p. 358).

Hormone therapy: For many women, risks of oral hormone therapy outweigh the benefits.

Hormone therapy may be used to relieve moderate to severe menopausal symptoms. For women who have had a hysterectomy, estrogen should be used alone. Forms may be oral, transdermal (a patch, lotions, or gels), or a tablet inserted vaginally. Women who have a uterus, if given estrogen in any form or

type, are a.lso given a progestin (as combination therapy) because unopposed estrogen increases risk of endometrial cancer (and possibly ovarian cancer if unopposed estrogen is taken > 10 yr). Oral hormone therapy also has other risks (see Table 247-1). For most women, these risks outweigh benefits. For other forms of hormone therapy, risks and other effects are not as well known. The risk of venous thromboembolism may be lower with transdermal estrogen.

Benefits of oral combination therapy include reduction in yearly incidence of osteoporosis and colorectal cancer, as well as relief of menopausal symptoms. For asymptomatic women, overall effects of therapy on quality of life are not very meaningful.

Risks of oral combination therapy are reflected in an increased yearly incidence of breast cancer, ischemic stroke, deep venous thromboembolism, pulmonary embolism, dementia, and coronary artery disease. Risk of coronary

[**Table 247-1.** Effects of Oral Hormone Therapy on Yearly Incidence* of Selected Disorders in Postmenopausal Women]

artery disease almost doubles during the first year of therapy and is particularly high for women with high pretreatment low-density lipoprotein levels; aspirin and statins do not prevent the increase in risk. Also, the breast cancers that develop are larger and more likely to be metastatic, and false-positive mammograms are more common. Urinary incontinence, particularly stress incontinence, develops more often, and existing incontinence tends to worsen.

Oral estrogen-only therapy does not affect incidence of coronary artery disease but increases incidence of ischemic stroke and deep venous thromboembolism. It decreases incidence of hip fractures. Effects on breast cancer, colorectal cancer, and pulmonary embolism are less clear. Estrogen-only therapy, like combination therapy, contributes to urinary incontinence. Dementia risk is probably increased with estrogen-only therapy.

Despite its beneficial effects on bone, hormone therapy (with or without a progestin) is not recommended for prevention and treatment of osteoporosis because other effective measures (eg, raloxifene, bisphosphonates), which usually have fewer risks, are available.

Oral estrogen therapy can be used to relieve hot flushes, night sweats (with consequent sleep disturbance), and vaginal dryness. For vaginal dryness or atrophy, topical forms of estrogen (eg, creams, vaginal tablets or rings) are as effective as oral forms. Vaginal tablets and rings that contain low doses (eg, 25 µg) deliver less estrogen to the systemic circulation; vaginal estrogen creams usually deliver as much as oral therapy.

Progestins (eg, megestrol acetate 10 to 20 mg po once/day, medroxyprogesterone acetate 10 mg po once/day or depot 150 mg IM once/mo) can be used alone to relieve hot flushes, but they do not relieve vaginal dryness. Progestins may have adverse effects (eg, abdominal bloating, breast tenderness, increased breast density, headache, increased low-density lipoprotein, decreased high-density lipoprotein); micronized progesterone appears to have fewer adverse effects but may increase the risk of venous thromboembolism. There are no long-term safety data about use of progestins.

When prescribing solely for the prevention of postmenopausal osteoporosis, clinicians should consider hormone therapy only for women at significant risk of osteoporosis and for whom nonestrogen drugs are considered inappropriate.

Chapter 248. Sexual Dysfunction in Women

Introduction

Most people—men and women—engage in sexual activity because of attraction or a desire for pleasure, affection, love, romance or intimacy. However, women are more likely to report emotional motivations. Many women initiate or agree to sexual activity because they want one or more of the following:

• To experience emotional intimacy

• To increase their sense of well-being

• To confirm their desirability

• To please or placate a partner

Especially in established relationships, women often have little or no initial sense of sexual desire but access sexual desire (responsive desire) once sexual stimulation triggers excitement and pleasure (subjective arousal) and genital congestion (physical genital arousal). Desire for sexual satisfaction, which may or may not include one or multiple orgasms, builds as sexual activity and intimacy continue, and a physically and emotionally rewarding experience fulfills and reinforces the woman's original motivations.

A woman's sexual response cycle is strongly influenced by her mental health and by the quality of her relationship with her partner. Initial desire typically lessens with age but increases with a new partner at any age.

Physiology

Sexual response consists of the following:

• Arousal

• Genital congestion

• Orgasm

Physiology of the female sexual response is incompletely understood but involves hormonal and CNS factors.

Estrogens and androgens both appear to influence arousal. Androgens probably act via androgen receptors and estrogen receptors (after intracellular conversion of testosterone to estradiol).

After menopause, ovarian estrogen production ceases, while ovarian androgen production varies. However, adrenal production of prohormones (eg, DHEAS) that are converted to both androgens and estrogens in peripheral cells decreases starting in a woman's 30s. Ovarian production of prohormones also declines after menopause. Whether this decrease plays any role in diminishing sexual desire, interest, or arousal is unclear.

The brain produces sex hormones (neurosteroids) from cholesterol, and production may increase after menopause. Whether this documented increase is universal, whether it facilitates arousal as peripheral production decreases, and whether it is affected by exogenous hormone administration are all unknown.

Arousal: Brain areas involved in cognition, emotion, motivation, and organization of genital congestion are activated. Neurotransmitters acting on specific receptors are involved. Based on known actions of drugs and on animal studies, some neurotransmitters appear to be prosexual; they include dopamine, norepinephrine, and melanocortin. Serotonin is usually sexually inhibitory, as are prolactin and γ-aminobutyric acid (GABA).

Genital congestion: This reflexive autonomic response occurs within seconds of an erotic stimulus and causes genital engorgement and lubrication. Smooth muscle cells around blood spaces in the vulva, clitoris, and vaginal arterioles dilate, increasing blood flow (engorgement) and transudation of interstitial fluid across the vaginal epithelium (lubrication). Women are not always aware of congestion, and it may occur without subjective arousal. As women age, basal genital blood flow decreases, but genital congestion in response to erotic stimuli (eg, erotic videos) may not.

Orgasm: Peak excitement occurs, characterized by contractions of pelvic muscles every 0.8 sec, and is followed by slow release of genital congestion. Thoracolumbar sympathetic outflow tracts appear to be involved, but orgasm is possible even after complete spinal cord transection (eg, when a vibrator is used to stimulate the cervix). Prolactin, ADH, and oxytocin are released at orgasm and may contribute to the sense of well-being, relaxation, or fatigue that follows. However, many women experience a sense of well-being and relaxation without experiencing orgasm.

Classification

Female sexual dysfunction may involve decreased or increased sexual responsiveness. Classification is determined by symptoms. There are 5 major categories of decreased responsiveness and one of increased responsiveness (persistent genital arousal disorder).

Sexual desire/interest disorder is absence of or a decrease in sexual interest, desire, sexual thoughts, and fantasies and an absence of responsive desire.

Sexual arousal disorder is lack of subjective or genital arousal or both.

Orgasmic disorder involves orgasm that is absent, markedly diminished in intensity, or markedly delayed in response to stimulation despite high levels of subjective arousal.

Vaginismus is reflexive tightening around the vagina when vaginal entry is attempted or completed despite women's expressed desire for penetration and when no structural or other physical abnormalities are present.

Dyspareunia is pain during attempted or completed vaginal penetration or intercourse. Provoked vestibulodynia (PVD, formerly called vulvar vestibulitis), the most common type of superficial (introital) dyspareunia, is a chronic pain syndrome associated with altered immune function and sensitization of the nervous system.

Persistent genital arousal disorder involves excessive genital arousal.

A disorder is diagnosed when symptoms cause distress. Some women may not be distressed or bothered by decreased or absent sexual desire, interest, arousal, or orgasm.

Almost all women with sexual dysfunction have features of more than one disorder. For example, the chronic dyspareunia of PVD often leads to sexual desire/interest and arousal disorders; impaired arousal may make sex less enjoyable or even painful, decreasing the likelihood of orgasm and subsequent sexual desire. However, dyspareunia due to impaired lubrication may occur as an isolated symptom in women with a high level of sexual desire, interest, and subjective arousal.

Female sexual disorders may be secondarily categorized as lifelong or acquired; situation-specific or generalized; and mild, moderate, or severe based on the degree of distress it causes the woman.

Although research is limited, these disorders probably apply equally to women in heterosexual and homosexual relationships.

Etiology

The traditional separation of psychologic and physical etiologies is artificial; psychologic distress causes

changes in hormonal and neurologic physiology, and physical changes may generate psychologic reactions that compound the dysfunction. There are often several causes of symptoms within and between categories of dysfunction, and the cause is often unclear.

Primarily psychologic factors: Mood disorders are closely correlated with low desire and arousal. In up to 80% of women with major depression and sexual dysfunction, sexual dysfunction becomes less severe when anti-depressants effectively treat the depression. However, sexual dysfunction persists or worsens when antidepressants are ineffective. Women with an anxiety disorder are also more likely to have sexual dysfunction involving desire, arousal, and orgasm. Various fears—of letting go, of being vulnerable, of being rejected, or of losing control—and low self-esteem can contribute.

Previous experiences can affect a woman's psychosexual development, as in the following:

• Past negative sexual or other experiences may lead to low self-esteem, shame, or guilt.

• Emotional, physical, or sexual abuse during childhood or adolescence can teach children to control and hide emotions—a useful defense mechanism—but such inhibition can make expressing sexual feelings difficult later.

• Early traumatic loss of a parent or another loved one may inhibit intimacy with a sex partner for fear of similar loss.

Concerns about a negative outcome (eg, unwanted pregnancy, sexually transmitted diseases [STDs], inability to have an orgasm, sexual dysfunction in a partner) can also impair sexual response.

Contextual causes (those specific to a woman's current circumstances) include the following:

• **Relationship context:** Lack of trust, negative feelings, or reduced attraction toward a sex partner (eg, due to the partner's behavior or to a growing awareness of a change in the partner's sexual orientation)

• **Sexual context:** For example, surroundings that are not sufficiently erotic, private, or safe

• **Cultural context:** For example, cultural restrictions on sexual activity

Distractions (eg, from family, work, or finances) can interfere with arousal.

Primarily physical factors: Various genital lesions, systemic and hormonal factors, and drugs may lead or contribute to dysfunction (see
Table 248-1).

SSRIs are a particularly common drug cause. Systemic estrogen therapy (postmenopausal or in hormonal contraceptives) has mixed effects. It can improve mood and help maintain skin and genital sexual sensitivity and vaginal lubrication. However, it also increases sex

[**Table 248-1.** Some Physical Factors Contributing to Female Sexual Dysfunction]

hormone-binding globulin (SHBG), decreasing the amount of free androgens available for tissue receptor binding. Decreasing free androgens can counteract the other sexual benefits of systemic estrogens, contributing to sexual dysfunction. Alcohol dependence can cause sexual dysfunction.

Diagnosis

• Interview with both partners, separately and together

• Gentle pelvic examination, primarily to identify causes of dyspareunia

Diagnosis of sexual dysfunction and its causes is based on history and physical examination. Ideally, history is taken from both partners, interviewed separately and together; it begins by asking the woman to

describe the problem in her own words and should include specific elements (see Table 248-2). Problematic areas (eg, past negative sexual experiences, negative sexual self-image) identified at the first visit can be investigated more fully at a follow-up visit.

Physical examination is most important for determining causes of dyspareunia; the technique may differ slightly from that used in a routine gynecologic examination. Explaining what will occur during the examination helps the woman relax and should be continued throughout the examination. The woman should be asked whether she wants to sit up and view her genitals in a mirror during the examination; doing so may impart a sense of control.

Wet-preparation examination of vaginal discharge and Gram stain with culture or DNA probe to detect *Neisseria gonorrhoeae* and chlamydiae are indicated when history or examination suggests vulvitis, vaginitis, or pelvic inflammatory disease.

Although low estrogen and testosterone activity may contribute to sexual dysfunction, measuring levels is rarely indicated. Low estrogen and testosterone are detected clinically. If hyperprolactinemia is clinically suspected, the prolactin level is measured. If hypothyroidism is clinically suspected, the TSH level is measured and sometimes other thyroid function tests are done.

Treatment

• Explanation of the female sexual response to the couple

• Treatment of the cause

• Substitution of other antidepressants for SSRIs or addition of bupropion

Treatment varies by disorder and cause; often, more than one treatment is required because disorders overlap. Sympathetic understanding of the patient and careful evaluation may themselves be therapeutic. Mood disorders are treated. Explaining what is involved in the female sexual response may also help.

Because SSRIs may contribute to several categories of sexual dysfunction, switching to an antidepressant that has fewer sexual adverse effects (eg, bupropion, moclobemide, mirtazapine, venlafaxine) may be considered. Alternatively, some evidence suggests that adding bupropion to an SSRI may help.

Sexual Desire/Interest Disorder

Sexual desire/interest disorder is absence of or a decrease in sexual interest, desire, sexual thoughts, and fantasies and absence of responsive desire.

[**Table 248-2.** Components of the Sexual History for Assessment of Female Sexual Dysfunction]

In sexual desire/interest disorder, motivations to become sexually aroused are scarce or absent. The decrease is greater than what might be expected based on a woman's age and the relationship duration.

Causes often involve primarily psychologic factors (eg, depression, anxiety, stress, relationship problems). Use of certain drugs (particularly SSRIs), anticonvulsants, chemotherapy drugs, β-blockers, and oral contraceptives, can reduce sexual desire, as can drinking excessive amounts of alcohol. Fluctuations in hormone levels (eg, at menopause, during pregnancy, with the menstrual cycle) can affect sexual desire.

Women with sexual desire/interest disorder tend to be anxious, to have a low self-image, and to have mood lability even if they do not have a clinical mood disorder.

Diagnosis is clinical (see p. 2523).

Treatment

• Education

• Psychologic therapies

• Hormonal therapy

If factors that limit trust, respect, attraction, and emotional intimacy between partners are the cause, the couple should be counseled that emotional intimacy is a normal requirement for female sexual response and needs to be enhanced with or without professional help. Education about sufficient and appropriate stimuli may help; women may need to remind their partner of their need for nonphysical, physical nongenital, and nonpenetrative genital stimulation. Recommendations for more intensely erotic stimuli and fantasies may help eliminate distractions; practical suggestions to improve privacy and a sense of security can help when fear of unwanted outcomes (eg, discovery, pregnancy, sexually transmitted diseases) inhibits arousability.

For patient-specific psychologic factors, psychologic therapies (eg, cognitive-behavioral therapy) may be required, although simple awareness of the importance of these factors may be sufficient for women to change patterns of thinking and behavior.

Hormonal causes require targeted treatment—eg, topical estrogen for atrophic vaginitis and bromocriptine for hyperprolactinemia.

Systemic estrogen therapy: Systemic estrogen therapy (see p. 2519) initiated at menopause or within the next few years may improve mood and help maintain skin and genital sexual sensitivity and vaginal lubrication. These benefits may enhance sexual desire and arousal despite decreasing free androgen levels. Transdermal preparations of estrogen are usually preferred after menopause, but no studies identify which preparations available in the US are the most beneficial sexually. Progestins or progesterone are also given to women who have not had a hysterectomy. If oral contraceptives or estrogen therapy appears to contribute to sexual desire/interest disorder, substituting another drug (eg, transdermal estrogen or barrier methods for oral contraceptives) may be indicated to increase free androgens.

Testosterone therapy: Benefits and risks of testosterone supplementation are under study. When no interpersonal, contextual, and intrapersonal factors are evident, some experienced clinicians consider supplementation (eg, with methyltestosterone 1.5 mg po once/day or transdermal testosterone 300 µg daily); preparations formulated for men are used.

Benefit has been shown mostly in women who are taking estrogen and who have had bilateral oophorectomy, but benefit is expected in some women who are taking estrogen and who have premature ovarian failure due to other conditions (eg, adrenal or pituitary dysfunction, chemotherapy, idiopathic). Benefit has been modest, but studies included only relatively sexually healthy women (with 2 to 3 sexually satisfying experiences/mo at baseline). Among postmenopausal women who are taking estrogen therapy and who can no longer be aroused by previously effective stimuli and contexts, benefit is conceivable; however, this group has not been studied.

However, testosterone therapy is not approved for women in the US. Also, the American Endocrine Society currently recommends against its use. Too little is known about long-term safety; in most studies, safety as well as efficacy data are limited to 6 mo. If testosterone is prescribed, full explanation of lack of long-term safety data and careful follow-up are essential. Periodically, the free testosterone level should be calculated or the bioavailable testosterone level should be measured (see p. 2342), and women should be checked for signs of hirsutism and for hyperlipidemia and impaired glucose tolerance.

Sexual Arousal Disorders

Sexual arousal disorders involve a lack of response to one or more types of sexual stimulation—subjective, physical genital, or both.

Sexual arousal disorders can be categorized as subjective, genital, or combined. All definitions are

clinically based, distinguished in part by the woman's response to genital and nongenital stimulation, as follows:

- **Subjective:** Women do not feel aroused by any type of sexual genital or nongenital stimulation (eg, kissing, dancing, watching an erotic video, physical stimulation), despite the occurrence of physical genital response (eg, genital congestion).

- **Genital:** Subjective arousal occurs in response to nongenital stimulation (eg, an erotic video) but not in response to genital stimulation. This disorder typically affects postmenopausal women and is often described as genital deadness. Testing confirms reduced genital congestion in response to sexual stimulation in some women; in others, genital congestion is normal, but genital sexual sensitivity seems reduced.

- **Combined:** Subjective arousal in response to any type of sexual stimulation is absent or low, and women report absence of physical genital arousal (ie, they report need of external lubricants and may state they know that swelling of the clitoris no longer occurs).

Etiology

Causes may involve psychologic (eg, depression, low self-esteem, anxiety, stress) or physical factors or both (see p. 2522). Inadequate sexual stimulation or the wrong setting for sexual activity can also contribute.

Genital arousal disorder may result from a low level of estrogen or possibly testosterone, as occurs during or after menopause, or from vulval dystrophy (eg, lichen sclerosus). Certain chronic disorders (eg, diabetes, multiple sclerosis) can damage autonomic or somatic nerves, leading to decreased congestion or sensation in the genital area.

Diagnosis

Diagnosis is clinical (see p. 2523).

Treatment

Subjective arousal disorder: See Sexual Desire/Interest Disorder on p. 2523.

Genital arousal disorder: When estrogen is deficient, initial treatment is local estrogen (or systemic estrogen if indicated for other postmenopausal symptoms). A phosphodiesterase inhibitor may be tried empirically if symptoms are refractory to estrogen therapy; it benefits only women with reduced genital congestion (eg, due to autonomic nerve damage). Other investigational therapy includes a trial of 0.2 mL topical 2% testosterone prepared by a pharmacist and applied twice weekly to the clitoris.

Orgasmic Disorder

Orgasmic disorder involves orgasm that is absent, markedly diminished in intensity, or markedly delayed in response to stimulation despite high levels of subjective arousal.

Women with orgasmic disorder often have difficulty relinquishing control in nonsexual circumstances.

Contextual factors (eg, consistently insufficient foreplay, poor communication about sexual preferences), psychologic factors (eg, anxiety, stress, lack of trust in a partner, fears), physical disorders, and drugs can contribute to orgasmic disorder (see p. 2522). Lack of knowledge about sexual function may also contribute.

Damage to genital sensory or autonomic nerves (eg, due to diabetes or multiple sclerosis) or, much more commonly, use of SSRIs may lead to acquired orgasmic disorder.

Treatment

• Self-stimulation

• Psychologic therapies

Data support encouraging self-stimulation. A vibrator placed on the mons pubis close to the clitoris may help, as may increasing the number and intensity of stimuli (mental, visual, tactile, auditory, written), simultaneously if necessary. Education about sexual function (eg, need to stimulate the clitoris) may help.

Psychologic therapies including cognitive-behavioral therapy and psychotherapy may help women identify and manage fear of relinquishing control, fear of vulnerability, or issues of trust with a partner.

In women taking an SSRI, symptoms may decrease when bupropion is added. One study supports the use of sildenafil.

Vaginismus

Vaginismus is reflexive tightening around the vagina when vaginal entry is attempted or completed (eg, using a penis, finger, or dildo) despite women's expressed desire for penetration and despite the absence of any structural or other physical abnormalities.

Vaginismus usually results from fear that intercourse will be painful; it usually begins with the first attempt at sexual intercourse. It may develop later after periods of stress. Women may develop a phobia-like avoidance of penetration. Most women with vaginismus thus cannot tolerate full or often even partial penetration. Some cannot tolerate insertion of a tampon or have never wanted to try. However, most women with vaginismus enjoy nonpenetrative sexual activity.

Reflex muscle tightening can also accompany dyspareunia of any cause, thereby adding to the pain and difficulty with entry. Women anticipate a recurrence of pain when intercourse is initiated, and muscles tighten, making attempts at sexual intercourse even more painful.

Diagnosis

• Clinical evaluation

Diagnosis is suspected based on symptoms. Physical abnormalities that cause pain, such as those that cause dyspareunia should be excluded by physical examination. However, the condition itself makes examination difficult. One strategy is to initiate treatment as described below and defer the confirmatory examination. When the examination is done, the physician can give the patient a sense of control by having her sit up and view her genitals using a mirror. The woman then spreads her labia and inserts her or the examiner's gloved finger past the hymen as she bears down. This simple digital examination can simultaneously confirm a normal vagina and the presumed diagnosis of vaginismus.

Treatment

• Progressive desensitization

Women progressively accustom themselves to self-touch near, on, and then through the introitus.

• The woman first touches herself daily as close to the introitus as possible, separating the labia with her fingers.

• Once her fear and anxiety due to introital self-touch has diminished, the woman will be more able to tolerate the physical examination.

• The next stage is to insert her finger past her hymen; pushing or bearing down during insertion enlarges the opening and eases entry.

- Once finger insertion causes no discomfort, vaginal cones in gradually increasing sizes are inserted progressively; leaving a cone inside for 10 to 15 min helps perivaginal muscles become accustomed to gently increasing pressure without reflex contraction. The woman first inserts a cone herself; when comfortable with the cone, she then allows her partner to help her insert one during a sexual encounter to confirm that it can go in comfortably when she is sexually excited.

- Once insertion in this context is comfortable, the couple should include penile vulvar stimulation during sexual play so that the woman becomes accustomed to feeling the penis on her vulva.

- Ultimately, the woman inserts her partner's penis partially or fully, holding it like an insert. She may feel more confident in the woman superior position.

Some men experience situational erectile dysfunction in this process and may benefit from a phosphodiesterase inhibitor.

Dyspareunia

Dyspareunia is pain during attempted or completed vaginal penetration.

Dyspareunia may occur at the moment of penetration (superficial or introital), with deeper entry, with penile movement, or post-coitally. Some pelvic muscle hypertonicity, manifested as both voluntary guarding and involuntary high muscle tension, is common in all types of chronic dyspareunia.

Etiology

Causes may involve psychologic and physical factors (see p. 2522).

Superficial dyspareunia may result from provoked vestibulodynia (PVD), atrophic vaginitis, vulvar disorders (eg, lichen sclerosus, vulvar dystrophies), congenital malformations, genital herpes simplex, radiation fibrosis, postsurgical introital narrowing, or recurrent tearing of the posterior fourchette.

Deep dyspareunia may result from pelvic muscle hypertonicity or uterine or ovarian disorders (eg, fibroids, chronic pelvic inflammatory disease, endometriosis).

Penile size and depth of penetration influence presence and severity of symptoms.

A subgroup of women with dyspareunia due to PVD (see p. 2528) have high self-expectations and fear of negative evaluation by other people, increased somatization, catastrophizing (gross exaggeration of possible consequences), and hypervigilance to pain.

Diagnosis

- Clinical evaluation

Diagnosis is based on symptoms and a pelvic examination.

For superficial dyspareunia, evaluation focuses on inspecting all the vulvar skin, including the creases between the labia minora and majora (eg, for fissures typical of chronic candidiasis), and the clitoral hood, urethral meatus, hymen, and openings of major vestibular gland ducts (for atrophy, signs of inflammation, and skin lesions typical of lichen sclerosus). PVD can be diagnosed using a cotton swab to elicit allodynia; nonpainful external areas are touched before moving to more typically painful areas (ie, outer edge of the hymenal ring, clefts adjacent to the urethral meatus). Pelvic muscle hypertonicity may be suspected if pain similar to the pain that occurs during intercourse can be elicited by palpating the deep levator ani muscles, particularly around the ischial spines. Palpating the urethra and bladder may identify abnormal tenderness.

For deep dyspareunia, evaluation requires a careful bimanual examination to determine whether cervical motion or uterine or adnexal palpation causes pain and to check for nodules in the cul-de-sac or vaginal

fornices. A rectovaginal examination is usually indicated to check the rectovaginal septum and posterior surface of the uterus and adnexa. Suspected uterine and ovarian disorders are evaluated with imaging studies as clinically indicated.

Treatment

• Treatment of cause (eg, topical estrogen for atrophic vaginitis)

• Education and counseling

• Pelvic muscle physiotherapy

Management should include the following:

• Encouraging and teaching the couple to develop satisfying forms of nonpenetrative sex

• Discussing psychologic issues contributing to and caused by the chronic pain

• When possible, treating the primarily physical abnormality that contributes to pain (eg, endometriosis, lichen sclerosus, vulvar dystrophies, vaginal infections, congenital malformations, radiation fibrosis —see elsewhere in THE MANUAL). PVD is also treated (see below).

• Treating coexisting pelvic muscle hypertonicity

• Treating comorbid sexual desire/interest or arousal disorders

Topical estrogen is helpful for atrophic vaginitis (see p. 2545) and recurrent posterior fourchette tearing.

Women with pelvic muscle hypertonicity, including some with PVD, may benefit from pelvic physical therapy using pelvic floor muscle training, possibly with biofeedback, to teach pelvic muscle relaxation. Sometimes a change in sexual position helps.

Provoked Vestibulodynia

Provoked vestibulodynia (vulvar vestibulitis, localized vulvar dysesthesia) is the most common type of superficial (introital) dyspareunia. Pain starts and stops precisely with introital pressure. Treatment may include measures used in chronic pain syndromes as well as topical lidocaine or cromoglycate, but efficacy of the latter is unproved.

Provoked vestibulodynia develops when the nervous system—from peripheral receptors to the cerebral cortex—is sensitized and remodeled. With sensitization, discomfort due to a stimulus that might otherwise be perceived as mild or trivial (eg, touch) is instead perceived as significant pain (allodynia). This disorder is probably a form of chronic pain syndrome (see p. 1629) of the vulva. The peripheral sensitization leads to a neurogenic inflammatory response. Some women also have GU disorders (eg, vulvovaginal candidiasis, hyperoxaluria), but the etiologic role of these disorders is unproved. Some women also have other pain disorders (eg, irritable bowel syndrome—see p. 162; interstitial cystitis—see p. 2364).

Symptoms and Signs

In vestibulodynia, introital pressure, penile movement, or a man's ejaculation typically causes immediate pain. Pain typically stops when penile movement stops and resumes when it starts again. Vestibulodynia may also cause postcoital vulvar burning and dysuria.

Diagnosis

• Clinical evaluation

Diagnosis is based on symptoms and confirmed by the Q-tip test for allodynia. Vaginismus causes similar

pain with introital pressure and penile containment and movement. However, unlike vestibulodynia, there is no allodynia. Also, pain due to vaginismus continues after penile movement stops but may progressively fade during intercourse despite continued penile movement.

Treatment

• Psychologic therapies used in chronic pain management

• Sometimes sex therapy

• Pelvic muscle physiotherapy

• Drugs to treat chronic pain

• Possibly topical lidocaine or cromoglycate

Optimal treatment of provoked vestibulodynia is unclear; many approaches are currently used, and there are probably still undefined subtypes that require different treatment. Because this disorder involves chronic pain, treatments are becoming more comprehensive, including management of stress and emotional reactions to pain.

Commonly used but unproven approaches involve avoiding topical irritants and using systemic drugs (eg, tricyclic antidepressants, anticonvulsants) or topical drugs (eg, 2% cromoglycate or 2 or 5% lidocaine in glaxal base) to interrupt chronic pain circuits. Cromoglycate stabilizes WBC membranes, including those of mast cells, interrupting the neurogenic inflammation thought to underlie vestibulodynia. Cromoglycate or lidocaine must be placed precisely on the area of allodynia using a 1-mL syringe without a needle. Physician supervision and use of a mirror (at least initially) are helpful. Psychologic therapies, including cognitive-behavioral therapy and sex therapy, may also help some women with vestibulodynia. Women with pelvic muscle hypertonicity may benefit from pelvic physical therapy using pelvic floor muscle training, possibly with biofeedback. Surgery (eg, excision of the hymen, proximal edge of the lower vagina, and innermost portion of the labia minora) is sometimes indicated to remove proliferated nerve endings. However, pain may recur as nerves regenerate. Investigational treatment includes botulinum toxin type A injection.

Persistent Genital Arousal Disorder

Persistent genital arousal disorder is excessive unwanted unprovoked genital arousal.

Cause is unknown. Anxiety and hypervigilance for recurrence of pain episodes may perpetuate the syndrome. Symptoms have been thought to sometimes be manifestations of seizure disorders, but in published series, brain imaging and EEG have not found abnormalities.

Unwanted, intrusive, spontaneous genital arousal (eg, tingling, throbbing) occurs, but sexual interest or desire is absent; arousal is unrelieved by orgasms. The feelings persist for hours or days. Older women may be very embarrassed by the symptoms.

Treatment

Treatment is unclear. Self-stimulation may provide relief but usually only temporarily. High-dose SSRI therapy has been reported effective, but data are few. Simple recognition of the existence of this disorder, with reassurance that it can spontaneously remit, may help some patients.

Chapter 249. Pelvic Relaxation Syndromes

Introduction

Pelvic relaxation syndromes result from laxities (similar to hernias) in the ligaments, fascia, and muscles supporting the pelvic organs (pelvic floor—see Fig. 249-1). About 9% of women require surgical repair for a pelvic relaxation syndrome. Common contributing factors include childbirth (particularly vaginal delivery), obesity, aging, injury (eg, due to pelvic surgery), and chronic straining. Less common factors include congenital malformations, increased abdominal pressure (eg, due to ascites, abdominal tumors, or chronic respiratory disorders), sacral nerve disorders, and connective tissue disorders. Pelvic relaxation syndromes involve various sites of prolapse and include cystocele, urethrocele, enterocele, rectocele, and uterine and vaginal prolapse. Usually, prolapse occurs in multiple sites.

Cystoceles, Urethroceles, Enteroceles, and Rectoceles

These disorders involve protrusion of an organ into the vaginal canal: cystoceles (bladder), urethroceles (urethra), enteroceles (small intestine and peritoneum), and rectoceles (rectum). Symptoms include pelvic or vaginal fullness or pressure. Diagnosis is clinical. Treatment includes pessaries, pelvic muscle exercises, and surgery.

Cystocele, urethrocele, enterocele, and rectocele are particularly likely to occur together. Urethrocele is virtually always accompanied by

[**Fig. 249-1.** Pelvic relaxation syndromes.]

cystocele (cystourethrocele). Cystocele and cystourethrocele commonly develop when the pubocervical vesical fascia is weakened. Enterocele usually occurs after a hysterectomy. Weakness in the pubocervical fascia and rectovaginal fascia allows the apex of the vagina, which contains the peritoneum and small bowel, to descend. Rectocele results from disruption of the levator ani muscles.

Severity of these disorders can be graded based on level of protrusion:

• 1st degree: To the upper vagina

• 2nd degree: To the introitus

• 3rd degree: External to the introitus

Symptoms and Signs

Pelvic or vaginal fullness, pressure, and a sensation of organs falling out are common. Organs may bulge into the vaginal canal or introitus, particularly during straining or coughing. Dyspareunia can occur. Stress incontinence often accompanies cystocele or cystourethrocele. Overflow incontinence or, particularly when sacral nerves are damaged, urge incontinence may also develop. Enteroceles may cause lower back pain. Rectoceles may cause constipation and incomplete defecation; patients may have to manually press the posterior vaginal wall to defecate.

Diagnosis

• Examination of the anterior or posterior vaginal wall while patients strain

Diagnosis is confirmed by examination.

Cystoceles and cystourethroceles are detected by applying a single-bladed speculum against the posterior vaginal wall while patients are in the lithotomy position. Asking patients to strain makes cystoceles or cystourethroceles visible or palpable as soft reducible masses bulging into the anterior vaginal wall. Inflamed paraurethral (Skene's) glands are differentiated by their more anterior and lateral

urethral location, tenderness, and occasionally expression of pus during palpation. Enlarged Bartholin's glands can be differentiated because they develop in the medial labia majora and may be tender if infected.

Enteroceles and rectoceles are detected by retracting the anterior vaginal wall while patients are in the lithotomy position. Asking patients to strain can make enteroceles and rectoceles visible and palpable during rectovaginal examination. Patients are also examined while standing with one knee elevated (eg, on a stool) and straining; sometimes abnormalities are detected only by rectovaginal examination during this maneuver.

Urinary incontinence, if present, is also evaluated.

Treatment

• Pessary and Kegel exercises

• Surgical repair of supporting structures if necessary

Treatment may initially consist of a pessary and Kegel exercises.

Pessaries are prostheses inserted in the vagina to maintain reduction of the prolapsed structures. Pessaries are of varying shapes and sizes, and some are inflatable. They may cause vaginal ulceration if they are not correctly sized and routinely cleansed (at least monthly if not more frequently).

Kegel exercises involve isometric contractions of the pubococcygeus muscle. Isolation of the correct muscle is difficult (about 50% of patients cannot do it) but important because a Valsalva maneuver is detrimental and buttock or thigh contraction is unhelpful. Contraction of the correct muscle is best initiated by asking patients to simulate attempting to hold in urine. Three sets of 8 to 10 contractions are done daily; contractions are initially held for 1 to 2 sec and increased up to 10 sec each when possible. Exercises can be facilitated by use of weighted vaginal cones, which help patients focus on contracting the correct muscle, by biofeedback devices, or by electrical stimulation, which causes the muscle to contract.

Surgical repair of supporting structures (anterior and posterior colporrhaphy) can help relieve symptoms that are severe or do not resolve with nonsurgical treatment. Perineorrhaphy (surgical shortening and tightening of the perineum) may also be needed. Colporrhaphy (surgical repair of the vagina) is usually deferred, if possible, until future childbearing is no longer desired because subsequent vaginal birth may disrupt the repair. Urinary incontinence can be surgically treated at the same time as colporrhaphy. After surgery, patients should avoid heavy lifting for 3 mo. After surgery to repair a cystocele or cystourethrocele, a urethral catheter is used for < 24 h.

Uterine and Vaginal Prolapse

Uterine prolapse is descent of the uterus toward or past the introitus. Vaginal prolapse is descent of the vagina or vaginal cuff after hysterectomy. Symptoms include vaginal pressure and fullness. Diagnosis is clinical. Treatment includes reduction, pessaries, and surgery.

Uterine prolapse is graded based on level of descent:

• 1st degree: To the upper vagina

• 2nd degree: To the introitus

• 3rd degree: Cervix is outside the introitus

• 4th degree (sometimes referred to as procidentia): Uterus and cervix entirely outside the introitus

Vaginal prolapse may be 2nd or 3rd degree.

Symptoms and Signs

Symptoms tend to be minimal with 1st-degree uterine prolapse. In 2nd- or 3rd-degree uterine prolapse, fullness, pressure, dyspareunia, and a sensation of organs falling out are common. Lower back or coccygeal pain may develop. Constipation is possible.

Third-degree uterine prolapse manifests as a bulge or protrusion of the cervix or cuff, although spontaneous reduction may occur before patients present. Vaginal mucosa may become dried, thickened, chronically inflamed, secondarily infected, and ulcerated. Ulcers may be painful or bleed and may resemble vaginal cancer. The cervix, if protruding, may also become ulcerated.

Symptoms of vaginal prolapse are similar. Cystocele or rectocele is usually present.

Urinary incontinence is common. The descending pelvic mass may intermittently obstruct urine flow, causing urinary retention and masking stress or overflow incontinence. Urinary frequency and urge incontinence may accompany vaginal prolapse.

Diagnosis

• Pelvic examination

Diagnosis is confirmed by speculum or bi-manual pelvic examination. Vaginal ulcers are biopsied to exclude cancer. Simultaneous urinary incontinence requires evaluation.

Treatment

• Treatment of symptomatic or 3rd-degree prolapse, beginning with pessaries and Kegel exercises

• Surgical repair of supporting structures if necessary, usually with hysterectomy

Asymptomatic 1st- or 2nd-degree uterine prolapse does not require treatment. Symptomatic or 3rd-degree prolapse can be treated nonsurgically if the perineum can structurally support a pessary. Severe or persistent symptoms require surgery, usually hysterectomy with surgical repair of the pelvic support structures (colporrhaphy) and suspension of the vagina (suturing of the upper vagina to a stable structure nearby). The abdominal approach results in greater structural support than the vaginal approach, but risk of short-term morbidity and mesh-related complications is greater. Surgery is delayed until all ulcers, if present, have healed.

Vaginal prolapse is treated similarly to uterine prolapse. Urinary incontinence requires concurrent treatment.

Chapter 250. Benign Gynecologic Lesions

Introduction

Benign gynecologic lesions include vulvar and vaginal cysts, cervical stenosis and polyps, uterine myomas, and benign ovarian masses, which can predispose to adnexal torsion.

Adnexal Torsion

Adnexal torsion is twisting of the ovary and sometimes the fallopian tube, interrupting the arterial supply and causing ischemia.

Adnexal torsion is uncommon, occurring most often during reproductive years. It usually indicates an ovarian abnormality. Risk factors include the following:

• Pregnancy

• Induction of ovulation

• Ovarian enlargement to > 4 cm (particularly by benign tumors)

Benign tumors are more likely to cause torsion than malignant ones. Torsion of normal adnexa, which is rare, is more common among children than adults.

Typically, one ovary is involved, but sometimes the fallopian tube is also involved. Adnexal torsion can cause peritonitis.

Symptoms

Torsion causes sudden, severe pelvic pain and sometimes nausea and vomiting. For days or occasionally weeks before the sudden pain, women may have intermittent, colicky pain, presumably resulting from intermittent torsion that spontaneously resolves. Cervical motion tenderness, a unilateral tender adnexal mass, and peritoneal signs are usually present.

Diagnosis

• Color Doppler transvaginal ultrasonography

Adnexal torsion is suspected based on typical symptoms and unexplained peritoneal signs plus severe cervical motion tenderness or an adnexal mass, particularly when criteria for pelvic inflammatory disease are not met or when symptoms are unilateral. Diagnosis is usually confirmed by color Doppler transvaginal ultrasonography.

Treatment

• Surgery to untwist the ovary

If torsion is suspected or confirmed by ultrasonography, laparoscopy or laparotomy is done immediately to attempt to salvage the ovary and fallopian tube by untwisting them. Salpingooophorectomy is required for nonviable or necrotic tissue. If an ovarian cyst or mass is present, cystectomy or oophorectomy is done.

Bartholin's Gland Cysts

Bartholin's gland cysts are mucus-filled and occur on either side of the vaginal opening (see Plate 69). They are the most common large vulvar cysts. Symptoms of large cysts include vulvar irritation, dyspareunia, pain during walking, and vulvar asymmetry. Bartholin's cysts may form abscesses, which are painful and usually red. Diagnosis is by physical examination. Large cysts and abscesses require drainage and sometimes excision; abscesses sometimes require

antibiotics.

Bartholin's glands are round, very small, nonpalpable, and located deep in the postero-lateral vaginal orifice. Obstruction of the Bartholin duct causes the gland to enlarge with mucus, resulting in a cyst. Cause of obstruction is usually unknown. Rarely, the cysts result from a sexually transmitted disease (eg, gonorrhea).

These cysts develop in about 2% of women, usually those in their 20s. With aging, cysts are less likely to develop.

A cyst may become infected, forming an abscess. Vulvar cancers rarely originate in Bartholin's glands (see p. 2581).

Symptoms and Signs

Most cysts are asymptomatic, but large cysts can be irritating, interfering with sexual intercourse and walking. Most cysts are non-tender, unilateral, and palpable near the vaginal orifice. Cysts distend the affected labia majora, causing vulvar asymmetry.

Abscesses cause severe vulvar pain and sometimes fever; they are tender and typically erythematous. A vaginal discharge may be present. Sexually transmitted diseases may coexist.

Diagnosis

• Clinical evaluation

Diagnosis is usually by physical examination. A sample of discharge, if present, may be tested for sexually transmitted diseases. In women > 40, excisional biopsy must be done to exclude vulvar cancer.

Treatment

• Surgery for symptomatic cysts and for all cysts in women > 40

In women < 40, asymptomatic cysts do not require treatment. Symptomatic cysts may require surgery. Because cysts often recur after simple drainage, surgery aims to produce a permanent opening from the duct to the exterior. Usually, one of the following is done:

• **Catheter insertion:** A small balloon-tipped catheter may be inserted, inflated, and left in the cyst for 4 to 6 wk; this procedure stimulates fibrosis and produces a permanent opening.

• **Marsupialization:** The everted edges of the cyst are sutured to the exterior.

Recurrent cysts may require excision.

In women > 40, all cysts must be surgically explored and removed by excisional biopsy.

Abscesses are treated with oral broad-spectrum antibiotics (eg, cephalexin 500 mg q 6 h for 7 to 10 days) and insertion of a balloon-tipped catheter.

Benign Ovarian Masses

Benign ovarian masses include functional cysts and tumors; most are asymptomatic.

Functional cysts: There are 2 types of functional cysts:

• **Follicular cysts:** These cysts develop from graafian follicles.

• **Corpus luteum cysts:** These cysts develop from the corpus luteum. They may hemorrhage into the

cyst cavity, distending the ovarian capsule or rupturing into the peritoneum.

Most functional cysts are < 1.5 cm in diameter; few exceed 5 cm. Functional cysts usually resolve spontaneously over days to weeks. Functional cysts are uncommon after menopause.

Benign tumors: Benign ovarian tumors usually grow slowly and rarely become malignant. They include the following:

- **Benign cystic teratomas:** These tumors are also called dermoid cysts because although derived from all 3 germ cell layers, they consist mainly of ectodermal tissue.

- **Fibromas:** These slow-growing tumors are usually < 7 cm in diameter.

- **Cystadenomas:** These tumors are most commonly serous or mucinous.

Symptoms and Signs

Most functional cysts and benign tumors are asymptomatic. Sometimes they cause menstrual abnormalities. Hemorrhagic corpus luteum cysts may cause pain or signs of peritonitis, particularly when they rupture. Occasionally, severe abdominal pain results from adnexal torsion of a cyst or mass, usually > 4 cm. Ascites and rarely pleural effusion may accompany fibromas.

Diagnosis

- Transvaginal ultrasonography

Masses are usually detected incidentally but may be suggested by symptoms and signs. A pregnancy test is done to exclude ectopic pregnancy. Transvaginal ultrasonography can usually confirm the diagnosis. If results are indeterminate, MRI or CT may help.

Masses with radiographic characteristics of cancer (eg, cystic and solid components, surface excrescences, multilocular appearance, irregular shape) require excision. Tumor markers may help in the diagnosis of specific tumors (see p. 2568). In women of reproductive age, simple, thin-walled cystic adnexal masses 5 to 8 cm (usually follicular) without characteristics of cancer do not require further evaluation unless they persist for > 3 menstrual cycles.

Treatment

- Removal of selected cysts

Most ovarian cysts < 8 cm resolve without treatment; serial ultrasonography is done to document resolution. If technically feasible, cyst removal from the ovary (ovarian cystectomy) via laparoscopy or laparotomy may be necessary for the following:

- Most cysts that are ≥ 10 cm and that persist for > 3 menstrual cycles

- Cystic teratomas < 10 cm

- Hemorrhagic corpus luteum cysts with peritonitis

- Fibromas and other solid tumors

Oophorectomy is done for the following:

- Fibromas that cannot be removed by cystectomy

- Cystadenomas

• Cystic teratomas > 10 cm

• Cysts that cannot be surgically removed separately from the ovary

• Most cysts that are detected in postmenopausal women and that are > 5 cm

Cervical Myomas

Cervical myomas are smooth, benign tumors of the cervix.

Cervical myomas are uncommon. Uterine myomas (fibroids) usually coexist. Large cervical myomas may partially obstruct the urinary tract or may prolapse into the vagina. Prolapsed myomas sometimes ulcerate, become infected, bleed, or a combination.

Symptoms and Signs

Most cervical myomas eventually cause symptoms. The most common symptom is bleeding, which may be irregular or heavy, sometimes causing anemia. Dyspareunia may occur. Infection may cause pain, bleeding, or discharge. Rarely, prolapse causes a feeling of pressure or a mass in the pelvis. Urinary outflow obstruction causes hesitancy, dribbling, or urine retention; UTIs may develop.

Diagnosis

• Physical examination

Diagnosis is by physical examination. Cervical myomas, particularly if prolapsed, may be visible with use of a speculum. Some are palpable during bimanual examination.

Transvaginal ultrasonography is done only for the following:

• To confirm an uncertain diagnosis

• To exclude urinary outflow obstruction

• To identify additional myomas

Hb, Hct, or CBC is measured to exclude anemia. Cervical cytology is done to exclude cervical cancer.

Treatment

• Removal of symptomatic myomas

Treatment is similar to that of fibroids (see p. 2537). Small, asymptomatic myomas are not treated. Most symptomatic cervical myomas are removed by myomectomy (particularly if childbearing capacity is important) or, if myomectomy is technically difficult, by hysterectomy. Prolapsed myomas should be removed transvaginally if possible.

Cervical Polyps

Cervical polyps are common benign growths of the cervix and endocervix.

Cervical polyps occur in about 2 to 5% of women. They usually originate in the endocervical canal. Endocervical polyps are probably caused by chronic inflammation. They rarely become malignant.

Most cervical polyps are asymptomatic. Endocervical polyps may bleed between menses or after intercourse or become infected, causing purulent vaginal discharge (leukorrhea). Endocervical polyps are usually reddish pink, glistening, and < 1 cm in all dimensions; they may be friable.

Diagnosis

Diagnosis is by speculum examination.

Treatment

Polyps that cause bleeding or discharge should be removed. Excision can be done in the office and does not require anesthetics. Bleeding after excision is rare and can be controlled with chemical cautery.

If bleeding or discharge persists after treatment, cervical cytology and endometrial biopsy are done to exclude cancer.

Cervical Stenosis

Cervical stenosis is stricture of the internal cervical os.

Cervical stenosis may be congenital or acquired. The most common acquired causes are

• Menopause

• Cervical surgery (eg, conization, cautery)

• Endometrial ablation procedures to treat uterine abnormalities that cause menorrhagia

• Cervical or uterine cancer

• Radiation therapy

Cervical stenosis may be complete or partial. It may result in a hematometra (accumulation of blood in the uterus) or, in premenopausal women, retrograde flow of menstrual blood into the pelvis, possibly causing endometriosis. A pyometra (accumulation of pus in the uterus) may also develop, particularly in women with cervical or uterine cancer.

Symptoms and Signs

Common symptoms in premenopausal women include amenorrhea, dysmenorrhea, abnormal bleeding, and infertility. Postmenopausal women may be asymptomatic for long periods. Hematometra or pyometra may cause uterine distention or sometimes a palpable mass.

Diagnosis

• Clinical evaluation

Diagnosis may be suspected based on symptoms and signs (particularly development of amenorrhea or dysmenorrhea after cervical surgery) or on inability to obtain endocervical cells or an endometrial sample for diagnostic tests (eg, for a Papanicolaou [Pap] test). Diagnosis of complete stenosis is established if a 1- to 2-mm diameter probe cannot be passed into the uterine cavity.

If cervical stenosis causes symptoms or uterine abnormalities (eg, hematometra, pyometra), cervical cytology and endometrial biopsy should be done to exclude cancer. For postmenopausal women with no history of abnormal Pap tests and for women without symptoms or uterine abnormalities, no further evaluation is needed.

Treatment

• Dilation and stenting if symptomatic

Treatment is indicated only if symptoms or uterine abnormalities are present and typically involves

cervical dilation and placement of cervical stent.

Skene's Duct Cyst

Skene's duct cysts develop adjacent to the distal urethra, sometimes causing perineal discharge, dyspareunia, urinary obstruction, or abscess formation.

Skene's glands (periurethral or paraurethral glands) are located adjacent to the distal urethra. Cysts form if the duct is obstructed, usually because the gland is infected. They occur mainly in adults. Cysts may form abscesses or cause urethral obstruction and recurrent UTIs.

Most cysts are < 1 cm and asymptomatic. Some are larger and cause dyspareunia. The first symptoms may be those of urinary out-flow obstruction (eg, hesitancy, dribbling, retention) or of UTIs. Abscesses are painful, swollen, tender, and erythematous but usually do not cause fever.

Diagnosis

• Clinical evaluation

Diagnosis is usually clinical. Most symptomatic cysts and abscesses are palpable adjacent to the distal urethra; however, a diverticulum of the distal urethra may be clinically indistinguishable, requiring ultrasonography or cystoscopy for differentiation.

Treatment

• Surgical excision if the cyst causes symptoms

Symptomatic cysts are excised. Abscesses are treated initially with oral broad-spectrum antibiotics (eg, cephalexin 500 mg q 6 h for 7 to 10 days) and are excised or marsupialized.

Vulvar Endometriomas

Vulvar endometriomas are rare, painful cysts that result from extrauterine implantation of functioning endometrial tissue (endometriosis—see p. 2538).

Rarely, endometriosis occurs in the vulva (or the vagina), sometimes producing cysts (endometriomas), often at the site of previous surgery (eg, episiotomy).

Endometriomas usually develop in the mid-line. They may be painful, particularly during intercourse. During menstruation, pain increases and endometriomas may enlarge. Endometriomas are tender and may appear blue. They can rupture, causing severe pain.

Diagnosis is by physical examination and biopsy. Treatment involves excisional biopsy.

Vulvar Inclusion and Epidermal Cysts

Vulvar inclusion cysts contain epithelial tissue; vulvar epidermal cysts develop from sebaceous glands. Both cysts eventually enlarge with cellular debris and sometimes become infected.

Inclusion cysts are the most common vulvar cysts; they may also occur in the vagina. They may result from trauma (eg, laceration, episiotomy repair) that entraps viable epithelial tissue below the surface, or they may develop spontaneously. Epidermal cysts result from obstruction of sebaceous gland ducts.

Uninfected cysts are usually asymptomatic but occasionally cause irritation; they are white or yellow and usually < 1 cm. Infected cysts may be red and tender and cause dyspareunia.

Diagnosis is clinical. Treatment, indicated only for symptomatic cysts, is excision; a local anesthetic can be used.

Chapter 251. Uterine Fibroids

(Leiomyomas; Myomas; Fibromyomas)

Uterine fibroids are benign uterine tumors of smooth muscle origin. Fibroids frequently cause abnormal vaginal bleeding (eg, menorrhagia, menometrorrhagia), pelvic pain and pressure, urinary and intestinal symptoms, and pregnancy complications. Diagnosis is by pelvic examination and ultrasonography. Treatment of symptomatic patients depends on the patient's desire for fertility and desire to keep her uterus and may include oral contraceptives, brief presurgical gonadotropin-releasing hormone therapy to shrink fibroids, and more definitive surgical procedures (eg, hysterectomy, myomectomy, endometrial ablation).

Uterine fibroids are the most common pelvic tumor, occurring in about 70% of women by age 45. However, many fibroids are small and asymptomatic. About 25% of white and 50% of black women have symptomatic fibroids. Fibroids are more common among women who have a high body mass index. Potentially protective factors include parturition and cigarette smoking.

Most fibroids in the uterus are subserous, followed by intramural, then submucosal. Occasionally, fibroids occur in the broad ligaments (intraligamentous), fallopian tubes, or cervix. Some fibroids are pedunculated. Most fibroids are multiple and develop from a single monoclonal smooth muscle cell. Because they have estrogen receptors, fibroids tend to enlarge during the reproductive years and regress after menopause.

Large fibroids may outgrow their blood supply and degenerate. Degeneration is described as hyaline, myxomatous, calcific, cystic, fatty, red (usually only during pregnancy), or necrotic. Although patients are often concerned about cancer in fibroids, sarcomatous change is extremely rare.

Symptoms and Signs

Fibroids can cause menorrhagia or menometrorrhagia. If fibroids grow, degenerate, or hemorrhage or if pedunculated fibroids twist, severe acute or chronic pressure or pain can result. Urinary symptoms (eg, urinary frequency or urgency) can result from bladder compression, and intestinal symptoms (eg, constipation) can result from intestinal compression.

Fibroids may prevent pregnancy; during pregnancy, they may cause recurrent spontaneous abortion, premature contractions, or abnormal presentation or make cesarean delivery necessary.

Diagnosis

• Ultrasonography or sonohysterography

The diagnosis is likely if bimanual pelvic examination detects an enlarged, mobile, irregular uterus that is palpable above the pelvic symphysis. Confirmation requires imaging, usually with ultrasonography or sonohysterography. In sonohysterography, saline is instilled into the uterus, enabling the sonographer to more specifically locate the fibroid in the uterus. If ultrasonography is inconclusive, MRI, the most accurate imaging test, is done.

Treatment

• Sometimes gonadotropin-releasing hormone (GnRH) analogs or other drugs for temporary relief of minor symptoms

• Myomectomy (to preserve fertility) or hysterectomy for symptomatic fibroids

Asymptomatic fibroids do not require treatment. Patients are reevaluated periodically (eg, every 6 to 12 mo).

For **symptomatic fibroids**, medical options, including suppression of ovarian hormones to stop the

bleeding, are suboptimal and limited. However, menorrhagia or menometrorrhagia should be treated before surgery is considered. GnRH analogs are commonly given before surgery to shrink fibroid tissues, often stopping menses and allowing blood counts to increase. In postmenopausal women, expectant management can be tried because symptoms may resolve as fibroids regress.

Drugs: Several drugs are used to relieve symptoms, reduce fibroid growth, or both.

GnRH analogs given IM or sc (eg, leuprolide 3.75 mg IM q mo, goserelin 3.6 mg sc q 28 days), as a subdermal pellet, or as nasal spray can decrease estrogen production. These drugs are most commonly used. GnRH analogs are most helpful when given preoperatively to reduce fibroid and uterine volume, making surgery technically more feasible and reducing blood loss. In general, these drugs should not be used in the long term because rebound growth to pretreatment size within 6 mo is common and bone demineralization may occur.

Exogenous progestins can partially suppress estrogen stimulation of uterine fibroid growth. Medroxyprogesterone acetate 5 to 10 mg po once/day or megestrol acetate 10 to 20 mg po once/day given 10 to 14 days each menstrual cycle can limit heavy bleeding, beginning after 1 or 2 treatment cycles. Alternatively, oral therapy every day of the month (continuous therapy) may be given; it often reduces bleeding and provides contraception. Depot medroxyprogesterone acetate 150 mg IM q 3 mo has effects similar to those of continuous oral therapy. Before IM therapy, oral progestins should be tried to determine whether patients can tolerate the adverse effects (eg, weight gain, depression, irregular bleeding). Progestin therapy causes fibroids to grow in some women.

Antiprogestins (eg, mifepristone) can also help reduce fibroid growth. The dose is 5 to 50 mg (once/day for 3 to 6 mo), which is lower than the 200-mg dose used for termination of pregnancy; thus, it must be mixed specially by the pharmacy and may not always be available.

Selective estrogen receptor modulators (SERMs; eg, raloxifene) may help reduce fibroid growth. However, whether efficacy in reducing symptoms is comparable to that of other drugs is unclear.

Danazol, an androgenic agonist, can suppress fibroid growth but has a high rate of adverse effects (eg, weight gain, acne, hirsutism, edema, hair loss, deepening of the voice, flushing, sweating, vaginal dryness) and is thus often less acceptable to patients.

NSAIDs can be used to treat pain but probably do not decrease bleeding.

Surgery: Surgery is usually reserved for women with any of the following:

• Rapidly enlarging pelvic mass

• Recurrent uterine bleeding refractory to drug therapy

• Persistent or intolerable pain or pressure

• Urinary or intestinal symptoms

• Infertility (if pregnancy is desired)

• Recurrent spontaneous abortions (if pregnancy is desired)

Hysterectomy or **myomectomy** is traditionally done; both are major surgery and have similar indications. Hysterectomy is the definitive treatment. After myomectomy, new fibroids may begin another growth phase, and about 25% of women who have a myomectomy have a hysterectomy about 4 to 8 yr later. However, if women desire pregnancy or want to keep their uterus, myomectomy is used. In about 55% of women with infertility due to fibroids alone, myomectomy can restore fertility, resulting in pregnancy after about 15 mo. Multiple myomectomy can be much more difficult to do than hysterectomy. Patient choice is important but must be based on full information about anticipated difficulties and sequelae of myomectomy vs hysterectomy.

Newer procedures may relieve symptoms, but duration of symptom relief and efficacy of the procedures in restoring fertility have not been evaluated. Such procedures include laparoscopic and hysteroscopic myomectomy (using an instrument with a wide-angle telescope and electrical wire loop for excision), high-intensity focused sonography, cryotherapy, and radiofrequency ablation. Complication rates after laparoscopic myomectomy may be higher, but rates appear to be operator-dependent. Uterine artery embolization has been used with the aim of causing infarction of fibroids throughout the uterus while preserving normal uterine tissue. After this procedure, women recover more quickly than after hysterectomy or myomectomy, but rates of complications and return visits tend to be higher.

Choice of treatment: Treatment should be individualized, but some factors can help with the decision:

- Asymptomatic fibroids: No treatment
- Postmenopausal women: Trial of expectant management (because symptoms tend to remit as fibroids regress)
- Surgically accessible symptomatic fibroids, particularly if conception may be desired: Myomectomy
- Symptomatic fibroids that are not clearly surgically accessible: Uterine artery embolization or another new technique (eg, high-intensity focused sonography)
- Intolerable symptoms when other treatments were ineffective, particularly if conception is not desired: Hysterectomy, possibly preceded by drug therapy (eg, with GnRH analogs)

Chapter 252. Endometriosis

Introduction

Endometriosis is a noncancerous disorder in which functioning endometrial tissue is implanted outside the uterine cavity. Symptoms depend on location of the implants and may include dysmenorrhea, dyspareunia, infertility, dysuria, and pain during defecation. Diagnosis is by biopsy, usually via laparoscopy. Treatments include anti-inflammatory drugs, drugs to suppress ovarian function and endometrial tissue growth, surgical ablation and excision of endometriotic implants, and, if disease is severe and no childbearing is planned, hysterectomy plus oophorectomy.

Endometriosis is usually confined to the peritoneal or serosal surfaces of pelvic organs, commonly the ovaries, broad ligaments, posterior cul-de-sac, and uterosacral ligaments. Less common sites include the serosal surfaces of the small and large intestines, ureters, bladder, vagina, cervix, surgical scars, pleura, and pericardium. Bleeding from peritoneal implants is thought to initiate inflammation, followed by fibrin deposition, adhesion formation, and, eventually, scarring, which distorts peritoneal surfaces of organs and pelvic anatomy.

Etiology and Pathophysiology

The most widely accepted hypothesis is that endometrial cells are transported from the uterine cavity and subsequently become implanted at ectopic sites. Retrograde flow of menstrual tissue through the fallopian tubes could transport endometrial cells intraabdominally; the lymphatic or circulatory system could transport endometrial cells to distant sites (eg, the pleural cavity). Another hypothesis is coelomic metaplasia: Coelomic epithelium is transformed into endometrium-like glands.

Microscopically, endometriotic implants consist of glands and stroma identical to intrauterine endometrium. These tissues contain estrogen and progesterone receptors and thus usually grow, differentiate, and bleed in response to changes in hormone levels during the menstrual cycle.

Incidence of endometriosis is increased in 1st-degree relatives of women with endometriosis, suggesting that heredity is a factor. Incidence is also increased in women who delay childbearing, who have shortened menstrual cycles (< 27 days) with menses that are abnormally long (> 8 days), or who have mullerian duct defects.

Reported incidence varies but is probably about 10 to 15% in actively menstruating women aged 25 to 44. Average age at diagnosis is 27, but endometriosis also occurs among adolescents. About 25 to 50% of infertile women have endometriosis. In patients with severe endometriosis and distorted pelvic anatomy, incidence of infertility is high because mechanisms of ovum pickup and tubal transport are impaired. Some patients with minimal endometriosis and normal pelvic anatomy are also infertile; reasons for impaired fertility include the following:

- Increased incidence of luteinized unruptured ovarian follicle syndrome (trapped oocyte)
- Increased peritoneal prostaglandin production or peritoneal macrophage activity (resulting in oocyte phagocytosis)
- Nonreceptive endometrium (because of luteal phase dysfunction or other abnormalities)

Potential protective factors seem to be multiple pregnancies, use of low-dose oral contraceptives (continuous or cyclic), and regular exercise (especially if begun before age 15, if done for > 7 h/wk, or both).

Symptoms and Signs

Pelvic pain, pelvic mass, alteration of menses, and infertility are typical. Some women with extensive endometriosis are asymptomatic; some with minimal disease have incapacitating pain. Dyspareunia and

midline pelvic pain before or during menses may develop. Such dysmenorrhea is an important diagnostic clue, particularly if it begins after several years of pain-free menses.

Symptoms can vary depending on location of implants.

• **Large intestine:** Pain during defecation, abdominal bloating, or rectal bleeding during menses

• **Bladder:** Dysuria, hematuria, suprapubic pain (particularly during urination), or a combination

• **Ovaries:** Formation of an endometrioma (a 2- to 10-cm cystic mass localized to an ovary), which occasionally ruptures or leaks, causing acute abdominal pain and peritoneal signs

• **Adnexal structures:** Formation of adnexal adhesions, resulting in a pelvic mass

• **Extrapelvic structures:** Vague abdominal pain (sometimes)

Pelvic examination may be normal, or findings may include a retroverted and fixed uterus, enlarged ovaries, fixed ovarian masses, thickened rectovaginal septum, induration of the cul-de-sac, and nodules on the uterosacral ligament. Rarely, lesions can be seen on the vulva or cervix or in the vagina, umbilicus, or surgical scars.

Diagnosis

• Biopsy, usually laparoscopic

• Sometimes imaging tests (to follow progression) but not for diagnosis

Diagnosis is suspected based on typical symptoms but must be confirmed by biopsy, usually via pelvic laparoscopy but sometimes via laparotomy, vaginal examination, sigmoidoscopy, or cystoscopy. Macroscopic appearance (eg, clear, red, brown, black) and size of implants vary during the menstrual cycle. However, typically, areas of endometriosis on the pelvic peritoneum are punctate red, blue, or purplish brown spots that are > 5 mm, often called powder burn lesions. Microscopically, both endometrial glands and stroma must be present to diagnose endometriosis.

Imaging tests (eg, ultrasonography, barium enema, IV urography, CT, MRI) are not specific or adequate for diagnosis. However, if they are done to rule out other disorders, they sometimes show the extent of endometriosis. They can also be used to monitor the disorder once it is diagnosed. Investigational serum markers for endometriosis (eg, serum cancer antigen 125 level > 35 units/mL, antiendometrial antibody) may help monitor the disorder but require further refinement before they are used routinely. Testing for other infertility disorders may be indicated (see p. 2592).

Staging the disorder helps physicians formulate a treatment plan and evaluate response to therapy. According to the American Society for Reproductive Medicine, endometriosis may be classified as stage I (minimal), II (mild), III (moderate), or IV (severe), based on number, location, and depth of implants and presence of filmy or dense adhesions (see Table 252-1).

Another staging system is based primarily on the presence and severity of pelvic pain.

[**Table 252-1.** Stages of Endometriosis]

However, because intraobserver and interob-server variability is high in the staging systems, a more reliable method of staging is being sought.

Treatment

• NSAIDs for discomfort

- Drugs to suppress ovarian function
- Conservative surgical resection or ablation of endometriotic tissue
- Conservative surgery plus drugs
- Total abdominal hysterectomy with bilateral salpingo-oophorectomy if disease is severe and patient has completed childbearing

Symptomatic treatment begins with NSAIDs. More definitive treatment must be individualized based on the patient's age, symptoms, and desire to preserve fertility and on the extent of the disorder.

Drugs and conservative surgery are symptomatic treatments; in most patients, endometriosis recurs after treatment is stopped unless ovarian function is permanently and completely ablated.

Drugs that suppress ovarian function inhibit the growth and activity of endometriotic implants. These drugs include continuous oral contraceptives (commonly used), gonadotropin-releasing hormone (GnRH) agonists, and danazol (see Table 252-2).

GnRH agonists temporarily suppress estrogen production; however, treatment is limited to ≤ 6 mo because long-term use may result in bone loss. If treatment lasts > 4 to 6 mo, add-back therapy, usually a low-dose oral contraceptive taken daily, can be given. Danazol, a synthetic androgen and an antigonadotropin, inhibits ovulation. However, its androgenic adverse effects limit its use. Cyclic or continuous

[**Table 252-2.** Drugs Used to Treat Endometriosis]

oral contraceptives given after danazol or GnRH agonists may slow disease progression and are warranted for women who wish to delay childbearing. After drug treatment, fertility rates range from 40 to 60%. Whether treating minimal or mild endometriosis improves fertility rates is unclear because the fertility rate among untreated women is unknown.

Most women with moderate to severe endometriosis are treated most effectively by ablating or excising as many implants as possible while preserving fertility. Specific indications for surgery include presence of endometriomas, significant pelvic adhesions, fallopian tube obstruction, incapacitating pelvic pain, and a desire to preserve fertility. Microsurgical techniques are used to prevent adhesions if women desire to preserve fertility. Laparoscopy can sometimes be used to remove lesions; peritoneal or ovarian lesions can sometimes be electrocauterized, excised, or vaporized with a laser. After this treatment, fertility rates are 40 to 70% and are inversely proportional to severity of the endometriosis. If resection is incomplete, use of oral contraceptives or GnRH agonists may increase fertility rates. Laparoscopic resection of the uterosacral ligaments with electrocautery or a laser may reduce midline pelvic pain. Some patients require presacral neurectomy.

Hysterectomy should usually be reserved for patients who have intractable pelvic pain and who have completed childbearing. If women < 50 require hysterectomy with oophorectomy, supplemental estrogen should be considered. Continuous progestin (eg, medroxyprogesterone acetate 2.5 mg po once/day) should be given with estrogen because if estrogen is given alone, residual tissue may grow. Hormone replacement can be started postoperatively or, if a substantial amount of endometriotic tissue remains, may be delayed for 4 to 6 mo; during this interval, progestins to suppress the remaining endometriotic tissue may be necessary.

Chapter 253. Vaginitis and Pelvic Inflammatory Disease

Introduction

The lower and upper female genital tracts are separated by the cervix. Inflammation of the lower tract may involve the vagina (vaginitis), vulva (vulvitis), or both (vulvovaginitis). Pelvic inflammatory disease is infection of the upper tract: uterus, fallopian tubes, and, if infection is severe, ovaries (one or both).

Vaginitis

Vaginitis is infectious or noninfectious inflammation of the vaginal mucosa, sometimes with inflammation of the vulva. Symptoms include vaginal discharge, irritation, pruritus, and erythema. Diagnosis is by in-office testing of vaginal secretions. Treatment is directed at the cause and at any severe symptoms.

Vaginitis is one of the most common gynecologic disorders. Some of its causes affect the vulva alone (vulvitis) or in addition (vulvovaginitis).

Etiology

The most common causes vary by patient age.

Children: In children, vaginitis usually involves infection with GI tract flora (nonspecific vulvovaginitis). A common contributing factor in girls aged 2 to 6 yr is poor perineal hygiene (eg, wiping from back to front after bowel movements; not washing hands after bowel movements; fingering, particularly in response to pruritus). Chemicals in bubble baths or soaps may cause inflammation. Foreign bodies (eg, tissue paper) may cause nonspecific vaginitis with a bloody discharge. Sometimes childhood vulvovaginitis is due to infection with a specific pathogen (eg, streptococci, staphylococci, *Candida* sp; occasionally, pinworm).

Women of reproductive age: In these women, vaginitis is usually infectious. The most common types are bacterial vaginosis (see p. 2543), candidal vaginitis (see p. 2544), and trichomonal vaginitis (see p. 1481), which is sexually transmitted. Normally in women of reproductive age, *Lactobacillus* sp is the predominant constituent of normal vaginal flora. Colonization by these bacteria keeps vaginal pH in the normal range (3.8 to 4.2), thereby preventing overgrowth of pathogenic bacteria. Also, high estrogen levels maintain vaginal thickness, bolstering local defenses. Factors that predispose to overgrowth of bacterial vaginal pathogens may include the following:

• An alkaline vaginal pH due to menstrual blood, semen, or a decrease in lactobacilli

• Poor hygiene

• Frequent douching

Vaginitis may result from foreign bodies (eg, forgotten tampons). Inflammatory vaginitis, which is noninfectious, is uncommon.

Postmenopausal women: Usually, a marked decrease in estrogen causes vaginal thinning, increasing vulnerability to infection and inflammation. Some treatments (eg, oophorectomy, pelvic radiation, certain chemotherapy drugs) also result in loss of estrogen. Decreased estrogen predisposes to atrophic vaginitis. Poor hygiene (eg, in patients who are incontinent or bedbound) can lead to chronic vulvar inflammation due to chemical irritation from urine or feces or due to nonspecific infection. Bacterial vaginosis, candidal vaginitis, and trichomonal vaginitis are uncommon among postmenopausal women but may occur in those with risk factors.

Women of all ages: At any age, conditions that predispose to vaginal or vulvar infection include fistulas between the intestine and genital tract, which allow intestinal flora to seed the genital tract, and pelvic radiation or tumors, which break down tissue and thus compromise normal host defenses. Noninfectious

vulvitis accounts for up to 30% of vulvovaginitis cases. It may result from hypersensitivity or irritant reactions to hygiene sprays or perfumes, menstrual pads, laundry soaps, bleaches, fabric softeners, fabric dyes, synthetic fibers, bathwater additives, toilet tissue, or, occasionally, spermicides, vaginal lubricants or creams, latex condoms, vaginal contraceptive rings, or diaphragms.

Symptoms and Signs

Vaginitis causes vaginal discharge, which must be distinguished from normal discharge. Normal discharge is common when estrogen levels are high—eg, during the first 2 wk of life because maternal estrogen is transferred before birth (slight bleeding often occurs when estrogen levels abruptly decrease) and during the few months before menarche, when estrogen production increases. Normal vaginal discharge is commonly milky white or mucoid, odorless, and nonirritating; it can result in vaginal wetness that dampens underwear. Discharge due to vaginitis is accompanied by pruritus, erythema, and sometimes burning, pain, or mild bleeding. Pruritus may interfere with sleep. Dysuria or dyspareunia may occur. In atrophic vaginitis, discharge is scant, dyspareunia is common, and vaginal tissue appears thin and dry. Although symptoms vary among particular types of vaginitis, there is much overlap (see Table 253-1).

[**Table 253-1.** Common Types of Vaginitis]

Vulvitis can cause erythema, pruritus, and sometimes tenderness and discharge from the vulva.

Diagnosis

• Clinical evaluation

• Vaginal pH and saline and KOH wet mounts

Vaginitis is diagnosed using clinical criteria and in-office testing. First, vaginal secretions are obtained with a water-lubricated speculum, and pH paper is used to measure pH in 0.2 intervals from 4.0 to 6.0. Then, secretions are placed on 2 slides with a cotton swab and diluted with 0.9% NaCl on one slide (saline wet mount) and with 10% K hydroxide on the other (KOH wet mount). The KOH wet mount is checked for a fishy odor (whiff test), which results from amines produced in trichomonal vaginitis or bacterial vaginosis. The saline wet mount is examined microscopically as soon as possible to detect trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation. The KOH dissolves most cellular material except for yeast hyphae, making identification easier. If clinical criteria and in-office test results are inconclusive, the discharge may be cultured for fungi or trichomonads.

Other causes of discharge are ruled out. If children have vaginal discharge, a vaginal foreign body is suspected. Cervical discharge due to cervicitis (eg, due to pelvic inflammatory disease [PID]) can resemble that of vaginitis; abdominal pain, cervical motion tenderness, or cervical inflammation suggests PID. Discharge that is watery, bloody, or both may result from vulvar, vaginal, or cervical cancer; cancers can be differentiated from vaginitis by examination and Papanicolaou (Pap) tests. Vaginal pruritus and discharge may result from skin disorders (eg, psoriasis, tinea versicolor), which can usually be differentiated by history and skin findings.

If children have trichomonal vaginitis, evaluation for sexual abuse is required. If they have unexplained vaginal discharge, cervicitis, which may be due to a sexually transmitted disease, should be considered. If women have bacterial vaginosis or trichomonal vaginitis (and thus are at increased risk of sexually transmitted diseases), cervical tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, common causes of sexually transmitted PID, are done.

Treatment

• Hygienic measures

• Symptomatic treatment

• Treatment of cause

The vulva should be kept as clean as possible. Soaps and unnecessary topical preparations (eg, feminine hygiene sprays) should be avoided. Intermittent use of ice packs or warm sitz baths with or without baking soda may reduce soreness and pruritus.

If symptoms are moderate or severe or do not respond to other measures, drugs may be needed. For pruritus, topical corticosteroids (eg, topical 1% hydrocortisone bid prn) can be applied to the vulva but not in the vagina. Oral antihistamines decrease pruritus and cause drowsiness, helping patients sleep.

Any infection or other cause is treated. Foreign bodies are removed. Prepubertal girls are taught good perineal hygiene (eg, wiping front to back after bowel movements and voiding, washing hands, avoiding fingering the perineum). If chronic vulvar inflammation is due to being bedbound or incontinent, better vulvar hygiene may help.

Bacterial Vaginosis

Bacterial vaginosis is vaginitis due to a complex alteration of vaginal flora in which lactobacilli decrease and anaerobic pathogens overgrow. Symptoms include a gray, thin, fishy-smelling vaginal discharge and itching. Diagnosis is confirmed by testing vaginal secretions. Treatment is usually with oral or topical metronidazole or topical clindamycin.

Bacterial vaginosis is the most common infectious vaginitis. The cause is unknown. Anaerobic pathogens that overgrow include *Prevotella* sp, *Peptostreptococcus* sp, *Gardnerella vaginalis, Mobiluncus* sp, and *Mycoplasma hominis*, which increase in concentration 10-fold to 100-fold and replace the normally protective lactobacilli. Risk factors include those for sexually transmitted diseases (see p. 1466). However, bacterial vaginosis can occur in virgins, and treating the male sex partner does not appear to affect subsequent incidence in sexually active women. Use of an intrauterine device is also a risk factor.

Bacterial vaginosis, once considered inconsequential, appears to increase risk of pelvic inflammatory disease, postabortion and postpartum endometritis, posthysterectomy vaginal cuff infection, chorioamnionitis, premature rupture of membranes, preterm labor, and preterm birth.

Symptoms and Signs

Vaginal discharge is malodorous, gray, and thin. Usually, a fishy odor is present, often becoming stronger when the discharge is more alkaline—after coitus and menses. Pruritus and irritation are common. Erythema and edema are uncommon.

Diagnosis

For the diagnosis, 3 of 4 criteria must be present:

• Gray discharge

• Vaginal secretion pH > 4.5

• Fishy odor on the whiff test

• Clue cells

Clue cells (bacteria adherent to epithelial cells obscuring their cell margins—see Plate 70) are identified by microscopic examination of a saline wet mount. Presence of WBCs on a saline wet mount suggests a concomitant infection (possibly trichomonal, gonorrheal, or chlamydial cervicitis) and the need for additional testing.

Treatment

• Topical metronidazole or clindamycin

Metronidazole 0.75% vaginal gel bid for 5 days or 2% clindamycin vaginal cream once/day for 7 days is the treatment of choice. Oral metronidazole 500 mg bid for 7 days or 2 g po once is effective but can have systemic adverse effects. Women who use clindamycin cream cannot use latex products (ie, condoms or diaphragms) for contraception because the drug weakens latex. Treatment of asymptomatic sex partners is unnecessary.

For vaginitis during the 1st trimester of pregnancy, metronidazole vaginal gel should be used, although treatment during pregnancy has not been shown to lower the risk of pregnancy complications. To prevent endometritis, clinicians may give metronidazole prophylactically before elective abortion to all patients or only to those who test positive for bacterial vaginosis.

Candidal Vaginitis

Candidal vaginitis is vaginal infection with *Candida* sp, usually *C. albicans*.

Most fungal vaginitis is caused by *C. albicans* (see also p. 703), which colonizes 15 to 20% of nonpregnant and 20 to 40% of pregnant women. Risk factors for candidal vaginitis include the following:

• Diabetes

• Use of a broad-spectrum antibiotic or corticosteroids

• Pregnancy

• Constrictive nonporous undergarments

• Immunocompromise

• Use of an intrauterine device

Candidal vaginitis is uncommon among postmenopausal women except among those taking systemic hormone therapy.

Symptoms and Signs

Vaginal vulvar pruritus, burning, or irritation (which may be worse with intercourse) and dyspareunia are common, as is a thick, white, cottage cheese-like vaginal discharge that adheres to the vaginal walls. Symptoms and signs increase the week before menses. Erythema, edema, and excoriation are common. Infected male sex partners may or may not have symptoms. Recurrences after treatment are uncommon.

Diagnosis

• Vaginal pH and wet mount

Vaginal pH is < 4.5; budding yeast, pseudohyphae, or mycelia are visible on a wet mount, especially with KOH (see Plate 71). If symptoms suggest candidal vaginitis but signs (including vulvar irritation) are absent and microscopy does not detect fungal elements, fungal culture is done. Women with frequent recurrences require culture to confirm the diagnosis and to rule out non-albicans *Candida*.

Treatment

• Antifungal drugs

• Avoidance of excess moisture accumulation

Keeping the vulva clean and wearing loose, absorbent cotton clothing that allows air to circulate can reduce vulvar moisture and fungal growth. Topical or oral drugs are highly effective (see Table 253-2). Adherence to treatment is better when a one-dose oral regimen of fluconazole 150 mg is used. Topical butoconazole, clotrimazole, miconazole, and tioconazole are available OTC. However, patients should be warned that topical creams and ointments containing mineral oil or vegetable oil weaken latex-based condoms. If symptoms persist or worsen during topical therapy, hypersensitivity to topical antifungals should be considered.

Frequent recurrences require long-term suppression with oral drugs (fluconazole 150 mg weekly to monthly or ketoconazole 100 mg once/day for 6 mo). Suppression is effective only while the drugs are being taken. These drugs may be contraindicated in patients with liver disorders. Patients taking ketoconazole should be monitored periodically with liver function tests.

[**Table 253-2.** Drugs for Candidal Vaginitis]

Inflammatory Vaginitis

Inflammatory vaginitis is vaginal inflammation without evidence of the usual infectious causes of vaginitis.

Etiology may be autoimmune. Vaginal epithelial cells slough superficially, and streptococci overgrow. The major risk factor is estrogen loss, which can result from menopause or premature ovarian failure (eg, due to oophorectomy, pelvic radiation, or chemotherapy). Genital atrophy predisposes to inflammatory vaginitis and increases risk of recurrence.

Symptoms and Signs

Purulent vaginal discharge, dyspareunia, dysuria, and vaginal irritation are common. Vaginal pruritus and erythema may occur. Burning, pain, or mild bleeding occurs less often. Vaginal tissue may appear thin and dry. Vaginitis may recur.

Diagnosis

• Vaginal pH and wet mount

Because symptoms overlap with other forms of vaginitis, testing (eg, vaginal fluid pH measurement, microscopy, whiff test) is necessary. The diagnosis is made if vaginal fluid pH is > 6, whiff test is negative, and microscopy shows predominantly WBCs and parabasal cells.

Treatment

• Clindamycin vaginal cream

Treatment is with clindamycin vaginal cream 5 g every evening for 1 wk. After treatment with clindamycin, women are evaluated for genital atrophy. Genital atrophy, if present, can be treated with topical estrogens (eg, 0.01% estradiol vaginal cream 2 to 4 g once/day for 1 to 2 wk, followed by 1 to 2 g once/day for 1 to 2 wk, then 1 g 1 to 3 times weekly; estradiol hemihydrate vaginal tablets 25 µg twice/wk; estradiol rings q 3 mo). Topical therapy is usually preferred because of concerns about the safety of oral hormonal therapy; topical therapy may have fewer systemic effects.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is infection of the upper female genital tract: the cervix, uterus, fallopian tubes, and ovaries; abscesses may occur. Common symptoms and signs include lower abdominal pain, cervical discharge, and irregular vaginal bleeding. Long-term complications include infertility, chronic pelvic pain, and ectopic pregnancy. Diagnosis includes PCR of cervical specimens for *Neisseria gonorrhoeae* and chlamydiae, microscopic examination of cervical discharge (usually), and ultrasonography or laparoscopy (occasionally). Treatment is

with antibiotics.

PID results from microorganisms ascending from the vagina and cervix into the endometrium and fallopian tubes. Infection of the cervix (cervicitis) causes mucopurulent discharge. Infection of the fallopian tubes (salpingitis) and uterus (endometritis) tend to occur together. If severe, infection can spread to the ovaries (oophoritis) and then the peritoneum (peritonitis). Salpingitis with endometritis and oophoritis, with or without peritonitis, is often called salpingitis even though other structures are involved.

Neisseria gonorrhoeae and *Chlamydia trachomatis* are common causes of PID; they are transmitted sexually. PID usually also involves other aerobic and anaerobic bacteria, including pathogens that cause bacterial vaginosis (see p. 2543).

PID commonly occurs in women < 35. It is rare before menarche, after menopause, and during pregnancy. Risk factors include previous PID and presence of bacterial vaginosis or any sexually transmitted disease. Other risk factors, particularly for gonorrheal or chlamydial PID, include younger age, non-white race, low socioeconomic status, and multiple or new sex partners.

Symptoms and Signs

Lower abdominal pain, fever, cervical discharge, and abnormal uterine bleeding are common, particularly during or after menses.

Cervicitis: The cervix appears red and bleeds easily. Mucopurulent discharge is common; usually, it is yellow-green and can be seen exuding from the endocervical canal.

Acute salpingitis: Lower abdominal pain is usually present and bilateral but may be unilateral, even when both tubes are involved. Pain can also occur in the upper abdomen. Nausea and vomiting are common when pain is severe. Irregular bleeding and fever each occur in up to one third of patients. In the early stages, signs may be mild or absent. Later, cervical motion tenderness, guarding, and rebound tenderness are common. Occasionally, dyspareunia or dysuria occurs. Many women with inflammation that is severe enough to cause scarring have minimal or no symptoms.

PID due to *N. gonorrhoeae* is usually more acute and causes more severe symptoms than that due to *C. trachomatis*, which can be indolent.

Complications: Acute gonococcal or chlamydial salpingitis may lead to the Fitz-Hugh-Curtis syndrome (perihepatitis that causes upper right quadrant pain). Infection may become chronic, characterized by intermittent exacerbations and remissions.

A tubo-ovarian abscess (collection of pus in the adnexa) develops in about 15% of women with salpingitis. It can accompany acute or chronic infection and is more likely if treatment is late or incomplete. Pain, fever, and peritoneal signs are usually present and may be severe. The abscess may rupture, causing progressively severe symptoms and possibly septic shock. Hydrosalpinx (fimbrial obstruction and tubal distention with nonpurulent fluid) is usually asymptomatic but can cause pelvic pressure, chronic pelvic pain, or dyspareunia. Tubo-ovarian abscess, hydrosalpinx, or pyosalpinx (pus confined to one or both fallopian tubes) may produce a palpable adnexal mass and may lead to infertility.

Salpingitis may cause tubal scarring and adhesions, which commonly result in chronic pelvic pain, infertility, and increased risk of ectopic pregnancy. Salpingitis may also result in menstrual irregularities.

Diagnosis

- High index of suspicion
- PCR or culture
- Pregnancy test

PID is suspected when women of reproductive age, particularly those with risk factors, have lower abdominal pain or cervical or unexplained vaginal discharge. PID is considered when irregular vaginal bleeding, dyspareunia, or dysuria is unexplained. PID is more likely if lower abdominal, unilateral or bilateral adnexal, and cervical motion tenderness are present. A palpable adnexal mass suggests tubo-ovarian abscess. Because even minimally symptomatic infection may have severe sequelae, index of suspicion should be high.

If PID is suspected, PCR of cervical specimens for *N. gonorrhoeae* and *C. trachomatis* (which is nearly 100% sensitive and specific) and a pregnancy test are done. If PCR is unavailable, cultures are done. At the point of care, cervical discharge is usually examined to confirm purulence; a Gram stain or saline wet mount is used, but these tests are neither sensitive nor specific. If a patient cannot be adequately examined because of tenderness, ultrasonography is done as soon as possible. WBC count may be elevated but is not helpful diagnostically.

If the pregnancy test is positive, ectopic pregnancy, which can produce similar findings, should be considered. Other common causes of pelvic pain include endometriosis, adnexal torsion, ovarian cyst rupture, and appendicitis. Differentiating features of these disorders are discussed elsewhere (see p. 2486). Fitz-Hugh-Curtis syndrome may mimic acute cholecystitis but can usually be differentiated by evidence of salpingitis during pelvic examination or, if necessary, with ultrasonography.

[
Table 253-3. Regimens for Treatment of Pelvic Inflammatory Disease*]

If an adnexal or pelvic mass is suspected clinically or if patients do not respond to antibiotics within 48 to 72 h, ultrasonography is done as soon as possible to exclude tubo-ovarian abscess, pyosalpinx, and disorders unrelated to PID (eg, ectopic pregnancy, adnexal torsion). If the diagnosis is uncertain after ultrasonography, laparoscopy should be done; purulent peritoneal material obtained by laparoscopy is the diagnostic gold standard.

Treatment

• Antibiotics to cover *N. gonorrhoeae, C. trachomatis*, and sometimes other organisms

Antibiotics are given empirically to cover *N. gonorrhoeae* and *C. trachomatis* and are modified based on laboratory test results. Patients with cervicitis or clinically mild to moderate PID do not require hospitalization. Outpatient treatment regimens (see Table 253-3) usually also aim to eradicate bacterial vaginosis (see p. 2543), which often coexists. Sex partners of patients with *N. gonorrhoeae* or *C. trachomatis* infection should be treated.

General indications for inpatient treatment include the following:

• Severe illness (eg, peritonitis, dehydration)

• Moderate or severe vomiting

• Pregnancy

• Suspicion of a pelvic mass

• Inability to exclude a surgical emergency (eg, appendicitis)

In these cases, IV antibiotics (see Table 253-3) are started as soon as cultures are obtained and are continued until patients have been afebrile for 24 h.

Tubo-ovarian abscess may require more prolonged IV antibiotics and hospitalization. Treatment with ultrasound- or CT-guided percutaneous or transvaginal drainage can be considered if response to antibiotics alone is incomplete. Laparoscopy or laparotomy is sometimes required for drainage. Suspicion of a ruptured tubo-ovarian abscess requires immediate laparotomy. In women of reproductive age,

surgery should aim to preserve the pelvic organs (with the hope of preserving fertility).

Chapter 254. Medical Examination of the Rape Victim

Introduction

Although legal and medical definitions vary, rape is typically defined as oral, anal, or vaginal penetration that involves threats or force against an unwilling person. Such penetration, whether wanted or not, is considered statutory rape if victims are younger than the age of consent. Sexual assault is rape or any other sexual contact that results from coercion, including seduction of a child through offers of affection or bribes; it also includes being touched, grabbed, kissed, or shown genitals. Rape and sexual assault, including childhood sexual assault, are common; the lifetime prevalence estimates for both ranges from 2 to 30% but tends to be about 15 to 20%. However, actual prevalence may be higher because rape and sexual assault tend to be underreported.

Typically, rape is an expression of aggression, anger, or need for power; psychologically, it is more violent than sexual. Nongenital or genital injury occurs in about 50% of rapes of females.

Females are raped and sexually assaulted more often than males. Male rape is often committed by another man, often in prison. Males who are raped are more likely than females to be physically injured, to be unwilling to report the crime, and to have multiple assailants.

Symptoms and Signs

Rape may result in the following:

- Extragenital injury
- Genital injury
- Psychologic symptoms
- Sexually transmitted diseases (STDs—eg, hepatitis, syphilis, gonorrhea, chlamydial infection, trichomoniasis, HIV infection [rarely])
- Pregnancy (uncommonly)

Most physical injuries are relatively minor, but some lacerations of the upper vagina are severe. Additional injuries may result from being struck, pushed, stabbed, or shot.

Psychologic symptoms of rape are potentially the most prominent. In the short term, most patients experience fear, nightmares, sleep problems, anger, embarrassment, shame, guilt, or a combination. Immediately after an assault, patient behavior can range from talkativeness, tenseness, crying, and trembling to shock and disbelief with dispassion, quiescence, and smiling. The latter responses rarely indicate lack of concern; rather, they reflect avoidance reactions, physical exhaustion, or coping mechanisms that require control of emotion. Anger may be displaced onto hospital staff members.

Friends, family members, and officials often react judgmentally, derisively, or in another negative way. Such reactions can impede recovery after an assault.

Eventually, most patients recover; however, long-range effects of rape may include post-traumatic stress disorder (PTSD—see p. 1500), particularly among women. PTSD is an anxiety disorder; symptoms include re-experiencing (eg, flashbacks, intrusive upsetting thoughts or images), avoidance (eg, of trauma-related situations, thoughts, and feelings), and hyperarousal (eg, sleep difficulties, irritability, concentration problems). Symptoms last for > 1 mo and significantly impair social and occupational functioning.

Evaluation

Goals of rape evaluation are

- Medical assessment and treatment of injuries and assessment, treatment, and prevention of pregnancy and STDs

- Collection of forensic evidence

- Psychologic evaluation

- Psychologic support

If patients seek advice before medical evaluation, they are told not to throw out or change clothing, wash, shower, douche, brush their teeth, or use mouthwash; doing so may destroy evidence.

Whenever possible, all people who are raped are referred to a local rape center, often a hospital emergency department; such centers are staffed by specially trained practitioners (eg, sexual assault nurse examiners). Benefits of a rape evaluation are explained, but patients are free to consent to or decline the evaluation. The police are notified if patients consent. Most patients are greatly traumatized, and their care requires sensitivity, empathy, and compassion. Females may feel more comfortable with a female physician; a female staff member should accompany all males evaluating a female. Patients are provided privacy and quiet whenever possible.

A form (sometimes part of a rape kit) is used to record legal evidence and medical findings (for typical elements in the form, see Table 254-1); it should be adapted to local requirements. Because the medical record may be used in court, results should be written legibly and in nontechnical language that can be understood by a jury.

History and examination: Before beginning, the examiner asks the patient's permission. Because recounting the events often frightens or embarrasses the patient, the examiner must be reassuring, empathetic, and nonjudgmental and should not rush the patient. Privacy should be ensured. The examiner elicits specific details, including

- Type of injuries sustained (particularly to the mouth, breasts, vagina, and rectum)

- Any bleeding from or abrasions on the patient or assailant (to help assess the risk of transmission of HIV and hepatitis)

- Description of the attack (eg, which orifices were penetrated, whether ejaculation occurred or a condom was used)

- Assailant's use of aggression, threats, weapons, and violent behavior

- Description of the assailant

Many rape forms include most or all of these questions (see Table 254-1). The patient should be told why questions are being asked (eg, information about contraceptive use helps determine risk of pregnancy after rape; information about previous coitus helps determine validity of sperm testing).

The examination should be explained step by step as it proceeds. Results should be reviewed with the patient. When feasible, photographs of possible injuries are taken. The mouth, breasts, genitals, and rectum are examined closely. Common sites of injury include the labia minora and posterior vagina. Examination using a Wood's lamp may detect semen or foreign debris on the skin. Colposcopy is particularly sensitive for subtle genital injuries. Some colposcopes have cameras attached, making it possible to detect and photograph injuries simultaneously. Whether use of toluidine blue to highlight areas of injury is accepted as evidence varies by jurisdiction.

Testing and evidence collection: Routine testing includes a pregnancy test and serologic tests for syphilis, hepatitis B, and HIV; if done within a few hours of rape, these tests provide information about pregnancy or infections present before the rape but not those that develop after the rape. Vaginal

discharge is examined to check for trichomonal vaginitis and bacterial vaginosis; samples from every penetrated orifice (vaginal, oral, or rectal) are obtained for gonorrheal and chlamydial testing. If the patient has amnesia for events around the time of rape, drug screening for flunitrazepam (the date rape drug) and gamma hydroxybutyrate should be considered. Testing for drugs of abuse and alcohol is controversial because evidence of intoxication may be used to discredit the patient.

Follow-up tests for the following are done:

- At 6 wk: Gonorrhea, chlamydial infection, human papillomavirus infection (initially using a cervical sample from a Papanicolaou test), syphilis, and hepatitis
- At 90 days: HIV infection
- At 6 mo: Syphilis, hepatitis, and HIV infection

However, testing for STDs is controversial because evidence of preexisting STDs may be used to discredit the patient in court.

If the vagina was penetrated and the pregnancy test was negative at the first visit, the test is repeated within the next 2 wk. Patients with lacerations of the upper vagina, especially children, may require laparoscopy to determine depth of the injury.

Evidence that can provide proof of rape is collected; it typically includes clothing; smears of the buccal, vaginal, and rectal mucosa; combed samples of scalp and pubic hair as well as control samples (pulled from the patient); fingernail clippings and scrapings; blood and saliva samples; and, if available, semen (see Table 254-1). Many types of evidence collection kits are available commercially, and some states recommend specific kits. Evidence is often absent or inconclusive after showering, changing clothes, or activities that involve sites of penetration, such as douching. Evidence becomes weaker or disappears as time passes, particularly after > 36 h; however, depending on the jurisdiction, evidence may be collected up to 7 days after rape.

A chain of custody, in which evidence is in the possession of an identified person at all times, must be maintained. Thus, specimens are placed in individual packages, labeled, dated, sealed, and held until delivery to another person (typically, law enforcement or laboratory personnel), who signs a receipt. In some jurisdictions, samples for DNA testing to identify the assailant are collected.

Treatment

- Psychologic support or intervention
- Prophylaxis for STDs and possibly hepatitis B or HIV infection
- Possibly emergency contraception

After the evaluation, the patient is provided with facilities to wash, change clothing, use mouthwash, and urinate or defecate if needed. A local rape crisis team can provide referrals for medical, psychologic, and legal support services.

Most injuries are minor and are treated conservatively. Vaginal lacerations may require surgical repair.

Psychologic support: Sometimes examiners can use commonsense measures (eg, reassurance, general support, nonjudgmental attitude) to relieve strong emotions of guilt or

[**Table 254-1.** Typical Examination for Alleged Rape]

anxiety. Possible psychologic and social effects are explained, and the patient is introduced to a specialist trained in rape crisis intervention. Because the full psychologic effects cannot always be ascertained at the first examination, follow-up visits are scheduled at 2-wk intervals. Severe psychologic effects (eg,

persistent flashbacks, significant sleep disruption, fear leading to significant avoidance) or psychologic effects still present at follow-up visits warrant psychiatric or psychologic referral.

Family members and friends can provide vital support, but they may need help from rape crisis specialists in handling their own negative reactions.

PTSD can be effectively treated psychosocially and pharmacologically (see p. 1501).

Prevention of infections: Routine empiric prophylaxis for STDs consists of ceftriaxone 125 mg IM in a single dose (for gonorrhea), metronidazole 2 g po in a single dose (for trichomoniasis and bacterial vaginosis), and either doxycycline 100 mg po bid for 7 days or azithromycin 1 g po once (for chlamydial infection). Alternatively, azithromycin 2 g po (which covers gonorrhea and chlamydial infection) can be given with metronidazole 2 g po, both as a single dose.

Empiric prophylactic treatment of hepatitis B and HIV after rape is controversial. For hepatitis B, the CDC recommends hepatitis B vaccination unless the patient has been previously vaccinated and has documented immunity. The vaccine is repeated 1 and 6 mo after the first dose. Hepatitis B immune globulin (HBIG) is not given. For HIV, most authorities recommend offering prophylaxis; however, the patient should be told that on average, the risk after rape from an unknown assailant is only about 0.2%. Risk may be higher with any of the following:

• Anal penetration

• Bleeding (assailant or victim)

• Male-male rape

• Rape by multiple assailants (eg, male victims in prisons)

• Rape in areas with a high prevalence of HIV infection

Treatment is best begun < 4 h after penetration and should not be given after > 72 h. Usually, a fixed-dose combination of zidovudine (ZDV) 300 mg and lamivudine (3TC) 150 mg is given bid for 4 wk if exposure appears low risk. If risk is higher, a protease inhibitor is added (see p. 1455).

Prevention of pregnancy: Although pregnancy caused by rape is rare (except in the few days before ovulation), emergency contraception (see p. 2590) should be offered to all women with a negative pregnancy test. Usually, oral contraceptives are used; if used > 72 h after rape, they are much less likely to be effective. An antiemetic may help if nausea develops. An intrauterine device may be effective if used up to 10 days after rape. If pregnancy results from rape, the patient's attitude toward the pregnancy and abortion should be determined, and if appropriate, the option of elective termination should be discussed.

Chapter 255. Breast Disorders

Introduction

Breast symptoms (eg, lumps, nipple discharge, pain) are common, accounting for > 15 million physician visits/yr. Although > 90% of symptoms have benign causes, breast cancer is always a concern. Because breast cancer is common and may mimic benign disorders, the approach to all breast symptoms and findings is to conclusively exclude or confirm cancer.

Evaluation

History: History includes the following:

• Duration of symptoms

• Relation of symptoms to menses and pregnancy

• Presence and type of pain, discharge, and skin changes

• Use of drugs, including hormone therapy

• Personal and family history of breast cancer

• Date and results of last mammogram

Breast examination: Principles of examination are similar for physician and patient. Breasts are inspected for asymmetry in shape, nipple inversion, bulging, and dimpling (see Fig. 255-1A and B for usual positions). Although size differential is common, each breast should have a regular contour. An underlying cancer is sometimes detected by having the patient press both hands against the hips or the palms together in front of the forehead (see Fig. 255-1C and D). In these positions, the pectoral muscles are contracted, and a subtle dimpling of the skin may appear if a growing tumor has entrapped a Cooper's ligament. The nipples are squeezed to check for discharge.

The axillary and supraclavicular lymph nodes are most easily examined with the patient seated or standing (see Fig. 255-1E). Supporting the patient's arm during the axillary examination allows the arm to be fully relaxed so that nodes deep within the axilla can be palpated.

The breast is palpated with the patient seated and again with the patient supine, the ipsilateral arm above the head, and a pillow under the ipsilateral shoulder (see Fig. 255-1F). The latter position is also used for breast self-examination; the patient examines the breast with her contralateral hand. Having the patient roll to one side, so that the breast on the examined side falls medially, may help differentiate breast and chest wall tenderness because the chest wall can be palpated separately from breast tissue.

[**Fig. 255-1.** Breast examination.]

The breast should be palpated with the palmar surfaces of the 2nd, 3rd, and 4th fingers, moving systematically in a small circular pattern from the nipple to the outer edges (see Fig. 255-1G). Precise location and size (measured with a caliper) of any abnormality should be noted on a drawing of the breast, which becomes part of the patient's record. A written description of the consistency of the abnormality and degree to which it can be distinguished from surrounding breast tissue should also be included. Detection of abnormalities during physical examination largely determines whether a biopsy is needed, even if a subsequent mammogram shows no abnormalities.

Testing: Imaging tests are used for screening and for evaluation of breast abnormalities. Annual screening mammography is recommended for women ≥ 50 yr and sometimes for women 40 to 50 yr (see p. 2561). Mammography is more effective in older women because with aging, fibroglandular tissue in breasts tends to be replaced with fatty tissue, which can be more easily distinguished from abnormal tissue. Low-dose x-rays of both breasts are taken in 1 (oblique) or 2 views (oblique and craniocaudal).

Only about 10% of abnormalities detected result from cancer. Accuracy of mammography depends partly on the techniques used and experience of the mammographer; false-negative results may exceed 15%. Some centers use computer analysis of digitized mammography images to help in diagnosis. Such systems are not recommended for stand-alone diagnosis, but they appear to improve sensitivity for detecting small cancers by radiologists.

Mammography is also used diagnostically to evaluate lumps, pain, and nipple discharge. It can determine size and location of a lesion and provide images of surrounding tissues and lymph nodes. Diagnostic mammography requires more views than screening mammography. For biopsy of a lesion seen on a mammogram but not detectable during physical examination, 2 needles or wires can be inserted via radiologic guidance to localize the lesion. The excised specimen should be x-rayed, and the x-ray compared with the prebiopsy mammogram to determine whether the lesion has been removed. Mammography is repeated when the breast is no longer tender, usually 6 to 12 wk after biopsy, to confirm removal of the lesion.

MRI is thought to be more accurate than clinical breast examination or mammography for screening women with a high (eg, > 15%) risk of breast cancer, such as those with a *BRCA* gene mutation. It is not considered appropriate for screening women with average or slightly increased risk. Because MRI can accurately determine tumor size, chest wall involvement, and presence of multiple tumors, it is often used in evaluation after breast cancer is diagnosed. Use of MRI to identify axillary node involvement is under study.

Breast Lumps

A breast lump may be discovered by patients incidentally or during breast self-examination or by the clinician during routine physical examination. Lumps may be painless or painful and are sometimes accompanied by nipple discharge or skin changes.

Etiology

Although cancer is the most feared cause, most breast lumps are nonmalignant. The most common causes include

• Fibrocystic changes

• Fibroadenomas

Fibrocystic changes (previously, fibrocystic disease) is a catchall term that refers to mastalgia, breast cysts, and nondescript lumpiness, which may occur in isolation or together; breasts have a nodular and dense texture and are frequently tender when palpated. Fibrocystic changes cause the most commonly reported breast symptoms and have many causes. Most causes are not associated with increased risk of cancer; they include adenosis, ductal ectasia, simple fibroadenoma, fibrosis, mastitis, mild hyperplasia, cysts, and apocrine or squamous metaplasia. Other causes, particularly if fibrocystic changes require biopsy, may slightly increase risk of breast cancer. Fibrocystic changes are more common among women who had early menarche, who had their first live birth at age > 30, or who are nulliparous.

Fibroadenomas are typically painless lumps that feel like small, slippery marbles. They usually develop in young women, often in adolescents, and may be mistaken for cancer, although they are benign and tend to be more circumscribed and mobile. Simple fibroadenoma does not appear to increase risk of breast cancer; complex fibroadenoma may increase risk slightly.

Breast infections (mastitis) causes pain, erythema, and swelling; an abscess can produce a discrete mass. Infections are extremely rare except during the puerperium (postpartum) or after penetrating trauma. They may occur after breast surgery. Puerperal mastitis, usually due to *Staphylococcus aureus*, can cause massive inflammation and severe breast pain, sometimes with an abscess. If infection occurs under other circumstances, an underlying cancer should be sought promptly.

Galactocele is a round, easily movable milk-filled cyst that usually occurs up to 6 to 10 mo after lactation

stops. Such cysts rarely become infected.

Cancers of various types can manifest as a lump. About 5% of patients have pain.

Evaluation

History: History of present illness should include how long the lump has been present and whether it comes and goes or is painful. Previous occurrence of lumps and the outcome of their evaluation should be queried.

Review of systems should determine whether nipple discharge is present and, if present, whether it is clear, milky, or bloody. Symptoms of advanced cancer (eg, weight loss, malaise, bone pain) should be sought.

Past medical history should include risk factors for breast cancer, including previous diagnosis of breast cancer, history of radiation therapy to the chest area before age 30 (eg, for Hodgkin lymphoma). Family history should note breast cancer in a 1st-degree relative (mother, sister, daughter) and, if family history is positive, whether the relative carried one of the 2 known breast cancer genes, *BRCA1* or *BRCA2*.

Physical examination: Examination focuses on the breast and adjacent tissue. The breast is inspected for skin changes over the area of the lump and the presence of any nipple discharge. Skin changes include erythema, exaggeration of normal skin markings, and trace edema sometimes termed peau d'orange (orange peel). The lump is palpated for size, tenderness, consistency (ie, hard or soft, smooth or irregular), and mobility (whether it feels freely mobile or fixed to the skin or chest wall). The axillary, supraclavicular, and infraclavicular areas are palpated for masses and adenopathy.

Red flags: Certain findings are of particular concern:

• Lump fixed to the skin or chest wall

• Stony hard, irregular lump

• Skin dimpling

• Matted or fixed axillary lymph nodes

• Bloody nipple discharge

Interpretation of findings: Painful, tender, rubbery lumps in younger women with a history of similar findings suggest fibrocystic changes.

Red flag findings suggest cancer. However, the characteristics of benign and malignant lesions, including presence or absence of risk factors, overlap considerably. For this reason and because failure to recognize cancer has serious consequences, most patients require testing to more conclusively exclude breast cancer.

Testing: Initially, physicians try to differentiate solid from cystic lumps because cysts are rarely cancerous. Typically, ultrasonography is done. Lesions that appear cystic are sometimes aspirated, and solid lumps are evaluated with mammography followed by imaging-guided biopsy (see p. 2560). Some physicians evaluate all lumps with needle aspiration; if no fluid is obtained or if aspiration does not eliminate the lump, mammography followed by imaging-guided biopsy is done.

Fluid aspirated from a cyst is sent for cytology only if it is bloody, if minimal fluid is obtained, or if a mass remains after aspiration. Patients are reexamined in 4 to 8 wk. If the cyst is no longer palpable, it is considered benign. If the cyst has recurred, it is reaspirated, and any fluid is sent for cytology regardless of appearance. A 3rd recurrence or persistence of the mass after initial aspiration (even if cytology was negative) requires biopsy.

Treatment

Treatment is directed at the cause. Fibroadenomas can usually be excised using a local anesthetic, but they frequently recur. After patients have had several fibroadenomas established as benign, they may decide against having subsequent ones excised.

Acetaminophen, NSAIDs, and athletic bras (to reduce trauma) can be used to relieve symptoms of fibrocystic changes. Vitamin E is sometimes used but has not been proved to be effective.

Key Points

• Most breast lumps are not cancer.

• Clinical features of benign and malignant disease overlap so much that testing should usually be done.

Nipple Discharge

Nipple discharge is a common complaint in women who are not pregnant or breastfeeding, especially during the reproductive years. Nipple discharge is not necessarily abnormal, even among postmenopausal women, although it is always abnormal in men.

Nipple discharge can be serous (yellow), mucinous (clear and watery), milky, sanguineous (bloody), purulent, multicolored and sticky, or serosanguineous (pink). It may occur spontaneously or only in response to breast manipulation.

Pathophysiology

Nipple discharge may be breast milk or an exudate produced by a number of conditions.

Breast milk production in nonpregnant and nonlactating women (galactorrhea) typically involves an elevated prolactin level, which stimulates glandular tissue of the breast. However, only some patients with elevated prolactin levels develop galactorrhea.

Etiology

Most frequently, nipple discharge has a benign cause (see Table 255-1). Cancer (usually intraductal carcinoma or invasive ductal carcinoma) causes < 10% of cases. The rest result from benign ductal disorders (eg, intraductal papilloma, mammary duct ectasia, fibrocystic changes), endocrine disorders, or breast abscesses or infections. Of these causes, intraductal papilloma is probably the most common; it is also the most common cause of a bloody nipple discharge without a breast mass.

Endocrine causes involve elevation of prolactin levels, which has numerous causes.

Evaluation

History: History of present illness should include whether the current discharge is unilateral or bilateral, what its color is, how long it has lasted, whether it is spontaneous or occurs only with nipple stimulation, and whether a lump or pain is present.

Review of symptoms should seek symptoms suggesting possible causes, including fever (mastitis or breast abscess); cold intolerance, constipation, or weight gain (hypothyroidism); amenorrhea, infertility, headache, or visual disturbances (pituitary tumor); and ascites or jaundice (liver disorders).

Past medical history should include possible causes of hyperprolactinemia, including chronic renal failure, pregnancy, liver disorders,

[Table 255-1. Some Causes of Nipple Discharge]

and thyroid disorders, as well as history of infertility, hypertension, depression, breastfeeding, menstrual patterns, and cancer. Clinicians should ask specifically about drugs that can cause prolactin release such as oral contraceptives, antihypertensive drugs (eg, methyldopa, reserpine, verapamil), H_2-antagonists (eg, cimetidine, ranitidine), opioids, and dopamine D_2 antagonists (eg, many psychoactive drugs, including phenothiazines and tricyclic anti-depressants).

Physical examination: Physical examination focuses on the breasts. The breasts are inspected for symmetry, dimpling of the skin, erythema, swelling, color changes in the nipple and skin, and crusting, ulceration, or retraction of the nipple. The breasts are palpated for masses and evidence of lymphadenopathy in the axillary or supraclavicular region. If there is no spontaneous discharge, the area around the nipples is systematically palpated to try to stimulate a discharge. A bright light and magnifying lens can help assess whether the nipple discharge is uniductal or multiductal.

Red flags: Certain findings are of particular concern:

• Spontaneous discharge

• Age ≥ 40

• Unilateral discharge

• Bloody or guaiac-positive discharge

• Palpable mass

• Male sex

Interpretation of findings: Important differentiating points are whether a mass is present, whether the discharge involves one or multiple ducts (either one or more ducts in both breasts or more than one duct in one breast), and whether the discharge is bloody (including guaiac-positive).

If a mass is present, cancer must be considered. Because cancer rarely involves both breasts or multiple ducts at presentation, a bilateral, guaiac-negative discharge suggests an endocrine cause, as does unilateral, multiductal discharge. However, if the discharge is guaiac-positive or involves only one duct, cancer must be considered.

For other suggestive findings, see Table 255-1.

Testing: If endocrine causes are suspected, the following are done:

• Prolactin level

• Thyroid-stimulating hormone (TSH) level

If discharge is guaiac-positive, the following is done:

• Cytology

If there is a palpable mass, evaluation as for breast lump, usually beginning with

• Ultrasonography

Lesions that appear cystic are sometimes aspirated, and solid lumps or any that remain after aspiration are evaluated with mammography followed by imaging-guided biopsy.

If there is no mass but cancer is otherwise suspected or if other tests are indeterminate

• Mammography

Abnormal results are evaluated by imaging-guided biopsy. If no lump is palpable and mammogram is normal, cancer is highly unlikely.

Treatment

Treatment is based on the cause.

If the cause is benign and the discharge is persistent and annoying, a nipple-flap duct resection, usually done as an outpatient procedure using a local anesthetic, can eliminate the discharge and relieve the patient's anxiety.

Key Points

• Nipple discharge is most often benign.

• Bilateral, multiductal, guaiac-negative discharge is usually benign and has an endocrine etiology.

• Unilateral, uniductal, bloody (or guaiac-positive) discharge could be cancer, especially in patients ≥ 40.

• Presence of a breast mass, a bloody (or guaiac-positive) discharge, or history of an abnormal mammogram or abnormal ultrasound requires follow-up with a surgical clinician who is experienced with breast disorders.

Mastalgia

Mastalgia (breast pain) is common and can be localized or diffuse and unilateral or bilateral.

Etiology

Localized breast pain is usually caused by a focal disorder that causes a lump (see p. 2554), such as a breast cyst, or an infection (eg, mastitis, abscess). Most breast cancers do not cause pain.

Diffuse, bilateral pain may be caused by fibrocystic changes or, uncommonly, diffuse, bilateral mastitis. However, diffuse bilateral pain is very common in women without breast abnormalities. The most common causes are

• Hormonal changes that cause breast tissue proliferation (eg, during the luteal phase or early pregnancy, in women taking estrogens or progestins)

• Large, pendulous breasts that stretch Cooper's ligaments

Evaluation

History: History of present illness should address the temporal pattern of pain and its nature (focal or diffuse, unilateral or bilateral). The relation between chronic or recurrent pain and menstrual cycle phase should be ascertained.

Review of systems should address other symptoms suggesting pregnancy (eg, abdominal enlargement, amenorrhea, morning nausea) or fibrocystic changes (eg, lumpiness).

Past medical history should cover disorders that could cause diffuse pain (eg, fibrocystic changes) and use of estrogens and progestins.

Physical examination: Examination focuses on the breast and adjacent tissue, looking for abnormalities such as skin changes (as for breast lumps—see p. 2554) and signs of infection, such as redness,

warmth, and tenderness.

Red flags: The following are of particular concern:

• Signs of infection

Interpretation of findings: Absence of abnormal findings suggests that pain is due to hormonal changes or large, pendulous breasts. Abnormal findings may suggest other specific problems.

Testing: Pregnancy testing should be done if pain is unexplained and has lasted less than several months, particularly if other symptoms or signs are consistent with pregnancy. Other testing is indicated infrequently—only if physical findings suggest another problem that requires testing.

Treatment

For menstrual-related mastalgia, acetaminophen or an NSAID is usually effective. If pain is severe, a brief course of danazol or tamoxifen may be given. These drugs inhibit estrogen and progesterone. If estrogen or a progestin is being taken, stopping may be necessary. For pregnancy-related breast pain, wearing a firm, supportive brassiere, taking acetaminophen, or both, can help.

Key Points

• Diffuse, bilateral breast pain is usually caused by hormonal changes or large, pendulous breasts and causes no abnormal physical findings.

Breast Cancer

Breast cancer most often involves glandular breast cells in the ducts or lobules. Most patients present with an asymptomatic lump discovered during examination or screening mammography. Diagnosis is confirmed by biopsy. Treatment usually includes surgical excision, often with radiation therapy, with or without adjuvant chemotherapy, hormonal therapy, or both.

About 213,000 new cases were identified in 2006. It is the 2nd leading cause of cancer death in women (after lung cancer), with about 41,000 deaths in 2006. Male breast cancer accounts for < 1% of total cases; manifestations, diagnosis, and management are the same, although men tend to present later.

Risk Factors

In the US, cumulative risk of developing breast cancer is 12% (1 in 8) by age 95, and risk of dying of it is about 4%. Much of the risk is incurred after age 60 (see Table 255-2). These statistics can be misleading because most people die before age 95, and cumulative risk of developing the cancer in any 20-yr period is considerably lower.

[**Table 255-2.** Breast Cancer Risks]

Factors that may affect breast cancer risk include the following:

• **Family history:** Having a 1st-degree relative (mother, sister, daughter) with breast cancer doubles or triples risk of developing the cancer, but breast cancer in more distant relatives increases risk only slightly. When ≥ 2 1st-degree relatives have breast cancer, risk may be 5 to 6 times higher.

• **Breast cancer gene:** About 5% of women with breast cancer carry a mutation in one of the 2 known breast cancer genes, *BRCA1* or *BRCA2*. If relatives of such a woman also carry the gene, they have a 50 to 85% lifetime risk of developing breast cancer. Women with *BRCA1* mutations also have a 20 to 40% lifetime risk of developing ovarian cancer; risk among women with *BRCA2* mutations is increased less. Women without a family history of breast cancer in at least 2 1st-degree relatives are unlikely to carry this gene and thus do not require screening for *BRCA1* and *BRCA2* mutations. Men who carry a *BRCA2* mutation also have an increased risk of developing breast cancer. The genes are more

common among Ashkenazi Jews. Women with *BRCA1* or *BRCA2* mutations may require closer surveillance or preventive measures, such as taking tamoxifen or raloxifene or undergoing double mastectomy.

- **Personal history:** Having had in situ or invasive breast cancer increases risk. Risk of developing cancer in the contralateral breast after mastectomy is about 0.5 to 1%/yr of follow-up.

- **Gynecologic history:** Early menarche, late menopause, or late first pregnancy increases risk. Women who have a first pregnancy after age 30 are at higher risk than those who are nulliparous.

- **Breast changes:** History of fibrocystic changes that require biopsy for diagnosis increases risk slightly. Women with multiple breast lumps but no histologic confirmation of a high-risk pattern should not be considered at high risk. Benign lesions that may slightly increase risk of developing invasive breast cancer include complex fibroadenoma, moderate or florid hyperplasia (with or without atypia), sclerosing adenosis, and papilloma. Risk is about 4 or 5 times higher than average in patients with atypical ductal or lobular hyperplasia and about 10 times higher if they also have a family history of invasive breast cancer in a 1st-degree relative. Increased breast density seen on screening mammography is associated with an increased risk of breast cancer.

- **Use of oral contraceptives:** Oral contraceptive use increases risk very slightly (by about 5 more cases per 100,000 women). Risk increases primarily during the years of contraceptive use and tapers off during the 10 yr after stopping. Risk is highest in women who began to use contraceptives before age 20 (although absolute risk is still very low).

- **Hormonal therapy:** Postmenopausal hormone (estrogen plus a progestin) therapy appears to increase risk modestly after only 3 yr of use (see also p. 2519). After 5 yr of use, the increased risk is about 7 or 8 more cases per 10,000 women for each year of use (about a 24% increase in relative risk). Use of estrogen alone does not appear to increase risk of breast cancer. Selective estrogen-receptor modulators (eg, raloxifene) reduce the risk of developing breast cancer.

- **Radiation therapy:** Exposure to radiation therapy before age 30 increases risk. Mantle-field radiation therapy for Hodgkin lymphoma about quadruples risk of breast cancer over the next 20 to 30 yr.

- **Diet:** Diet may contribute to development or growth of breast cancers, but conclusive evidence about the effect of a particular diet (eg, one high in fats) is lacking. Obese postmenopausal women are at increased risk, but there is no evidence that dietary modification reduces risk. For obese women who are menstruating later than normal, risk may be decreased.

Pathology

Most breast cancers are epithelial tumors that develop from cells lining ducts or lobules; less common are nonepithelial cancers of the supporting stroma (eg, angiosarcoma, primary stromal sarcomas, phyllodes tumor). Cancers are divided into carcinoma in situ and invasive cancer.

Carcinoma in situ is proliferation of cancer cells within ducts or lobules and without invasion of stromal tissue. Usually, ductal carcinoma in situ (DCIS) is detected only by mammography and is localized to one area; it may become invasive. Lobular carcinoma in situ (LCIS) is a nonpalpable lesion usually discovered via biopsy; it is rarely visualized with mammography. LCIS is often multifocal and bilateral. It is not malignant, but its presence indicates increased risk of subsequent invasive carcinoma in either breast; about 1 to 2% of patients with LCIS develop cancer annually.

Invasive carcinoma is primarily adenocarcinoma. About 80% is the infiltrating ductal type; most of the remaining cases are infiltrating lobular. Rare types include medullary, mucinous, and tubular carcinomas.

Paget's disease of the nipple (not to be confused with the metabolic bone disease also called Paget's disease) is a form of ductal carcinoma in situ that extends into the overlying skin of the nipple and areola, manifesting with an inflammatory skin lesion (see p. 754). Characteristic malignant cells called Paget cells are present in the epidermis. The cancer may become invasive.

Pathophysiology

Breast cancer invades locally and spreads initially through the regional lymph nodes, bloodstream, or both. Metastatic breast cancer may affect almost any organ in the body—most commonly, lungs, liver, bone, brain, and skin.

Most skin metastases occur near the site of breast surgery; scalp metastases are also common. Metastatic breast cancer frequently appears years or decades after initial diagnosis and treatment.

Estrogen and progesterone receptors, present in some breast cancers, are nuclear hormone receptors that promote DNA replication and cell division when the appropriate hormones bind to them. Thus, drugs that block these receptors may be useful in treating tumors with the receptors. About two thirds of postmenopausal patients have an estrogen-receptor positive (ER+) tumor. Incidence of ER+ tumors is lower among premenopausal patients.

Another cellular receptor is human epidermal growth factor receptor 2 (HER2; also, HER2/neu or ErbB2); its presence correlates with a poorer prognosis at any given stage of cancer.

Symptoms and Signs

Most breast cancers are discovered as a lump by the patient or during routine physical examination or mammography. Less commonly, the presenting symptom is breast pain or enlargement or a nondescript thickening in the breast. Paget's disease of the nipple manifests as skin changes, including erythema, crusting, scaling, and discharge; these changes usually appear so benign that the patient ignores them, delaying diagnosis for a year or more. About 50% of patients with Paget's disease of the nipple have a palpable mass at presentation. A few patients with breast cancer present with signs of metastatic disease (eg, pathologic fracture, pulmonary dysfunction).

A common finding during physical examination is a dominant mass—a lump distinctly different from the surrounding breast tissue. Diffuse fibrotic changes in a quadrant of the breast, usually the upper outer quadrant, are more characteristic of benign disorders; a slightly firmer thickening in one breast but not the other may be a sign of cancer. More advanced breast cancers are characterized by fixation of the lump to the chest wall or to overlying skin, by satellite nodules or ulcers in the skin, or by exaggeration of the usual skin markings resulting from lymphedema (so-called peau d'orange). Matted or fixed axillary lymph nodes suggest tumor spread, as does supraclavicular or infraclavicular lymphadenopathy. Inflammatory breast cancer is characterized by diffuse inflammation and enlargement of the breast, often without a lump, and has a particularly aggressive course.

Diagnosis

• Screening by mammography, breast examination, or sometimes MRI

• Biopsy, including analysis for estrogen and progesterone receptors and for HER2 protein

Testing is required to differentiate benign lesions from cancer. Because early detection and treatment of breast cancer improves prognosis, this differentiation must be conclusive before evaluation is terminated.

If advanced cancer is suspected based on physical examination, biopsy should be done first; otherwise, the approach is as for breast lumps (see p. 2554). A prebiopsy bilateral mammogram may help delineate other areas that should be biopsied and provides a baseline for future reference. However, mammogram results should not alter the decision to do a biopsy if that decision is based on physical findings. Biopsy can be needle or incisional biopsy or, if the tumor is small, excisional biopsy. Any skin taken with the biopsy specimen should be examined because it may show cancer cells in dermal lymphatic vessels. Routinely, stereotactic biopsy (needle biopsy during mammography) or ultrasound-guided biopsy is being used to improve accuracy.

Evaluation after cancer diagnosis: Part of a positive biopsy specimen should be analyzed for estrogen

and progesterone receptors and for HER2 protein.

WBCs should be tested for *BRCA1* and *BRCA2* genes when

• Family history includes multiple cases of early-onset breast cancer.

• Ovarian cancer develops in patients with a family history of breast or ovarian cancer.

• Breast and ovarian cancers occur in the same patient.

• Patients have an Ashkenazi Jewish heritage.

• Family history includes a single case of male breast cancer.

Chest x-ray, CBC, and liver function tests and serum Ca should be done to check for metastatic disease. Generally, measuring serum carcinoembryonic antigen (CEA), cancer antigen (CA) 15-3, or CA 27-29 is not recommended because results have no effect on treatment or outcome.

Bone scanning should be done if patients have any of the following:

• Tumors > 2 cm

• Bone pain

• Lymph node involvement

• Elevated serum alkaline phosphatase or Ca levels

Abdominal CT is done if patients have any of the following:

• Abnormal liver function results

• Hepatomegaly

• Locally advanced cancer with or without axillary lymph node involvement

MRI is often used to evaluate breast cancer after it is diagnosed because MRI can accurately determine tumor size, chest wall involvement, and presence of multiple tumors. Use of MRI to identify axillary node involvement is under study.

Grading is based on histologic examination of the tissue taken during biopsy.

Staging follows the TNM (tumor, node, metastasis) classification. Staging is refined during surgery, when regional lymph nodes can be evaluated.

Screening: Screening includes mammography, clinical breast examination (CBE) by health care practitioners, MRI (for high-risk patients), and monthly breast self-examination (BSE).

Mammography, done annually, is recommended for women ≥ 50; it reduces mortality rate by 25 to 35% in this age group. Mammography is more accurate in older women, partly because with aging, fibroglandular tissue in breasts tends to be replaced with fatty tissue, which can be more easily distinguished from abnormal tissue. However, there is considerable disagreement about screening for women 40 to 50 yr; recommendations include annual mammography (American Cancer Society), mammography every 1 to 2 yr (National Cancer Institute), and no periodic mammography (American College of Physicians). Concerns about screening too soon or too often include increased radiation exposure and overdiagnosis of tumors (eg, DCIS) that may not develop into invasive cancer during the patient's lifetime. Young age at the time of radiation exposure increases the risk of cancer.

Only about 10% of abnormalities detected on screening mammography result from cancer, and false-negative results may exceed 15%. Accuracy depends partly on the techniques used and experience of the mammographer. Some centers use computer analysis of digitized mammography images (full-field digital mammography) to help in diagnosis. Such systems may be slightly more sensitive for invasive cancers in women < 50 when results are interpreted by radiologists, but probably not when interpreted primarily via computer detection.

CBE is usually part of routine annual care for women > 35; it can detect 7 to 10% of cancers that cannot be seen on a mammogram. In the US, CBE augments rather than replaces screening mammography. However, in some countries where mammography is considered too expensive, CBE is the sole screen; reports on its effectiveness in this role vary.

MRI is thought to be better than CBE or mammography for screening women with a high (eg, > 15%) risk of breast cancer, such as those with a *BRCA* gene mutation. MRI has higher sensitivity but may be less specific. Because specificity is lower, MRI is not considered appropriate for screening women with average or slightly increased risk.

BSE alone has not been shown to reduce mortality rate, but evidence of its usefulness is mixed, and it is widely practiced. Because a negative BSE may tempt some women to forego mammography or CBE, the need for these procedures should be reinforced when BSE is taught. Patients should be instructed to do BSE on the same day each month. For menstruating women, 2 or 3 days after menses ends is recommended because breasts are less likely to be tender and swollen.

Prognosis

Long-term prognosis depends on tumor stage (see Table 255-3). Nodal status (including number and location of nodes) correlates with disease-free and overall survival better than any other prognostic factor.

Poor prognosis is associated with the following other factors:

- **Young age:** Prognosis appears worse for patients diagnosed with breast cancer during their 20s and 30s than for patients diagnosed during middle age.

- **Larger primary tumor:** Larger tumors are more likely to be node-positive, but they also confer a worse prognosis independent of nodal status.

- **High-grade tumor:** Patients with poorly differentiated tumors have a worse prognosis.

- **Absence of estrogen and progesterone receptors:** Patients with ER+ tumors have a somewhat better prognosis and are more likely to benefit from hormone therapy. Patients with progesterone receptors on a tumor may also have a better prognosis. Patients with both estrogen and progesterone receptors on a tumor may have a better prognosis than those who have only one of these receptors, but this benefit is not clear.

- **Presence of HER2 protein:** When the *HER2* gene (*HER2/neu* [*erb-b2*]) is amplified, HER2 is overexpressed, increasing cell growth and reproduction and often resulting in more aggressive tumor cells. Overexpression of HER2 is an independent risk factor for a poor prognosis; it may also be associated with high histologic grade, ER-tumors, greater proliferation, and larger tumor size, which are all poor prognostic factors.

- **Presence of *BRCA* genes:** For any given stage, patients with the *BRCA1* gene appear to have a worse prognosis than those with sporadic tumors, perhaps because they have a higher proportion of high-grade, hormone receptor-negative cancers. Patients

[**Table 255-3.** Staging and Survival Rates in Breast Cancer]

with the *BRCA2* gene probably have the same prognosis as those without the genes if the tumors have

similar characteristics. With either gene, risk of a 2nd cancer in remaining breast tissue is increased (to perhaps as high as 40%)

Treatment

• Surgery

• Usually radiation therapy

• Sometimes hormone therapy, chemotherapy, or both

For most patients, primary treatment is surgery, often with radiation therapy. Chemotherapy, hormone therapy, or both may also be used, depending on tumor and patient characteristics (see Table 255-4).

Surgery: For patients with invasive cancer, survival rates do not differ significantly whether modified radical mastectomy (simple mastectomy plus lymph node dissection) or breast-conserving surgery plus radiation therapy is used. Breast-conserving surgery includes lumpectomy, wide excision, and quadrantectomy (see Fig. 255-2). Thus, patient preference can guide choice of treatment within limits. The main advantage of breast-conserving surgery plus radiation therapy is cosmetic. In 15% of patients thus treated, cosmetic results are excellent. However, the need for total removal of the tumor with a tumor-free margin overrides cosmetic considerations. With both types of surgery, lymph node dissection or node sampling should be done. Routine use of extensive procedures is not justified because the main value of lymph node removal is diagnostic, not therapeutic. However, results of frozen section analysis may change the extent of surgery needed. Some surgeons get prior agreement for more invasive surgery in case nodes are positive; others wake the patient and do a 2nd procedure if needed.

Some physicians use preoperative chemotherapy to shrink the tumor before removing

[**Table 255-4.** Treatment by Cancer Type]

[**Fig. 255-2.** Surgery for breast cancer.]

it and applying radiation therapy; thus, some patients who might otherwise have required mastectomy can have breast-conserving surgery. Early data suggest that this approach does not affect survival.

Radiation therapy after mastectomy significantly reduces incidence of local recurrence on the chest wall and in regional lymph nodes and may improve overall survival in patients with primary tumors > 5 cm or with involvement of ≥ 4 axillary nodes. Adverse effects of radiation therapy (eg, fatigue, skin changes) are usually transient and mild. Late adverse effects (eg, lymphedema, brachial plexopathy, radiation pneumonitis, rib damage, secondary cancers, cardiac toxicity) are less common.

After axillary dissection (or radiation therapy), lymphatic drainage of the ipsilateral arm can be impaired, sometimes resulting in substantial swelling due to lymphedema; magnitude of the effect is roughly proportional to the number of nodes removed.

If lymphedema develops, venipuncture, BP measurement, and IV infusions are usually avoided on the affected side. A specially trained therapist must treat lymphedema. Special massage techniques once or twice daily may help drain fluid from congested areas toward functioning lymph basins; low-stretch bandaging is applied immediately after manual drainage, and patients should exercise daily as prescribed. After the lymphedema resolves, typically in 1 to 4 wk, patients continue daily exercise and overnight bandaging of the affected limb indefinitely.

Alternative node sampling methods include selective fine-needle aspiration of abnormalities identified at the time of breast biopsy (eg, by ultrasonography) and the commonly done sentinel node biopsy. Both result in less lymphedema than lymph node dissection. With sentinel node biopsy, sensitivity for axillary node involvement is ≥ 95%. However, the effect on mortality rate has not been established. For this

biopsy, blue dye or radioactive colloid is injected around the breast, and a scanner is used to locate the first nodes the substance drains into (ie, sentinel nodes). If the sentinel node is cancerous, lymph node dissection is necessary.

Reconstructive procedures include

• Submuscular or subcutaneous (less common) placement of a silicone or saline implant

• Use of a tissue expander with delayed placement of the implant

• Muscle flap transfer using the latissimus dorsi or the lower rectus abdominis

• Creation of a free flap by anastomosing the gluteus maximus to the internal mammary vessels

Free flap transfer is being increasingly used for DCIS.

Adjuvant systemic therapy: Patients with LCIS are often treated with daily oral tamoxifen. For postmenopausal women, raloxifene is an alternative.

For patients with invasive cancer, chemotherapy or hormone therapy is usually begun soon after surgery and continued for months or years; these therapies delay or prevent recurrence in almost all patients and prolong survival in some. However, some experts believe that these therapies are not necessary for tumors < 1 cm with no lymph node involvement (particularly in postmenopausal patients) because the prognosis is already excellent. If tumors are > 5 cm, adjuvant systemic therapy may be started before surgery.

Relative reduction in risk of recurrence and death with chemotherapy or hormone therapy is the same regardless of the clinical-pathologic stage of the cancer. Thus, absolute benefit is greater for patients with a greater risk of recurrence or death (ie, a 20% relative risk reduction reduces a 10% recurrence rate to 8% but a 50% rate to 40%). Adjuvant chemotherapy reduces annual odds of death (relative risk) on average by 25 to 35% for premenopausal patients; for postmenopausal patients, the reduction is about half of that (9 to 19%), and the absolute benefit in 10-yr survival is much smaller.

Postmenopausal patients with ER-tumors benefit the most from adjuvant chemotherapy (see Table 255-5). However, predictive genomic testing of the primary breast cancer is being used increasingly to determine whether combination chemotherapy or hormone therapy alone is indicated.

Combination chemotherapy regimens (eg, cyclophosphamide, methotrexate, plus 5-fluorouracil; doxorubicin plus cyclophosphamide; docetaxel plus cyclophosphamide) are more effective than a single drug. Regimens given for 4 to 6 mo are preferred; they are as effective as regimens given for 6 to 24 mo. Acute adverse effects depend on the regimen but usually include nausea, vomiting, mucositis, fatigue, alopecia, myelosuppression, and thrombocytopenia. Growth factors that stimulate bone marrow (eg, filgrastim, pegfilgrastim) are commonly used to reduce risk of fever and infection due to chemotherapy. Long-term adverse effects are infrequent with most regimens; death due to infection or bleeding is rare (< 0.2%).

High-dose chemotherapy plus bone marrow or stem cell transplantation offers no therapeutic advantage over standard therapy and should not be used.

If tumors overexpress HER2 (HER2+), adding the humanized monoclonal antibody trastuzumab to chemotherapy provides substantial benefit. Trastuzumab is usually continued for a year, although the optimal duration of therapy is unknown. A serious potential side effect is decreased cardiac ejection fraction.

With hormone therapy (eg, tamoxifen, raloxifene, aromatase inhibitors), benefit is greatest when tumors have estrogen and progesterone receptors, nearly as great when they have only estrogen receptors, minimal when they have only progesterone receptors, and absent when they have neither receptor. In patients with ER+ tumors, particularly low-risk tumors, hormone therapy may be used instead of

chemotherapy.

- **Tamoxifen:** This drug competitively binds with estrogen receptors. Adjuvant tamoxifen for 5 yr reduces annual odds of death by about 25% in premenopausal and postmenopausal women regardless of axillary

[Table 255-5. Preferred Breast Cancer Adjuvant Systemic Therapy*]

lymph node involvement; treatment for 2 yr is not as effective, but treatment for > 5 yr has no advantage and may increase the likelihood that any recurrent cancer is tamoxifen-resistant. Tamoxifen can induce or exacerbate menopausal symptoms but reduces incidence of contralateral breast cancer and lowers serum cholesterol. Tamoxifen increases bone density in postmenopausal women and may reduce risk of fractures and ischemic heart disease. However, it significantly increases risk of developing endometrial cancer; reported incidence is 1% in postmenopausal women after 5 yr of use. Thus, if such women have spotting or bleeding, they must be evaluated for endometrial cancer (see p. 2571). Nonetheless, the improved survival for women with breast cancer far outweighs increased risk of death due to endometrial cancer. Risk of thromboembolism is also increased. Raloxifene, although indicated for prevention, is not indicated for treatment.

- **Aromatase inhibitors:** These drugs (anastrozole, exemestane, letrozole) block peripheral production of estrogen in postmenopausal women. More effective than tamoxifen, these drugs are becoming the preferred treatment for early-stage hormone receptor-positive cancer in postmenopausal patients. Letrozole may be used in postmenopausal women who have completed 5 yr of daily tamoxifen. Optimal duration of aromatase inhibitor therapy is uncertain.

Metastatic disease: Any indication of metastases should prompt immediate evaluation. Treatment of metastases increases median survival by 6 mo or longer. These treatments (eg, chemotherapy), although relatively toxic, may palliate symptoms and improve quality of life. Thus, the decision to be treated may be highly personal.

Choice of therapy depends on the following:

- Hormone-receptor status of the tumor

- Length of the disease-free interval (from remission to manifestation of metastases)

- Number of metastatic sites and organs affected

- Patient's menopausal status

Systemic hormone therapy or chemotherapy is usually used to treat symptomatic metastatic disease. Initially, patients with multiple metastatic sites outside the CNS should be given systemic therapy. If metastases are asymptomatic, there is no proof that treatment substantially increases survival, and it may reduce quality of life.

Hormone therapy is preferred over chemotherapy for patients with ER+ tumors, a disease-free interval of > 2 yr, or disease that is not immediately life threatening. In premenopausal women, tamoxifen is often used first. Reasonable alternatives include ovarian ablation by surgery, radiation therapy, and use of a luteinizing-releasing hormone agonist (eg, buserelin, goserelin, leuprolide). Some experts combine ovarian ablation with tamoxifen or an aromatase inhibitor. In postmenopausal women, aromatase inhibitors are being increasingly used as primary hormone therapy. If the cancer initially responds to hormone therapy but progresses months or years later, additional forms of hormone therapy (eg, progestins, the antiestrogen fulvestrant) may be used sequentially until no further response occurs.

The most effective chemotherapy drugs are capecitabine, doxorubicin (including its liposomal formulation), gemcitabine, the taxanes paclitaxel and docetaxel, and vinorelbine. Response rate to a combination of drugs is higher than that to a single drug, but survival is not improved and toxicity is increased. Thus, some oncologists use single drugs sequentially.

For tumors that overexpress HER2, trastuzumab is effective in treating and controlling visceral metastatic sites. It is used alone or with hormone therapy or chemotherapy. Lapatinib is being used increasingly. Its role is evolving.

Radiation therapy alone may be used to treat isolated, symptomatic bone lesions or local skin recurrences not amenable to surgical resection. Radiation therapy is the most effective treatment for brain metastases, occasionally providing long-term control.

IV bisphosphonates (eg, pamidronate, zoledronate) decrease bone pain and bone loss and prevent or delay skeletal complications due to bone metastases. About 10% of patients with bone metastases eventually develop hypercalcemia, which can also be treated with IV bisphosphonates.

Prevention

Chemoprevention with tamoxifen or raloxifene is indicated for women with the following:

• Age > 60

• Age > 35 and previous LCIS

• Presence of *BRCA1* or *BRCA2* mutations

• 5-yr risk of developing breast cancer > 1.66% based on the multivariable Gail model, which includes the women's current age, age at menarche, age at first live childbirth, number of 1st-degree relatives with breast cancer, and results of prior breast biopsies

A computer program to calculate breast cancer risk by the Gail model is available from the NCI at 1-800-4CANCER and online at http://www.cancer.gov/bcrisktool/. Recommendations of the U. S. Preventive Services Task Force (USPSTF), Chemoprevention of breast cancer, are available at http://www.ahrq.gov/clinic/uspstf/uspsbrpv.htm.

Patients should be informed of risks before beginning chemoprevention. Risks of tamoxifen include uterine cancer, thromboembolic complications, cataracts, and possibly stroke. Risks are higher for older women. Raloxifene appears to be about as effective as tamoxifen in postmenopausal women and to have a lower risk of thromboembolic complications and cataracts. Raloxifene, like tamoxifen, may also increase bone density. Raloxifene should be considered as an alternative to tamoxifen for chemoprevention in postmenopausal women.

Phyllodes Tumor

Phyllodes tumor (cystosarcoma phyllodes) is a nonepithelial breast tumor that may be benign or malignant.

Tumors are frequently large (4 to 5 cm) at diagnosis. About half are malignant, accounting for < 1% of breast cancers. Between 20% and 35% of these tumors recur locally, and distant metastases occur in 10 to 20% of patients.

Usual treatment is wide excision, but a mastectomy may be more appropriate if the mass is large or histology suggests cancer. Prognosis is good unless metastases are present.

Chapter 256. Gynecologic Tumors

Introduction

Gynecologic cancers often involve the uterus, ovaries, cervix, vulva, vagina, fallopian tubes, or, usually secondarily, the peritoneum. The most common gynecologic cancer in the US is endometrial cancer, followed by ovarian cancer. Cervical cancer is not very common in developed countries because Papanicolaou (Pap) test screening is widely available and effective. Gestational trophoblastic disease is a gynecologic tumor that may behave aggressively whether malignant or not.

Many gynecologic cancers manifest as pelvic masses (for diagnostic approach to pelvic masses, see p. 2485).

Ovarian Cancer

Ovarian cancer is often fatal because it is usually advanced when diagnosed. Symptoms are usually absent in early stages and nonspecific in advanced stages. Evaluation usually includes ultrasonography, CT or MRI, and measurement of tumor markers (eg, cancer antigen 125). Diagnosis is by histologic analysis. Staging is surgical. Treatment requires hysterectomy, bilateral salpingo-oophorectomy, excision of as much involved tissue as possible, and, unless cancer is localized, chemotherapy.

In the US, ovarian cancer is the 2nd most common gynecologic cancer (affecting about 1/70) and the deadliest (1% of all women die of it); it is the 5th leading cause of cancer-related deaths in women, causing an estimated 15,000 deaths in 2008. Incidence is higher in developed countries.

Etiology

Ovarian cancer affects mainly perimenopausal and postmenopausal women. Nulliparity, delayed childbearing, early menarche, and delayed menopause increase risk. Oral contraceptive use decreases risk.

A personal or family history of endometrial, breast, or colon cancer increases risk. Probably 5 to 10% of ovarian cancer cases are related to mutations in the autosomal dominant *BRCA* gene, which is associated with a 50 to 85% lifetime risk of developing breast cancer. Women with *BRCA1* mutations have a 20 to 40% lifetime risk of developing ovarian cancer; risk among women with *BRCA2* mutations is increased less.

XY gonadal dysgenesis predisposes to ovarian germ cell cancer.

Pathology

Ovarian cancers are histologically diverse (see Table 256-1). At least 80% originate in the epithelium; 75% of these cancers are serous cystadenocarcinoma. The remaining 20% of ovarian cancers originate in primary ovarian germ cells or in sex cord and stromal cells or are metastases to the ovary (most commonly, from the breast or GI tract). Germ cell cancers usually occur in women < 30.

[**Table 256-1.** Types of Ovarian Cancers]

Ovarian cancer spreads by direct extension, exfoliation of cells into the peritoneal cavity (peritoneal seeding), lymphatic dissemination to the pelvis and around the aorta, or, less often, hematogenously to the liver or lungs.

Symptoms and Signs

Early cancer is usually asymptomatic; an adnexal mass, often solid, irregular, and fixed, may be

discovered incidentally. Pelvic and rectovaginal examinations typically detect diffuse nodularity. A few women present with severe abdominal pain secondary to torsion of the ovarian mass (see p. 2532). Most women with advanced cancer present with nonspecific symptoms (eg, dyspepsia, bloating, early satiety, gas pains, backache). Later, pelvic pain, anemia, cachexia, and abdominal swelling due to ovarian enlargement or ascites usually occur.

Germ cell or stromal tumors may have functional effects (eg, hyperthyroidism, feminization, virilization).

Diagnosis

• Ultrasonography (for suspected early cancers) or CT or MRI (for suspected advanced cancers)

• Tumor markers

• Surgical staging

Ovarian cancer is suspected in women with the following:

• Unexplained adnexal masses

• Unexplained abdominal bloating

• Changes in bowel habits

• Unintended weight loss

• Unexplained abdominal pain

An ovarian mass is more likely to be cancer in older women. Benign functional cysts (see p. 2533) can simulate functional germ cell or stromal tumors in young women.

A pelvic mass plus ascites usually indicates ovarian cancer but sometimes indicates Meigs' syndrome (a benign fibroma with as-cites and right hydrothorax).

Imaging: If early cancer is suspected, ultrasonography is done first; the following findings suggest cancer:

• A solid component

• Surface excrescences

• Size > 6 cm

• Irregular shape

• Low vascular resistance detected by transvaginal Doppler flow studies

If advanced cancer is suspected (eg, based on ascites, abdominal distention, or nodularity or fixation detected during physical examination), CT or MRI is usually done before surgery to determine extent of the cancer.

Tumor markers: Tumor markers, including the β subunit of human chorionic gonadotropin (β-hCG), LDH, α-fetoprotein, inhibin, and cancer antigen (CA) 125, are typically measured in young patients, who are at higher risk of nonepithelial tumors (eg, germ cell tumors, stromal tumors). In perimenopausal and postmenopausal patients, only CA 125 is measured because most ovarian cancers in this age group are epithelial tumors. CA 125 is elevated in 80% of advanced epithelial ovarian cancers but may be mildly elevated in endometriosis, pelvic inflammatory disease, pregnancy, fibroids, peritoneal inflammation, or nonovarian peritoneal cancer. A mixed solid and cystic pelvic mass in postmenopausal women, especially

if CA 125 is elevated, suggests ovarian cancer.

Biopsy: A biopsy is not routinely recommended unless a patient is not a surgical candidate. In those rare cases, samples are obtained by needle biopsy for masses or by needle aspiration for ascitic fluid.

For masses that appear benign on ultrasonography, histologic analysis is not required, and ultrasonography is repeated after 6 wk. Such benign-appearing masses include benign cystic teratomas (dermoid cysts), follicular cysts, and endometriomas.

Staging: Suspected or confirmed ovarian cancer is staged surgically (see Table 256-2). If early-stage cancer is suspected, staging may be done by laparoscopy. Otherwise, an abdominal midline incision that allows adequate access to the upper abdomen is required. All peritoneal surfaces, hemidiaphragms, and abdominal and pelvic viscera are inspected and palpated. Washings from the pelvis, abdominal gutters, and diaphragmatic recesses are obtained, and multiple biopsies of the peritoneum in the central and lateral pelvis and in the abdomen are done. For early-stage cancer, the infracolic omentum is removed, and pelvic and para-aortic lymph nodes are sampled.

Cancers are also graded histologically from 1 (least aggressive) to 3 (most aggressive).

Screening: Screening asymptomatic women using ultrasonography and serum CA 125 measurements can detect some cases of ovarian cancer but has not been shown to improve outcome, even for high-risk subgroups (including women with *BRCA* mutations). However, women should be screened for abnormalities of the *BRCA* gene if their family history includes any of the following:

• Diagnosis of ovarian cancer in a 1st-degree relative before age 40

• Diagnosis of breast and ovarian cancer in only one 1st-degree relative if one of the cancers was diagnosed before age 50

• Two cases of ovarian cancer among 1st- and 2nd-degree relatives of the same lineage

[**Table 256-2.** Surgical Staging of Ovarian Carcinoma*]

• Two cases of breast cancer and one case of ovarian cancer among 1st- or 2nd-degree relatives of the same lineage

• One case of breast and one case of ovarian cancer among 1st- or 2nd-degree relatives of the same lineage if breast cancer was diagnosed before age 40 or if ovarian cancer was diagnosed before age 50

• Two cases of breast cancer among 1st- or 2nd-degree relatives of the same lineage if both cases were diagnosed before age 50

• Two cases of breast cancer among 1st- or 2nd-degree relatives of the same lineage if one was diagnosed before age 40

Also, if Ashkenazi Jewish women have one family member with breast cancer diagnosed before age 50 or with ovarian cancer, screening should be considered.

Prognosis

The 5-yr survival rates with treatment are

• Stage I: 70 to 100%

• Stage II: 50 to 70%

• Stage III: 20 to 50%

• Stage IV: 10 to 20%

Prognosis is worse when tumor grade is higher or when surgery cannot remove all visibly involved tissue; then, prognosis is best when the involved tissue can be reduced to < 1 cm in diameter. With stages III and IV, recurrence rate is about 70%.

Treatment

• Usually hysterectomy and bilateral salpingooophorectomy

• Usually postoperative chemotherapy, often with carboplatin and paclitaxel

Hysterectomy and bilateral salpingooophorectomy are usually indicated except for stage I nonepithelial or low-grade unilateral epithelial cancers in young patients; fertility can be preserved by not removing the unaffected ovary and uterus. All visibly involved tissue is surgically removed if possible. If it cannot be removed completely, removing as much as possible (cytoreductive surgery) improves the efficacy of other therapies. Cytoreductive surgery usually includes supracolic omentectomy, sometimes with rectosigmoid resection (usually with primary reanastomosis), radical peritoneal stripping, resection of diaphragmatic peritoneum, or splenectomy.

Postoperative treatment depends on the stage and grade (see Table 256-3).

[**Table 256-3.** Postoperative Treatment of Ovarian Cancer by Stage and Type]

Even if chemotherapy results in a complete clinical response (ie, normal physical examination, normal serum CA 125, and negative CT scan of the abdomen and pelvis), about 50% of patients with stage III or IV cancer have residual tumor. Of patients with persistent elevation of CA 125, 90 to 95% have residual tumor. Recurrence rate in patients with a clinical complete response after initial chemotherapy (6 courses of carboplatin and paclitaxel) is 60 to 70%.

If cancer recurs or progresses after effective chemotherapy, chemotherapy is restarted. Other useful drugs may include topotecan, liposomal doxorubicin, docetaxel, vinorelbine, gemcitabine, hexamethylmelamine, and oral etoposide. Targeted therapy with biologic agents is under study.

Prevention

For patients with *BRCA1* or *BRCA2* gene mutations, risk of ovarian and, to a lesser degree, breast cancer is reduced if prophylactic bilateral salpingo-oophorectomy is done after childbearing is completed. These patients should be referred to a gynecologic oncologist for evaluation. Other resources include the National Cancer Institute Cancer Information Service (1-800-4-CANCER) and the Women's Cancer Network (www.wcn.org).

Fallopian Tube Cancer

Fallopian tube cancer is usually adenocarcinoma, manifesting as an adnexal mass or as vague symptoms. Diagnosis, staging, and treatment are surgical.

Primary fallopian tube cancer is rare. Average age at diagnosis is 50 to 60. Risk factors include chronic salpingitis, other inflammatory disorders (eg, TB), and infertility.

Most (> 95%) fallopian tube cancers are papillary serous adenocarcinomas; a few are sarcomas. Spread, like that of ovarian cancer, is by direct extension, by peritoneal seeding, or through the lymphatics.

Symptoms and Signs

Most patients present with an adnexal mass or vague abdominal or pelvic symptoms (eg, abdominal

discomfort, bloating, pain). A few patients present with hydrops tubae profluens (a triad of pelvic pain, copious watery discharge, and adnexal mass), which is more specific.

Diagnosis

• CT

• Surgery to confirm diagnosis and to stage

Typically, CT is done. A distended solid adnexal mass and normal ovary suggest fallopian tube cancer. A pregnancy test is done to rule out ectopic pregnancy unless patients are postmenopausal.

If cancer is suspected, surgery is necessary for diagnosis, staging, and treatment. Staging (similar to that of ovarian cancer) requires the following:

• Washings from the pelvis, abdominal gutters, and diaphragmatic recesses

• Multiple pelvic and abdominal peritoneal biopsies

• Pelvic and para-aortic lymph node dissection

Treatment

• Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and supracolic omentectomy

Treatment includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and supracolic omentectomy. If cancer appears advanced, cytoreductive surgery is indicated.

Postoperative treatment is identical to that for ovarian cancer. External beam radiation is rarely indicated.

Endometrial Cancer

Endometrial cancer is usually adenocarcinoma. Typically, postmenopausal vaginal bleeding occurs. Diagnosis is by biopsy. Staging is surgical. Treatment requires hysterectomy, bilateral salpingo-oophorectomy, usually pelvic and para-aortic lymph node dissection, and excision of all tissue likely to be involved. For advanced cancer, radiation, hormone, or cytotoxic therapy is usually indicated.

Endometrial cancer is more common in developed countries where the diet is high in fat. In the US, this cancer is the 4th most common cancer among women, affecting 1 in 50.

Etiology

Endometrial cancer affects mainly postmenopausal women, particularly those aged 50 to 65. Major risk factors are

• Obesity

• Diabetes

• Hypertension

Other risk factors include

• Unopposed estrogen

• Tamoxifen use for > 5 yr

- Previous pelvic radiation therapy
- A personal or family history of breast or ovarian cancer
- Family history of hereditary nonpolyposis colorectal cancer or possibly, among 1st-degree relatives, endometrial cancer

Unopposed estrogen (high circulating levels of estrogen with no or low levels of progesterone) may be associated with obesity, polycystic ovary syndrome, nulliparity, late menopause, estrogen-producing tumors, anovulation (ovulatory dysfunction), and estrogen therapy without progesterone. Heredity contributes to endometrial cancer in about 6% of cases, usually in families with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome.

Pathology

Endometrial cancer is usually preceded by endometrial hyperplasia. Adenocarcinoma accounts for > 80% of endometrial cancers. Other types include papillary serous, clear cell, squamous, mucinous carcinoma, and sarcomas.

The cancer may spread from the surface of the uterine cavity to the cervical canal; through the myometrium to the serosa and into the peritoneal cavity; via the lumen of the fallopian tube to the ovary, broad ligament, and peritoneal surfaces; via the bloodstream, leading to distant metastases; or via the lymphatics. The higher (more undifferentiated) the grade of the tumor, the greater the likelihood of deep myometrial invasion, pelvic or para-aortic lymph node metastases, or extra-uterine spread.

Symptoms and Signs

Most (> 90%) women have abnormal uterine bleeding (eg, postmenopausal bleeding, premenopausal recurrent metrorrhagia); one third of women with postmenopausal bleeding have endometrial cancer. A vaginal discharge may occur weeks or months before postmenopausal bleeding.

Diagnosis

- Endometrial biopsy
- Surgical staging

The following suggest endometrial cancer:

- Postmenopausal bleeding
- Abnormal bleeding in premenopausal women
- A routine Papanicolaou (Pap) test showing endometrial cells in postmenopausal women
- A routine Pap test showing atypical endometrial cells in any woman

If cancer is suspected, outpatient endometrial biopsy is done; it is > 90% accurate. If results are inconclusive or suggest cancer, outpatient fractional D & C with hysteroscopy is done. An alternative is transvaginal ultrasonography; however, a histologic diagnosis is required.

Once cancer is diagnosed, pretreatment evaluation includes serum electrolytes, kidney and liver function tests, CBC, chest x-ray, and ECG. If an abdominal mass or hepatomegaly is detected during physical examination or if liver function tests are abnormal, pelvic and abdominal CT are also done to check for extrauterine or metastatic cancer.

Staging: Staging is based on histologic differentiation (grade 1 [least aggressive] to 3 [most aggressive]) and extent of spread, including invasion depth, cervical involvement (glandular involvement vs stromal

invasion), and extrauterine metastases (see Table 256-4). Staging is surgical and includes peritoneal fluid cytology, exploration of the abdomen and pelvis, and biopsy or excision of suspect extrauterine lesions. Pelvic and para-aortic

[**Table 256-4.** Staging of Endometrial Carcinoma*]

lymph nodes are removed. During staging, a total abdominal hysterectomy and bilateral salpingo-oophorectomy are done. Surgical staging is traditionally done via laparotomy but may be done via laparoscopy or use of a robotics surgical system.

Prognosis

Prognosis is worse with higher-grade tumors, more extensive spread, and older patient age. Average 5-yr survival rates are 70 to 95% with stage I or II and 10 to 60% with stage III or IV. Overall, 63% of patients are cancer-free ≥ 5 yr after treatment.

Treatment

- Usually total hysterectomy and bilateral salpingo-oophorectomy
- Pelvic and para-aortic lymphadenectomy for deep (> 50% myometrial invasion) grade 1 and 2 and for grade 3
- Pelvic radiation therapy with or without chemotherapy for stage II or III
- Multimodal, individualized therapy for stage IV

If cancer appears to be stage I/grade 1 without deep myometrial invasion, the probability of unrecognized lymph node metastasis is < 2%. Treatment is usually total hysterectomy and bilateral salpingo-oophorectomy via laparotomy, laparoscopy, or robotics.

For grade 1 or 2 with ≥ 50% myometrial invasion or grade 3, complete pelvic and paraaortic lymphadenectomy is also done. Whether the extent of para-aortic node dissection should reach the inferior mesenteric artery vs the renal vessels remains a topic of debate.

Stage II or III cancer requires pelvic radiation therapy with or without chemotherapy. Treatment of stage III cancer must be individualized, but surgery is an option; generally, patients who undergo combined surgery and radiation therapy have a better prognosis. Except in patients with bulky parametrial disease, a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be done.

Treatment of stage IV is variable and patient dependent but typically involves a combination of surgery, radiation therapy, and chemotherapy. Occasionally, hormonal therapy should also be considered.

Hormone therapy with a progestin causes regression for up to 3 yr in 20 to 25% of patients. Pulmonary, vaginal, and mediastinal metastases may regress. Treatment continues as long as the response is favorable.

Several cytotoxic drugs (particularly carboplatin plus paclitaxel) are effective. They are given mainly to women with metastatic or recurrent cancer. With monthly regimens of doxorubicin 60 mg/m^2 plus cisplatin 60 mg/m^2 IV, overall response rate may be ≥ 50%.

Treatment of endometrial hyperplasia consists of progestins or surgery (eg, D & C), depending on the complexity of the lesion and the patient's desire to avoid hysterectomy. If young patients with grade 1 tumors and no myometrial invasion (documented by MRI) wish to preserve fertility, progestin alone is an option. About 46 to 80% of patients have a complete response within 3 mo on average. After 3 mo, patients should be evaluated via D & C rather than endometrial biopsy.

Uterine Sarcomas

Uterine sarcomas are a group of disparate, highly malignant cancers developing from the uterine corpus.

Sarcomas account for < 5% of uterine cancers. Risk factors are similar to those for endometrial carcinoma (see p. 2571). The most common types are mixed mesodermal tumors (malignant mixed mullerian tumor, in which the sarcoma is mixed with adenocarcinoma; recently renamed carcinosarcoma), leiomyosarcomas, and endometrial stromal tumors.

Symptoms and Signs

Most sarcomas manifest as abnormal vaginal bleeding and, less commonly, as pelvic pain or a palpable pelvic mass.

Diagnosis

• Transvaginal ultrasonography and endometrial biopsy or fractional D & C

Symptoms usually prompt transvaginal ultrasonography and endometrial biopsy or fractional D & C. If cancer is identified, CT or MRI is typically done preoperatively.

Staging is done surgically, as follows:

• Stage I: Confined to the corpus

• Stage II: Confined to the corpus and cervix

• Stage III: Spread outside the uterus but confined to the pelvis

• Stage IV: Spread outside the true pelvis or into the mucosa of the bladder or rectum

Prognosis

Prognosis is generally poorer than that with endometrial cancer of similar stage; survival is generally poor when the cancer has spread beyond the uterus. Histology is not an independent prognostic factor. In one study, 5-yr survival rates were 51% for stage I, 13% for stage II, 10% for stage III, and 3% for stage IV. Most commonly, the cancer recurs locally, in the abdomen, and the lungs.

Treatment

• Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and complete exploration of the abdomen

Treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete exploration of the abdomen. Pelvic and para-aortic nodes are dissected in patients with carcinosarcoma. The usefulness of lymphadenectomy in patients with leiomyosarcoma or endometrial stromal sarcoma is controversial; no therapeutic value has been shown.

Adjuvant radiation therapy is typically used and appears to delay local recurrence but does not improve overall survival rate. Chemotherapy drugs vary with tumor type. Overall, response to chemotherapy is poor, although progestins are frequently effective for endometrial stromal tumors.

Gestational Trophoblastic Disease

Gestational trophoblastic disease is proliferation of trophoblastic tissue in pregnant or recently pregnant women. Manifestations may include excessive uterine enlargement, vomiting, vaginal bleeding, and preeclampsia, particularly during early pregnancy. Diagnosis includes

measurement of the β subunit of human chorionic gonadotropin, pelvic ultrasonography, and confirmation by biopsy. Tumors are removed by suction curettage. If disease persists after removal, chemotherapy is indicated.

Gestational trophoblastic disease is a tumor originating from the trophoblast, which surrounds the blastocyst and develops into the chorion and amnion (see p. 2605). This disease can occur during or after an intrauterine or ectopic pregnancy. If the disease occurs during a pregnancy, spontaneous abortion, eclampsia, or fetal death typically occurs; the fetus rarely survives. Some forms are malignant; others are benign but behave aggressively.

Pathology

Classification is morphologic:

- **Hydatidiform mole:** In this abnormal pregnancy, villi become edematous (hydropic), and trophoblastic tissue proliferates.

- **Chorioadenoma destruens (invasive mole):** The myometrium is invaded locally by a hydatidiform mole.

- **Choriocarcinoma:** This invasive, usually widely metastatic tumor is composed of malignant trophoblastic cells and lacks hydropic villi; most of these tumors develop after a hydatidiform mole.

- **Placental site trophoblastic tumor:** This rare tumor consists of intermediate trophoblastic cells that persist after a term pregnancy; it may invade adjacent tissues or metastasize.

Hydatidiform moles are most common among women < 17 or > 35 and those who have had previous gestational trophoblastic disease. They occur in about 1/2000 gestations in the US. For unknown reasons, incidence in Asian countries approaches 1/200. Most (> 80%) hydatidiform moles are benign. The rest may persist, tending to become invasive; 2 to 3% of hydatidiform moles are followed by choriocarcinoma.

Symptoms and Signs

Initial manifestations of a hydatidiform mole suggest early pregnancy, but the uterus often becomes larger than expected within 10 to 16 wk gestation. Commonly, women test positive for pregnancy, have vaginal bleeding and severe vomiting, and fetal movement and fetal heart sounds are absent. Passage of grape-like tissue strongly suggests the diagnosis. Complications may include uterine infection, sepsis, hemorrhagic shock, and preeclampsia, which may occur during early pregnancy.

Placental site trophoblastic tumors tend to cause bleeding.

Choriocarcinoma usually manifests with symptoms due to metastases.

Gestational trophoblastic disease does not impair fertility or predispose to prenatal or perinatal complications (eg, congenital malformations, spontaneous abortions).

Diagnosis

- Serum β-hCG

- Pelvic ultrasonography

Gestational trophoblastic disease is suspected in women with a positive pregnancy test and any of the following:

- Uterine size much larger than expected for dates

- Symptoms or signs of preeclampsia
- Passage of grapelike tissue
- Suggestive findings (eg, mass containing multiple cysts instead of a fetus) seen during ultrasonography done to evaluate pregnancy
- Unexplained metastases in women of child-bearing age
- Unexpectedly high levels of human chorionic gonadotropin (β-hCG) detected during pregnancy testing
- Unexplained complications of pregnancy

If gestational trophoblastic disease is suspected, testing includes measurement of serum β-hCG and pelvic ultrasonography. Findings (eg, very high β-hCG levels, classic ultrasonographic findings) may suggest the diagnosis, but biopsy is required. Invasive mole and choriocarcinoma are suspected if biopsy findings suggest invasive disease or if β-hCG levels remain higher than expected after treatment for hydatidiform mole (see below).

Treatment

- Tumor removal by suction curettage
- Further evaluation for persistent disease and spread of tumor
- Chemotherapy for persistent disease
- Posttreatment contraception for persistent disease

Hydatidiform mole, invasive mole, and placental site trophoblastic tumor are evacuated by suction curettage. Alternatively, if childbearing is not planned, hysterectomy may be done.

After tumor removal, gestational trophoblastic disease is classified clinically to determine whether additional treatment is needed. The clinical classification system does not correspond to the morphologic classification system. Invasive mole and choriocarcinoma are classified clinically as persistent disease. The clinical classification is used because both are treated similarly and because exact histologic diagnosis may require hysterectomy.

A chest x-ray is taken, and serum β-hCG is measured. If the β-hCG level does not normalize within 10 wk, the disease is classified as persistent. Persistent disease requires CT of the brain, chest, abdomen, and pelvis. Results dictate whether disease is classified as nonmetastatic or metastatic. In metastatic disease, prognosis (including risk of death) may be poor or good (see Table 256-5). Poor prognosis is suggested by the following (National Institutes of Health [NIH] criteria):

- Urinary hCG excretion > 100,000 IU in 24 h
- Duration of disease > 4 mo (interval since prior pregnancy)
- Brain or liver metastases
- Disease after full-term pregnancy
- Serum hCG > 40,000 mIU/mL
- Unsuccessful prior chemotherapy
- WHO score > 8

[Table 256-5. WHO Scoring System in Metastatic Gestational Trophoblastic Disease]

Persistent disease is usually treated with chemotherapy. Treatment is considered successful if at least 3 consecutive serum β-hCG measurements at 1-wk intervals are normal. Typically, oral contraceptives (any is acceptable) are given for 6 to 12 mo; alternatively, any effective contraceptive method can be used.

Nonmetastatic disease can be treated with a single chemotherapy drug (methotrexate or dactinomycin). Alternatively, hysterectomy is considered for patients > 40 or those desiring sterilization and may be required for those with severe infection or uncontrolled bleeding. If single-drug chemotherapy is ineffective, hysterectomy or multidrug chemotherapy is indicated. Virtually 100% of patients with nonmetastatic disease can be cured.

Low-risk metastatic disease is treated with single-drug or multidrug chemotherapy. High-risk metastatic disease requires aggressive multidrug chemotherapy. Cure rates are 90 to 95% for low-risk and 60 to 80% for high-risk disease.

Hydatidiform mole recurs in about 1% of subsequent pregnancies. Patients who have had a mole require ultrasonography early in subsequent pregnancies, and the placenta should be sent for pathologic evaluation.

Cervical Cancer

Cervical cancer is usually a squamous cell carcinoma caused by human papillomavirus infection; less often, it is an adenocarcinoma. Cervical neoplasia is asymptomatic; the first symptom of early cervical cancer is usually irregular, often postcoital vaginal bleeding. Diagnosis is by a screening cervical Papanicolaou test and biopsy. Staging is clinical. Treatment usually involves surgical resection, or radiation therapy plus chemotherapy. If the cancer has widely metastasized, chemotherapy is often used alone.

Cervical cancer is the 3rd most common gynecologic cancer and the 8th most common cancer among women in the US. Mean age at diagnosis is about 50, but the cancer can occur as early as age 20.

Cervical cancer results from cervical intraepithelial neoplasia (CIN), which appears to be caused by infection with human papillomavirus (HPV) type 16, 18, 31, 33, 35, or 39. Risk factors for cervical cancer include

• Younger age at first intercourse

• A high lifetime number of sex partners

• Intercourse with men whose previous partners had cervical cancer

Other factors such as cigarette smoking and immunodeficiency also appear to contribute.

Pathology

CIN is graded as 1 (mild cervical dysplasia), 2 (moderate dysplasia), or 3 (severe dysplasia and carcinoma in situ). CIN 3 is unlikely to regress spontaneously; if untreated, it may, over months or years, penetrate the basement membrane, becoming invasive carcinoma.

About 80 to 85% of all cervical cancers are squamous cell carcinoma; most of the rest are adenocarcinomas. Sarcomas and small cell neuroendocrine tumors are rare.

Invasive cervical cancer usually spreads by direct extension into surrounding tissues or via the lymphatics to the pelvic and paraaortic lymph nodes. Hematogenous spread is possible but rare.

Symptoms and Signs

CIN is usually asymptomatic. Early cervical cancer can be asymptomatic. The first symptom is usually irregular vaginal bleeding, which is most often postcoital but may occur spontaneously between menses. Larger cancers are more likely to bleed spontaneously and may cause a foul-smelling vaginal discharge or pelvic pain. More widespread cancer may cause obstructive uropathy, back pain, and leg swelling due to venous or lymphatic obstruction; pelvic examination may detect an exophytic necrotic tumor in the cervix.

Diagnosis

• Papanicolaou (Pap) test

• Biopsy

• Clinical staging, usually by biopsy, pelvic examination, and chest x-ray

Cervical cancer may be diagnosed during a routine gynecologic examination. It is considered in women with

• Visible cervical lesions

• Abnormal routine Pap test results

• Abnormal vaginal bleeding

CIN is usually evident on Pap tests, but about 50% of patients with cervical cancer have not had a Pap test for ≥ 10 yr. Patients at highest risk are the least likely to obtain regular preventive health care and to be tested regularly.

Reporting of cervical cytology results is standardized (see Table 256-6). Further evaluation is indicated if atypical or cancerous cells are found, particularly in women at risk. If cytology does not show any obvious cancer, colposcopy (examination of the vagina and cervix with a magnifying lens) can be used to identify areas that require biopsy. Colposcopy-directed biopsy with endocervical curettage is usually diagnostic. If not, cone biopsy (conization) is required; a cone of tissue is removed using a loop electrical excision procedure (LEEP), laser, or cold knife.

Staging: Cancers are clinically staged based on biopsy, physical examination, and chest x-ray results (see Table 256-7). If the stage is > IB1, CT or MRI of the abdomen and pelvis is typically done to identify metastases, although results are not used for staging. If MRI and CT are not available, cystoscopy, sigmoidoscopy, and IV urography, when clinically indicated, may be used for staging.

[**Table 256-6.** Bethesda Classification of Cervical Cytology*]

The purpose of this staging system is to establish a large database for study; thus, the system uses worldwide uniform diagnostic criteria. The system excludes results of tests that are less likely to be available worldwide (eg, MRI) because most cases of cervical cancer occur in developing countries. Because such tests are not used, findings such as parametrial invasion and lymph node metastases are often missed, and thus understaging is possible.

[**Table 256-7.** Clinical Staging of Cervical Carcinoma*]

When imaging tests suggest that pelvic or para-aortic lymph nodes are grossly enlarged (> 2 cm), surgical exploration, typically with a retroperitoneal approach, is occasionally indicated. Its sole purpose is to remove enlarged lymph nodes so that radiation therapy can be more precisely targeted and more effective.

Prognosis

In squamous cell carcinoma, distant metastases usually occur only when the cancer is advanced or recurrent. The 5-yr survival rates are as follows:

• Stage I: 80 to 90%

• Stage II: 60 to 75%

• Stage III: 30 to 40%

• Stage IV: 0 to 15%

Nearly 80% of recurrences manifest within 2 yr. Adverse prognostic factors include lymph node involvement, large tumor size and volume, deep cervical stromal invasion, parametrial invasion, vascular space invasion, and nonsquamous histology.

Treatment

• Excision or curative radiation therapy if there is no spread to parametria or beyond

• Radiation therapy and chemotherapy if there is spread to the parametria or beyond

• Chemotherapy for metastatic and recurrent cancer

Treatment may include surgery, radiation therapy, and chemotherapy. If hysterectomy is indicated but patients cannot tolerate it, radiation therapy plus chemotherapy is used.

CIN and squamous cell carcinoma stage IA1: Cone biopsy with LEEP, laser, or cold knife is usually sufficient treatment. Hysterectomy is done for stage IA1 cancer if there are adverse prognostic factors (nonsquamous histology or lymphatic or vascular invasion). Radical hysterectomy is recommended by some experts; it includes bilateral pelvic lymphadenectomy and removal of all adjacent ligaments (eg, cardinal, uterosacral) and parametria and the upper 2 cm of the vagina. Hysterectomy can also be done if women no longer desire fertility. If there are no adverse prognostic factors, simple (extrafascial) hysterectomy is usually sufficient because risk of recurrence and lymph node metastasis is < 1%. Pelvic lymph node dissection is not indicated.

Stages IA2 to IIA: Treatment options include a radical hysterectomy and pelvic lymphadenectomy alone (stages IA2 to IB1) or a radical hysterectomy and pelvic lymphadenectomy with possible combined chemotherapy and pelvic radiation (stages IB2 to IIA). Chemotherapy is usually given concurrently. With either treatment, the 5-yr cure rates in stage IB or IIA are 85 to 90%. Surgery provides additional staging data and preserves the ovaries. If extracervical spread is noted during surgery, postoperative radiation therapy may prevent local recurrence.

In some patients who have early-stage cervical cancer and who wish to preserve fertility, a radical trachelectomy may be done. In this procedure, the cervix, parametria immediately adjacent to the cervix, upper 2 cm of the vagina, and pelvic lymph nodes are removed. The remaining uterus is reattached to the upper vagina, preserving the potential for fertility. Ideal candidates for this procedure are patients with the following:

• Histologic subtypes such as squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma

• Stage IA1/grade 2 or 3 with vascular space invasion

• Stage IA2

• Stage IB1 with lesions < 2 cm in size

Invasion of the upper cervix and lower uterine segment should be excluded by MRI. Rates of recurrence and death are similar to those after radical hysterectomy. If patients who have this procedure plan to have

children, delivery must be cesarean.

Stages IIB to IVA: Radiation therapy plus chemotherapy (eg, cisplatin) is more suitable as primary therapy. Surgical staging should be considered to determine whether paraaortic lymph nodes are involved and thus whether extended-field radiation therapy is indicated; a retroperitoneal approach is used. Staging may be done via laparoscopy. External beam radiation therapy shrinks the central tumor and treats regional lymph nodes. This therapy is followed by brachytherapy (local radioactive implants, usually using cesium) to the cervix, which destroys the central tumor. Radiation therapy may cause acute complications (eg, radiation proctitis and cystitis) and, occasionally, late complications (eg, vaginal stenosis, intestinal obstruction, rectovaginal and vesicovaginal fistula formation).

Chemotherapy is usually given with radiation therapy, often to sensitize the tumor to radiation. Treatment is often ineffective for bulky and advanced-stage tumors.

Although stage IVA cancers are usually treated with radiation therapy initially, pelvic exenteration (excision of all pelvic organs) may be considered. If after radiation therapy, cancer remains but is confined to the central pelvis, exenteration is indicated and cures up to 50% of patients. The procedure may include a continent urostomy, low anterior rectal anastomosis without colostomy, omental carpet to close the pelvic floor (J-flap), and vaginal reconstruction with gracilis or rectus abdominis myocutaneous flaps.

Stage IVB and recurrent cancer: Chemotherapy is the primary treatment, but only 15 to 25% of patients respond to it and only briefly. Cisplatin is the most active drug and the current standard, but adding topotecan appears to improve overall response and survival. Combinations of paclitaxel, topotecan, gemcitabine, cisplatin, and vinorelbine are under study for treatment of recurrent squamous cell carcinoma. Paclitaxel is also used to treat recurrent or metastatic nonsquamous cancer. Metastases outside the radiation field appear to respond better to chemotherapy than does previously irradiated cancer or metastases in the pelvis.

Prevention

Pap tests: Routine cervical Pap tests are recommended yearly, starting when patients first begin having sexual intercourse or reach age 18. Pap test and HPV test can be done simultaneously. If both are normal or if 3 consecutive Pap tests are normal, some physicians test at 2- to 3-yr intervals. Testing continues until patients are age 65 to 70, have normal results for 10 yr, or have a hysterectomy. Sexually active women are advised that condoms should be used during intercourse to prevent spread of HPV. HPV testing is the preferred method of follow-up evaluation for women ages 20 to 30 with inconclusive Pap results such as ASCUS (atypical squamous cells of undetermined significance). If testing shows that the patient does not have HPV, a repeat Pap is recommended in 12 mo. If HPV is present, colposcopy should be done. Routine HPV testing plus a Pap test is recommended for women ≥ 30.

HPV vaccine: A newly developed vaccine (see p. 1176) targets the 4 viral subtypes (HPV 6, 11, 16, and 18) most commonly associated with cervical intraepithelial lesions, genital warts, and cervical cancer. The vaccine aims to prevent cervical cancer but does not treat it. Three doses are given: the first dose is followed by one 2 mo and one 6 mo later. The vaccine is best given before sexual activity begins, but women who are sexually active should be vaccinated.

Vaginal Cancer

Vaginal cancer is usually a squamous cell carcinoma, most often occurring in women > 60. The most common symptom is abnormal vaginal bleeding. Diagnosis is by biopsy. Treatment for many small localized cancers is hysterectomy plus vaginectomy and lymph node dissection; for most others, radiation therapy is used.

Vaginal cancer accounts for 1% of gynecologic cancers in the US. Average age at diagnosis is 60 to 65. Risk factors include human papillomavirus infection and cervical or vulvar cancer. Exposure to diethylstilbestrol in utero predisposes to clear cell adenocarcinoma of the vagina, which is rare; mean age at diagnosis is 19.

Most (95%) primary vaginal cancers are squamous cell carcinomas; others include primary and secondary adenocarcinomas, secondary squamous cell carcinomas (in older women), clear cell adenocarcinomas (in young women), and melanomas. The most common vaginal sarcoma is sarcoma botryoides (embryonal rhabdomyosarcoma); peak incidence is at age 3.

Most vaginal cancers occur in the upper third of the posterior vaginal wall. They may spread by direct extension (into the local paravaginal tissues, bladder, or rectum), through inguinal lymph nodes from lesions in the lower vagina, through pelvic lymph nodes from lesions in the upper vagina, or hematogenously.

Symptoms and Signs

Most patients present with abnormal vaginal bleeding: postmenopausal, postcoital, or intermenstrual. Some also present with a watery vaginal discharge or dyspareunia. A few patients are asymptomatic, and the lesion is discovered during routine pelvic examination or evaluation of an abnormal Papanicolaou (Pap) test. Vesicovaginal or rectovaginal fistulas are manifestations of advanced disease.

Diagnosis

• Biopsy

• Clinical staging

Punch biopsy is usually diagnostic, but wide local excision is occasionally necessary. Cancers are staged clinically (see Table 256-8), based primarily on physical examination, endoscopy (ie, cystoscopy, proctoscopy), chest x-ray (for pulmonary metastases), and usually CT (for abdominal or pelvic metastases). Survival rates depend on the stage.

[**Table 256-8.** Vaginal Cancer by Stage]

Treatment

• Hysterectomy plus vaginectomy and lymph node dissection for tumors confined to the wall of the upper third of the vagina

• Radiation therapy for most others

Stage I tumors within the upper third of the vagina can be treated with radical hysterectomy, upper vaginectomy, and pelvic lymph node dissection. Most other primary tumors are treated with radiation therapy, usually a combination of external beam radiation therapy and brachytherapy. If radiation therapy is contraindicated because of vesicovaginal or rectovaginal fistulas, pelvic exenteration is done.

Vulvar Cancer

Vulvar cancer is usually a squamous cell skin cancer, most often occurring in elderly women. It usually manifests as a palpable lesion. Diagnosis is by biopsy. Treatment includes excision and inguinal and femoral lymph node dissection.

Vulvar cancer accounts for about 3 to 4% of gynecologic cancers in the US. Average age at diagnosis is about 70, and incidence increases with age. Risk factors include vulvar intraepithelial neoplasia (VIN), human papillomavirus infection, heavy cigarette smoking, lichen sclerosus, squamous hyperplasia, squamous carcinoma of the vagina or cervix, and chronic granulomatous diseases.

Pathology

VIN is a precursor to vulvar cancer. VIN may be multifocal. Sometimes adenocarcinoma of the vulva, breast, or Bartholin's glands also develops.

About 90% of vulvar cancers are squamous cell carcinomas; about 5% are melanomas. Others include adenocarcinomas and transitional cell, adenoid cystic, and adenosquamous carcinomas; all may originate in Bartholin's glands. Sarcomas and basal cell carcinomas with underlying adenocarcinoma also occur.

Vulvar cancer may spread by direct extension (eg, into the urethra, bladder, vagina, perineum, anus, or rectum), hematogenously, to the inguinal lymph nodes, or from the inguinal lymph nodes to the pelvic and paraaortic lymph nodes.

Symptoms and Signs

The most common presentation is a palpable vulvar lesion, frequently noticed by the woman or by a clinician during pelvic examination. Women often have a long history of pruritus. They may not present until cancer is advanced. The lesion may become necrotic or ulcerated, sometimes resulting in bleeding or a watery vaginal discharge. Melanomas may appear bluish black, pigmented, or papillary.

Diagnosis

• Biopsy

• Surgical staging

Vulvar cancer may mimic sexually transmitted genital ulcers (see p. 1468), basal cell carcinoma, vulvar Paget's disease (a pale eczematoid lesion), Bartholin's gland cyst, or condyloma acuminatum. A dermal punch biopsy using a local anesthetic is usually diagnostic. Occasionally, wide local excision is necessary to differentiate VIN from cancer. Subtle lesions may be delineated by staining the vulva with toluidine blue or by using colposcopy.

Staging: Staging is based on tumor size and location and on regional lymph node spread as determined by lymph node dissection done as part of initial surgical treatment (see Table 256-9).

Prognosis

Overall 5-yr survival rates depend on stage. Risk of lymph node spread is proportional to

[**Table 256-9.** Vulvar Cancer by Stage]

the tumor size and invasion depth. Melanomas metastasize frequently, depending mostly on invasion depth but also on tumor size.

Treatment

• Wide excision and lymph node dissection for all cancers

• Radiation therapy, chemotherapy, or both for stage III or IV cancer

Wide (≥ 2-cm margin) radical excision of the local tumor and a unilateral or bilateral inguinal and femoral lymph node dissection are necessary for cancers of all stages and are sufficient for stages I and II. For lateralized lesions ≤ 2 cm, unilateral wide local excision and unilateral lymph node dissection can be used. Lesions near the midline and most lesions > 2 cm require bilateral lymph node dissection.

For stage III, lymph node dissection followed by postoperative external beam radiation therapy, often with chemotherapy (eg, 5-fluorouracil, cisplatin), is usually done before wide radical excision. The alternative is more radical or exenterative surgery.

For stage IV, treatment is some combination of pelvic exenteration, radiation therapy, and systemic chemotherapy.

Chapter 257. Family Planning

Introduction

A couple's decision to begin, prevent, or interrupt a pregnancy may be influenced by many medical factors, including maternal medical disorders, risks involved in pregnancy, and genetic evaluation. Often, religious, social, and other factors also affect family planning decisions; health care practitioners must be sensitive to these factors.

One or both members of a couple can use contraception to prevent pregnancy temporarily or sterilization to prevent pregnancy permanently. If contraception fails, abortion (termination of pregnancy) can be induced.

Contraception

The contraceptive methods most commonly used in the US (in order of popularity) are oral contraceptives, female sterilization, condoms, male sterilization, progestin injections, withdrawal (coitus interruptus), intrauterine devices (IUDs), periodic abstinence, spermicides, and diaphragms (see Table 257-1). Over several years, pregnancy rates are < 1%/yr with methods unrelated to coitus (IUDs, progestin injections, subdermal progestin implants, and oral contraceptives when taken consistently) and about 5%/yr with coitus-related methods (eg, condoms, diaphragms, spermicides, withdrawal); pregnancy rates tend to be higher during the first year, then decrease in later years as users become more facile and women's fertility decreases. In contrast, the pregnancy rate is 90%/yr with frequent, unprotected intercourse. Condoms are often preferred despite their relatively high failure rate because they protect against sexually transmitted diseases, especially HIV. Emergency contraception, done post-coitus, should not be used as a regular method of contraception.

[**Table 257-1.** Comparison of Common Contraceptive Methods]

Oral Contraceptives

Oral contraceptives (OCs) simulate ovarian hormones: They provide negative feedback to the hypothalamus; its release of gonadotropin-releasing hormone is inhibited, thus inhibiting pituitary release of gonadotropins that stimulate ovulation. The endometrium becomes thin, and cervical mucus becomes thick and impervious to sperm.

An OC may be a combination of an estrogen and a progestin or a progestin alone. Most combination formulations are taken daily for 3 wk, then no pill or a placebo is taken during the 4th wk to allow for withdrawal bleeding. However, one formulation is taken daily for 12 wk, then not taken during the 13th wk, so that withdrawal bleeding occurs only 4 times/yr. Two new formulations provide active hormones for 24 days and placebo for 4 days so that a tablet is taken every day.

Progestin alone is taken daily; it often results in irregular bleeding and may be less effective than combination OCs. Progestin alone is not used unless estrogen is contraindicated—eg, during breastfeeding.

Combination formulations have similar efficacy; the pregnancy rate after 1 yr is < 0.3% with perfect use and about 8% with typical (ie, inconsistent) use. Low-dose formulations (20 to 35 µg of estrogen) are usually preferred to higher-dose formulations (50 µg of estrogen) because low-dose formulations appear equally effective and, except for a higher incidence of bleeding during the first few months of use, have fewer adverse effects.

Intermittently stopping OCs appears to have no benefit, so OCs can be taken continuously until menopause, which is indicated by an elevated follicle-stimulating hormone level. Combination OCs are not prescribed for women > 35 who smoke cigarettes or have other contraindications (see Table 257-2).

Adverse effects: OCs may cause breakthrough bleeding (which may resolve with time or when the

estrogen dose is increased) or amenorrhea (which may resolve when the progestin dose is decreased). In a few women, ovulation remains inhibited for a few months after they stop taking OCs. OCs do not adversely affect the outcome of pregnancy when conception occurs during or after their use.

Estrogens increase aldosterone production and cause Na retention, which can produce dose-related, reversible increases in BP and weight, up to about 2 kg; weight gain may be accompanied by bloating, edema, and breast tenderness. Most progestins used in OCs are related to 19-nortestosterone and are androgenic; norgestimate and desogestrel are less androgenic than levonorgestrel, norethindrone, norethindrone acetate, and ethynodiol diacetate. Androgenic effects may include acne, nervousness, and an anabolic effect resulting in weight gain. If a woman gains > 4.5 kg/yr, a less androgenic OC should be used. Drospirenone, a new progestin, is related to spironolactone, not 19-nortestosterone; it is antiandrogenic and diuretic.

OCs increase the risk of certain disorders and decrease the risk of others (see Table 257-3).

[**Table 257-2.** Contraindications to Combination Oral Contraceptive Use]

Incidence of deep venous thrombosis and thromboembolism increases in relation to estrogen dose; formulations with 20 to 35 µg increase risk to about 3 to 4 times normal (but risk is still only about half of that during pregnancy). Formulations containing the less androgenic progestin desogestrel may have a slightly higher risk than formulations containing levonorgestrel, but this difference has not been established. Varicose veins do not appear to further increase risk. Hypercoagulability is probably caused by increases in clotting factors, particularly VII and X, and possibly increased platelet adhesion. If deep vein thrombophlebitis or pulmonary embolism is suspected, OCs should be stopped, pending results of diagnostic tests. OCs should be stopped as soon as possible before any major surgery and 1 mo before elective major surgery; they should not be restarted until 1 mo after the surgery.

Current use of OCs does not increase overall risk of breast cancer, nor does former use in women aged 35 to 65. Also, use does not increase risk in high-risk groups (eg, women with certain benign breast disorders or a family history of breast cancer). Risk of cervical cancer is increased in women who have used OCs for > 5 yr; the reason is unknown. OC users should have annual cervical cytology screening (eg, Papanicolaou [Pap] test).

Although increased stroke risk has been attributed to OCs, low-dose combination OCs do not appear to increase risk in healthy, normotensive, nonsmoking women. Nonetheless,

[**Table 257-3.** Some Risks and Benefits of Combination Oral Contraceptives]

if focal neurologic symptoms, aphasia, or other symptoms that may herald stroke develop, OCs should be stopped. CNS effects of OCs include nausea, vomiting, headache, depression, and sleep disturbances.

Although progestins may cause reversible, dose-related insulin resistance, use of current OCs, which have a low progestin dose, rarely results in hyperglycemia. Serum high-density lipoprotein (HDL) cholesterol levels may decrease when OCs with a high progestin dose are used but usually increase when OCs with low progestin and estrogen doses are used. Most alterations in serum levels of other metabolites are not clinically significant. Thyroxine-binding globulin capacity may increase; free thyroxine levels, thyroid-stimulating hormone levels, and thyroid function are not affected. Levels of pyridoxine, folate, most other B vitamins, ascorbic acid, Ca, manganese, and zinc decrease; vitamin A levels increase.

OCs accelerate growth of existing gallstones but do not cause new stones to form. Thus, incidence of cholelithiasis increases during the first few years of OC use, then decreases. Women who develop idiopathic recurrent jaundice of pregnancy (cholestasis of pregnancy) may become jaundiced if they take OCs; these women should not take OCs.

Rarely, benign hepatic adenomas that can spontaneously rupture develop. Incidence increases as duration of use and OC dose increase; adenomas usually regress spontaneously after the OC is stopped.

Melasma occurs in some women; it is accentuated by sunlight and disappears slowly after OCs are stopped. Because treatment is difficult (see p. 721), OCs are stopped when melasma first appears. OCs do not increase risk of malignant melanoma.

Benefits: OCs decrease risk of endometrial and ovarian cancers by about 50% for at least 20 yr after OCs are stopped. They also decrease risk of benign ovarian tumors, abnormal uterine bleeding, dysmenorrhea, premenstrual syndrome, iron deficiency anemia, benign breast disorders, and functional ovarian cysts. Ectopic pregnancy and salpingitis, which can impair fertility, are also less likely.

Drug interactions: Although OCs can slow the metabolism of certain drugs (eg, meperidine), the effects are not clinically important.

Some drugs (eg, cyclophosphamide, rifampin) can induce liver enzymes that accelerate transformation of OCs to less biologically active metabolites; women who take these drugs should not be given OCs concurrently. Whether certain antibiotics (eg, penicillin, ampicillin, sulfonamides) and anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital, prim-idone, topiramate) reduce the effectiveness of OCs is less clear. If therapeutic doses of antibiotics are prescribed, using a barrier method in addition to OCs may be prudent. Women who take anticonvulsants should use a 50-µg estrogen formulation because a lower dose often causes breakthrough bleeding.

Administration: Before OCs are started and annually thereafter, breast and pelvic examinations, liver palpation, and measurement of BP and weight are necessary. BP is also measured 3 mo after starting OCs. OC users should have annual cervical cytology screening (eg, Pap test), particularly if they have taken OCs > 5 yr or if they are young, sexually active women. For women with a history of a liver disorder, normal liver function must be documented before OCs are prescribed. Women at risk of diabetes (eg, those who have a family history or who have had high-birth-weight infants or unexplained fetal deaths in previous pregnancies) require annual plasma glucose screening and a complete serum lipid profile (repeated annually if results are abnormal). Use of low-dose OCs is not contraindicated by abnormal glucose or lipid test results, except for triglycerides > 250 mg/dL.

When to start OCs after pregnancy is guided by when ovulation is expected. After an abortion, ovulation usually occurs after 2 to 4 wk and before the first menses; older gestational age predicts later ovulation. In women who have a term delivery and are not breastfeeding, ovulation occasionally occurs as early as 4 wk after delivery but usually not until after menses. In women who are breastfeeding, ovulation usually occurs ≥ 10 wk after delivery and after menses.

After spontaneous or induced abortion of a fetus < 12 wk gestation, OCs are started immediately. If the fetus is 12 to 28 wk gestation, OCs are delayed 1 wk.

After a term delivery, risk of thromboembolism, which normally increases postpartum, also influences when OCs are started. If women deliver after 28 wk and are not breast-feeding, combination OCs are delayed 2 wk because combination OCs may enhance risk of thromboembolism. For women who are breast-feeding, progestin-only OCs are started a few days after delivery because progestin-only OCs are not thrombogenic. Progestin-only OCs are used because OCs that contain estrogen reduce the amount of milk produced as well as the protein and fat concentration in milk.

Barrier Contraceptives

Barrier contraceptives include condoms, diaphragms, cervical caps, vaginal spermicides (foams, creams, suppositories), and the contraceptive sponge.

Condoms: Condom use is the only reversible male method other than withdrawal, which is probably much less effective. Condoms decrease risk of sexually transmitted diseases (only latex condoms can fully protect against HIV) and may prevent precancerous changes in the cervix.

The condom is applied before penetration; the tip should extend about 1 cm beyond the penis to collect the ejaculate. During removal, care is taken to avoid spilling condom contents. A new condom is used for

each act of coitus. Pregnancy rates in the 1st yr are 2% with perfect use but 15% with typical (ie, inconsistent) use. Adding a spermicide, which may be included in the condom's lubricant or inserted into the vagina, may lower these rates.

Diaphragm: The diaphragm, a dome-shaped rubber cup with a flexible rim that fits over the cervix, is a barrier to sperm. Diaphragms are made in various sizes. A health care practitioner fits a diaphragm to a woman so that it is comfortable for her and her partner. After childbirth or a significant weight change, the woman is refitted. The diaphragm should remain in place for > 8 h after the last coitus. Spermicides should be used before each coitus in case the diaphragm is displaced. Pregnancy rates in the 1st yr are about 6% with perfect use but about 16% with typical use.

Cervical cap: The cervical cap resembles the diaphragm but is smaller and more rigid. It comes in several sizes and is fitted by a health care practitioner. It can be left in place for 48 h. For nulliparous women, pregnancy rates in the 1st yr are 9% with perfect use and about 18% with typical use. Pregnancy rates for parous women are about twice as high because obtaining a secure fit is difficult.

Vaginal spermicides: Vaginal foams, creams, and suppositories provide a physical barrier to sperm and contain a spermicide, usually nonoxynol-9. They are combined with other barrier methods and are placed in the vagina before each coitus. These products appear to have similar efficacy.

Contraceptive sponge: The contraceptive sponge, previously off the market, is available again. It contains nonoxynol-9, does not need to be fitted by a health care practitioner, and can be inserted before coitus. Its efficacy is less than that of the diaphragm.

Periodic Abstinence

(Natural Family Planning)

Although the ovum can be fertilized for only about 12 h after ovulation, sperm can fertilize an ovum for up to 5 days after coitus. Thus, periodic abstinence requires abstinence from coitus during the 5 days before ovulation. Several methods can be used to identify the time of ovulation; they include the calendar method, basal body temperature, and the characteristics of cervical mucus.

The calendar rhythm method aims to predict ovulation solely by menstrual dates. Ovulation occurs about 14 days before onset of menses; but even when menstrual cycles are regular, this method is often inaccurate. The interval of abstinence during the menstrual cycle is determined by subtracting 18 days from the shortest of the previous 12 cycles and 11 days from the longest (see Fig. 257-1). For example, if cycles vary between 26 and 29 days, abstinence is required from days 8 through 18 of each cycle. The greater the variance in cycle length, the longer abstinence lasts.

Methods that incorporate better predictors of ovulation are more effective but require training and effort:

- **Basal body temperature:** Women measure their temperature with a basal temperature thermometer daily for several minutes before they arise in the morning. Temperature increases by about 0.5° C, usually to > 37° C, after ovulation. Abstinence is required from the onset of menses until > 72 h after the temperature increase.

- **Cervical mucus:** Cervical mucus may be absent for a few days after menses. After cervical mucus appears, it tends to be cloudy, thick, and inelastic. A change in cervical mucus indicates ovulation more accurately than body temperature. The amount of mucus increases, and the mucus becomes thinner, clearer, and more elastic (stretching between the fingers) than usual. It resembles raw egg whites. Coitus is avoided completely during menses (because mucus cannot be checked). Coitus is permitted during the days when mucus is completely absent, but during these days, coitus is restricted to every other day (so that semen is not confused with mucus). Coitus is avoided from the time mucus first appears after menses until 4 days after the amount peaks. Coitus is permitted without restriction from 4 days after the amount of mucus peaks until menses begin.

- **Symptothermal method:** This method relies on the combination of increase in temperature,

appearance of cervical mucus, and calendar rhythm method. Intercourse is avoided from the 1st day requiring abstinence according to the calendar method until 3 days after the amount of cervical mucus decreases and the temperature increases.

[Fig. 257-1. Natural family planning methods.]

The 1-yr pregnancy rates with of any of these methods is 25% with typical use. With perfect use, rates are 9% for the calendar method, 2% for the temperature method, 3% with the mucus method, and 2% with the symptothermal method. The symptothermal method is considered the most effective method of periodic abstinence because achieving perfect use is easier.

Progestin Injections

Depot medroxyprogesterone acetate (DMPA) is a long-acting injectable formulation of medroxyprogesterone acetate. Pregnancy rates in the 1st yr are 0.3% with perfect use and are slightly higher with typical use (ie, delays between injections).

The injection must be given during the first 5 days of the menstrual cycle to prevent ovulation. The dose is 150 mg q 3 mo by deep gluteal or deltoid IM injection. The injection site is not massaged, ensuring slow absorption. Alternatively, a formulation can be injected sc; the dose is 104 mg sc q 3 mo. Levels are usually effective starting 24 h after IM or sc injection and are maintained up to 4 mo or more. If the interval between injections is > 13 wk, a negative pregnancy test is required before giving the next injection.

The most common adverse effect is disruption of the menstrual cycle. In the 3 mo after the first DMPA injection, about 30% of women have amenorrhea. Another 30% have spotting or irregular bleeding (usually light) > 11 days/mo; anemia does not usually result. As use continues, bleeding and menses tend to decrease; after 2 yr, about 70% of women receiving DMPA have amenorrhea. Because DMPA has a long duration of action, ovulation may be delayed for up to 1 yr after the last injection; after ovulation occurs, fertility is usually rapidly restored.

Women typically gain 1.5 to 4 kg during the 1st yr of DMPA use and continue to gain weight thereafter. Usually, women who want to take DMPA are advised to decrease caloric intake and increase energy expenditure. Headache is a common reason for stopping DMPA, but severity tends to decrease over time. Most women using DMPA do not have headaches, and preexisting tension headaches and migraines usually do not worsen. Mild, reversible, clinically insignificant deterioration of glucose tolerance and lipid profile may occur. There is no evidence of increased fracture risk. Adolescents and young women using DMPA should consume 1500 mg of Ca and 400 units of vitamin D daily; supplements should be taken if necessary. Unlike OCs, DMPA does not contribute to hypertension or thromboembolism.

DMPA does not appear to increase risk of breast, ovarian, or invasive cervical cancer. DMPA reduces risk of endometrial cancer and pelvic inflammatory disease. By stimulating erythropoiesis, DMPA reduces risk of iron deficiency anemia and, for women with sickle cell disease, risks of anemia and crises.

Transdermal and Intravaginal Steroid Contraceptives

A 20-cm^2 transdermal patch can deliver 150 µg of the progestin norelgestromin (the active metabolite of norgestimate) and 20 µg of ethinyl estradiol daily into the systemic circulation for 7 days; then, the patch is removed, and a new patch is applied to a different area of the skin. Steroid blood levels are much more constant than with OCs. After 3 patches, no patch is used for the 4th wk to allow withdrawal bleeding. Overall contraceptive efficacy, incidence of bleeding, and adverse effects are similar to those of OCs, but adherence may be better. The patch may be less effective in overweight women.

Use of a flexible vaginal ring containing ethinyl estradiol and the progestin etonogestrel, which are absorbed through the vaginal epithelium, provides relatively constant blood levels. The ring is 58 mm in diameter and 4 mm thick. It is inserted and removed by the woman; it is left in place for 3 wk, then removed for 1 wk to allow for withdrawal bleeding. Bleeding with the ring in place is uncommon. Contraceptive efficacy and adverse effects are similar to those of OCs, and adherence may be better.

Subdermal Implants

Progestin subdermal implants are available as a new, single-rod implant that can be inserted through a trocar without a skin incision. The implant releases etonogestrel at a rate of 50 µg/day. The implant provides effective contraception for 3 yr.

The most common adverse effects are similar to those of other progestins (uterine bleeding, amenorrhea, headache). Whether weight gain results is unclear. Removing the implant requires a skin incision. After implant removal, ovarian activity normalizes immediately.

Intrauterine Devices

Only about 1 million women in the US use intrauterine devices (IUDs), despite their advantages over OCs:

• IUDs are highly effective.

• IUDs have no systemic effects.

• Only one contraceptive decision every 5 or 10 yr is required.

IUDs induce endometrial inflammation; this inflammation attracts neutrophils, which are toxic to sperm and prevent fertilization of the ovum.

In the US, 2 types are used: levonorgestrel-releasing IUD (effective for 5 yr; cumulative pregnancy rate of 0.5%) and copper-bearing T380A (effective for ≥ 10 yr; cumulative pregnancy rate of < 2%). IUDs are inserted high in the fundus at any time during the cycle. Contraindications include pregnancy and untreated cervicitis or vaginitis. After IUD removal, fertility rate returns to normal after about 1 yr.

Adverse effects: During the 1st yr, 10 to 15% of women stop use; fewer stop thereafter. Of those who stop, > 50% do so because of bleeding and pain, which occur in about 15% of users during the 1st yr and 7% during the 2nd yr. Bleeding stops completely within 1 yr in 20% of women using the levonorgestrel-releasing IUD.

Spontaneous expulsion occurs in about 5% during the 1st yr (usually within the first few weeks) and in fewer women thereafter. Expulsion is more common among younger women and among nulligravidas. If another IUD is inserted, it is usually retained. Because about 20% of expulsions are unnoticed, a plastic string is attached to the IUD so that the user can check for its presence periodically.

Uterine perforation occurs in about 1/1000. Perforation occurs only during IUD insertion. Sometimes only the distal portion of the IUD penetrates; then over the next few months, uterine contractions force the IUD into the peritoneal cavity. Perforation is considered if a woman cannot feel the string but did not notice expulsion. If the string is not visible during pelvic examination, the uterine cavity is probed with a sound or biopsy instrument unless pregnancy is suspected. If the IUD cannot be felt, ultrasonography is done. If the IUD is not seen, an abdominal x-ray is taken to exclude an intraperitoneal location. Intraperitoneal IUDs may cause intestinal adhesions. IUDs that have perforated the uterus are removed, often via laparoscopy.

Occasionally, salpingitis develops during the 1st mo because of contamination during insertion; risk is not high enough to warrant routine antibiotic prophylaxis. IUD strings do not provide access for bacteria. Pelvic infections that occur after 1 mo are sexually transmitted; unless severe, they can be treated with the IUD in place.

Pregnancies that occur with an IUD in place are usually intrauterine (95%). About 5% are an ectopic pregnancy (see p. 2663), which must be ruled out in any woman who becomes pregnant with an IUD in place. With intrauterine pregnancies, there is a high risk of spontaneous abortion (about 55%) and preterm delivery but not of congenital defects, fetal death, or pelvic infection during pregnancy. Risk of abortion decreases to 20% if the IUD is removed.

IUDs do not increase and may decrease risk of endometrial adenocarcinoma and cervical cancer.

Emergency Contraception

• Levonorgestrel 0.75 mg po in 2 doses 12 h apart

• Levonorgestrel 1.5 mg po once

Emergency contraception is use of contraceptive hormones within 72 h of unprotected coitus. Emergency contraception can decrease the pregnancy rate for a single act of unprotected coitus at midcycle, which is typically about 8%. The most commonly used regimen is 2 doses of levonorgestrel 0.75 mg; one is taken within 72 h of unprotected intercourse, followed by one 12 h later. If taken within 72 h of one act of unprotected intercourse, levonorgestrel reduces risk of pregnancy by 89%, but if taken within 24 h, it reduces risk by 95%. Taking levonorgestrel 1.5 mg once seems to be equally effective. Another regimen —2 tablets, each containing ethinyl estradiol 50 µg and levonorgestrel 0.25 mg, followed by 2 more tablets 12 h later—has been used, but it is slightly less effective. The high estrogen dose often causes nausea and may cause vomiting.

Inserting a copper IUD within 10 days of coitus is more expensive but more effective than hormone tablets; pregnancy rate is 0.1%.

Sterilization

In the US, one third of couples attempting to prevent pregnancy, particularly if the woman is > 30, choose sterilization with vasectomy or tubal ligation. Sterilization should be assumed to be permanent. However, if pregnancy is desired, reanastomosis may restore fertility in 45 to 60% of men after vasectomy and in 50 to 80% of women after tubal ligation. Also, in vitro fertilization may be used successfully.

Vasectomy: The vasa deferentia are cut, and the cut ends are ligated or fulgurated. Vasectomy can be done in about 20 min; a local anesthetic is used. Sterility requires about 15 to 20 ejaculations after the operation and should be documented by 2 sperm-free ejaculates. Complications of vasectomy include hematoma (≤ 5%), sperm granulomas (inflammatory responses to sperm leakage), and spontaneous reanastomosis, which usually occurs shortly after the procedure.

Tubal ligation: The fallopian tubes are cut and a segment is excised, or the tubes are closed by ligation, fulguration, or various mechanical devices (plastic bands, spring-loaded clips). Sterilization using mechanical devices causes less tissue damage and thus may be more reversible. Via laparoscopy, tubal ligation can be done using a small periumbilical incision and a general or local anesthetic. Tubal ligation is often done immediately after or the day after delivery.

Another method is to occlude the lumen of the tubes by inserting microinserts with inner coils via hysteroscopy. This procedure does not require incisions or cutting, clipping, or burning of the tubes. After microinserts are placed, tubal occlusion (and thus sterility) is confirmed by hysterosalpingography done about 3 mo after the procedure.

Pregnancy rates after tubal ligation are < 0.5% during the 1st yr and 1.5 to 2% after 10 yr. Rates are lower if the tube has been partly excised.

Adverse effects are uncommon: death in a few patients per 100,000, hemorrhage or intestinal injuries in about 0.5%, and other complications (eg, infarction, failure of occlusion) in up to about 5%. About 30% of pregnancies that occur after tubal ligation are ectopic.

Induced Abortion

Induced abortion is legally available to about two thirds of women worldwide. In the US, abortion is legal during the 1st trimester (≤ 12 wk); after that, legality varies by state. In the US, about half of pregnancies are unintended; about 40% of these are terminated by elective abortion, with 90% during the 1st

trimester.

Common methods of inducing abortion are instrumental evacuation through the vagina and medical induction (stimulation of uterine contractions). Uterine surgery (hysterotomy or hysterectomy) is a last resort, which is usually avoided because mortality rates are higher. Hysterotomy also results in a uterine scar, which may rupture in subsequent pregnancies.

Typically, gestational age, which usually dictates abortion method, is established by ultrasonography. Rh_0(D) immune globulin, when indicated, is given to women with Rh-negative blood to prevent sensitization. First-trimester abortions often require only local anesthesia; later abortions sometimes require general anesthesia.

Instrumental evacuation: Instrumental evacuation is used in 97% of all abortions.

At 4 to 6 wk, the uterus can be curetted gently via a cannula attached to a vacuum source. Because failure to terminate the pregnancy is more common in early than in later weeks, instrumental evacuation should usually not be done until a gestational sac is seen. Before this time, abortion is usually induced medically.

At 7 to 12 wk, dilation and curettage (D & C) is usually used; large-diameter suction cannulas are usually required, so the cervix must be dilated. Typically, progressively increasing sizes of tapered dilators are used. Cervical damage due to dilation can be prevented or minimized by using laminaria (dried seaweed stems) or other osmotic dilators, which can be inserted into the cervix and left for ≥ 4 h (usually overnight). They dilate the cervix by expanding or stimulating prostaglandin release.

At 12 to 18 wk, dilation and evacuation (D & E) is usually used. The cervix is dilated, usually with laminaria or other osmotic dilators and dilating instruments. Forceps are used to dismember and remove the fetus, and a suction cannula is used to aspirate the amniotic fluid, placenta, and fetal debris. D & E requires more skill than do other methods of instrumental evacuation.

Medical induction: Medical induction can be done for pregnancies of < 7 to 9 wk or > 15 wk.

For pregnancies of up to 9 wk, mifepristone (RU 486) 200 to 600 mg po, a progesterone-receptor blocker, followed by misoprostol 400 µg po or 800 µg intravaginally, is about 95% effective in terminating pregnancies.

After 15 wk, prostaglandins are used. They include vaginal prostaglandin E_2(dinoprostone) suppositories, intravaginal prostaglandin E_1 analog (misoprostol) tablets, and IM injections of prostaglandin $F_{2\alpha}$ (dinoprost tromethamine). Using two 200-µg intravaginal tablets of misoprostol q 6 h is nearly 100% successful within 48 h of treatment.

Adverse effects of prostaglandins include nausea, vomiting, diarrhea, hyperthermia, facial flushing, vasovagal symptoms, bronchospasm, and decreased seizure threshold. In women with a severe kidney or liver disorder, activation of the prostaglandin may be decreased, so dose should be increased.

Complications

Complication rates with abortion (serious complications in < 1%; mortality in < 1 in 100,000) are higher than those with contraception, although the rates have decreased in the last few decades. Complication rates increase as gestational age increases.

Serious early complications include perforation of the uterus (0.1%) or, less often, of the intestine or another organ by an instrument. Major hemorrhage (0.06%) may result from trauma or an atonic uterus. Laceration of the cervix (0.1 to 1%) ranges from superficial tenaculum tears to cervicovaginal tears, rarely with fistulas. General or local anesthesia rarely causes serious complications.

The most common delayed complications include bleeding and significant infection (0.1 to 2%), which

usually occur simultaneously because placental fragments are retained, and thrombophlebitis. If bleeding occurs or infection is suspected, pelvic ultrasonography is done; retained placental fragments may be visible on ultrasound scans. Mild inflammation is expected, but if infection is moderate or severe, peritonitis or sepsis may occur. Sterility may result from synechiae in the endometrial cavity or tubal fibrosis due to infection. Forceful dilation of the cervix in more advanced pregnancies may contribute to incompetent cervix. Elective abortion probably does not increase risks for the fetus or woman during subsequent pregnancies.

Psychologic complications do not typically occur but may occur in women who had psychologic symptoms before pregnancy, who terminated a desired pregnancy for medical reasons (maternal or fetal), who have considerable ambivalence about the abortion, who are adolescents, who had a late abortion, or who obtained an abortion illegally.

Chapter 258. Infertility

Introduction

Infertility is inability of a couple to conceive after 1 yr of unprotected intercourse.

Frequent, unprotected intercourse results in conception for 50% of couples within 3 mo, for 75% within 6 mo, and for 90% within 1 yr. Infertility can be caused by the following:

• Sperm disorders (35% of couples)

• Decreased ovarian reserve or ovulatory dysfunction (20%)

• Tubal dysfunction and pelvic lesions (30%)

• Abnormal cervical mucus (≤ 5%)

• Unidentified factors (10%)

Inability to conceive often leads to feelings of frustration, anger, guilt, resentment, and inadequacy.

Couples wishing to conceive are encouraged to have frequent intercourse for the few days when ovulation is most likely, probably midway between menstrual cycles. Measuring morning basal body temperature (BBT) daily can help determine when ovulation is occurring in women with regular menstrual cycles. A decrease suggests impending ovulation; an increase of ≥ 0.5°C suggests ovulation has just occurred. Commercially available luteinizing hormone (LH) prediction test kits, which identify the midcycle LH surge, can also help determine when ovulation occurs and are less disruptive than measuring BBT. Use of caffeine and tobacco, which can impair fertility, is discouraged.

If these measures do not result in pregnancy, a diagnostic evaluation is done. It begins with history, examination, and counseling of both partners. Men are evaluated for sperm disorders, and women for ovulatory and tubal dysfunction and pelvic lesions.

Support groups for couples (eg, American Fertility Association, RESOLVE) may help. If the likelihood of conceiving is low (usually after 2 yr of treatment), the clinician should mention adoption.

Sperm Disorders

Sperm disorders include defects in quality or quantity of sperm produced and defects in sperm emission. Diagnosis is by semen and genetic testing. The most effective treatment is usually in vitro fertilization via intracytoplasmic sperm injection.

Pathophysiology

Spermatogenesis occurs continuously. Each germ cell requires about 72 to 74 days to mature fully. Spermatogenesis is most efficient at 34° C. Within the seminiferous tubules, Sertoli cells regulate maturation, and Leydig cells produce the necessary testosterone. Fructose is normally produced in the seminal vesicles and secreted through the ejaculatory ducts. Sperm disorders may result in an inadequate quantity of sperm—too few (oligospermia) or none (azoospermia)—or defects in sperm quality, such as abnormal motility or structure.

Etiology

Impaired spermatogenesis: Spermatogenesis can be impaired by heat, disorders (GU, endocrine, or genetic), drugs, or toxins (see Table 258-1), resulting in an inadequate quantity or defective quality of sperm.

Impaired sperm emission: Sperm emission may be impaired because of retrograde ejaculation into the

bladder, which is often due to

• Diabetes

• Neurologic dysfunction

• Retroperitoneal dissection (eg, for Hodgkin lymphoma)

• Prostatectomy

Sperm emission can also be impaired by

• Obstruction of the vas deferens

• Congenital absence of both vasa deferentia or epididymides, often in men with mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene

• Absence of both seminal vesicles

Almost all men with symptomatic cystic fibrosis have congenital bilateral absence of the vas deferens.

Other causes: Men with microdeletions affecting the Y chromosome can develop oligospermia via various mechanisms, depending on the specific deletion. Another rare mechanism of infertility is destruction or inactivation of sperm by sperm antibodies, which are usually produced by the man.

Diagnosis

• Semen analysis

• Sometimes genetic testing

When couples are infertile, the man should always be evaluated for sperm disorders. History and physical examination focus on

[**Table 258-1.** Causes of Impaired Spermatogenesis]

potential causes (eg, GU disorders). Normal volume of each testis is 20 to 25 mL. Semen analysis should be done. If oligospermia or azoospermia is detected, genetic testing, including standard karyotyping, PCR of tagged chromosomal sites (to detect microdeletions affecting the Y chromosome), and evaluation for mutations of the *CFTR* gene, should be done. Before a man with a *CFTR* gene mutation and his partner attempt to conceive, the partner should also be tested to exclude cystic fibrosis carrier status.

Before semen analysis, the man is typically asked to refrain from ejaculation for 2 to 3 days. However, recent data indicate that daily ejaculation does not reduce the sperm count in men unless there is a problem. Because sperm count varies, testing requires ≥ 2 specimens obtained ≥ 1 wk apart; each specimen is obtained by masturbation into a glass jar, preferably at the laboratory site. If this method is difficult, the man can use a condom at home; the condom must be free of lubricants and chemicals. After being at room temperature for 20 to 30 min, the ejaculate is evaluated (see Table 258-2). Additional computer-assisted measures of sperm motility (eg, linear sperm velocity) are available; however, their correlation with fertility is unclear.

If a man without hypogonadism or congenital bilateral absence of the vas deferens has an ejaculate volume < 1 mL, urine is analyzed for sperm after ejaculation. A disproportionately large number of sperm in urine vs semen suggests retrograde ejaculation.

Endocrine evaluation is warranted if the semen analysis is abnormal and especially if the sperm concentration is < 10 million/mL.

[Table 258-2. Semen Analysis]

Minimum initial testing should include serum follicle-stimulating hormone (FSH) and testosterone levels. If testosterone is low, serum luteinizing hormone (LH) and prolactin should also be measured. Men with abnormal spermatogenesis often have normal FSH levels, but any increase in FSH is a clear indication of abnormal spermatogenesis. Elevations in prolactin require evaluation for a tumor involving or impinging on the anterior pituitary or may indicate ingestion of various prescription or recreational drugs.

Specialized sperm tests, available at some infertility centers, may be considered if routine tests of both partners do not explain infertility and in vitro fertilization or gamete intrafallopian tube transfer is being contemplated. The immunobead test detects sperm antibodies, and the hypo-osmotic swelling test measures the structural integrity of sperm plasma membranes. The hemizona assay and sperm penetration assay determine the ability of sperm to fertilize the egg in vitro. The usefulness of these specialized tests is controversial.

If necessary, testicular biopsy can distinguish between obstructive and nonobstructive azoospermia.

Treatment

• Clomiphene

• Assisted reproductive techniques if clomiphene is ineffective

Underlying GU disorders are treated. For men with sperm counts of 10 to 20 million/mL and no endocrine disorder, clomiphene citrate (25 to 50 mg po once/day taken 25 days/mo for 3 to 4 mo) can be tried. Clomiphene, an anti-estrogen, may stimulate sperm production and increase sperm counts. However, whether it improves sperm motility or morphology is unclear, and it has not been proved to increase fertility.

If sperm count is < 10 million/mL or clomiphene is unsuccessful in men with normal sperm motility, the most effective treatment is usually in vitro fertilization with injection of a single sperm into a single egg (intracytoplasmic sperm injection). Alternatively, intrauterine insemination using washed semen samples and timed to coincide with ovulation is sometimes tried. If pregnancy is going to occur, it usually occurs by the 6th treatment cycle.

Decreased number and viability of sperm may not preclude pregnancy. In such cases, fertility may be enhanced by controlled ovarian hyperstimulation of the woman plus artificial insemination or assisted reproductive techniques (eg, in vitro fertilization, intracytoplasmic sperm injection).

If the male partner cannot produce enough fertile sperm, a couple may consider insemination using donor sperm. Risk of AIDS and other sexually transmitted diseases is minimized by freezing donor sperm for ≥ 6 mo, after which donors are retested for infection before insemination proceeds.

Abnormal Cervical Mucus

Abnormal cervical mucus may impair fertility by inhibiting penetration or increasing destruction of sperm.

Normally, cervical mucus is stimulated to change from thick and impenetrable to thin and stretchable by an increase in estradiol levels during the follicular phase of the menstrual cycle. Abnormal cervical mucus may

• Remain impenetrable to sperm around the time of ovulation

• Promote sperm destruction by facilitating influx of vaginal bacteria (eg, due to cervicitis)

• Contain antibodies to sperm (occasionally)

Abnormal mucus rarely impairs fertility significantly, except in women with chronic cervicitis or cervical stenosis due to prior treatment for cervical intraepithelial neoplasia.

Diagnosis

Women are examined to check for cervicitis and cervical stenosis. Unless they have one of these disorders, postcoital testing of cervical mucus to determine whether viable sperm are present (which used to be routine during infertility evaluation) is usually unnecessary. Usefulness of postcoital testing has not been documented.

Treatment

Treatment may include intrauterine insemination or drugs to thin the mucus (eg, guaifenesin). Neither treatment has been proved effective.

Decreased Ovarian Reserve

Decreased ovarian reserve is a decrease in the quantity or quality of oocytes, leading to impaired fertility.

Ovarian reserve may begin to decrease at age 30 or even earlier and decreases rapidly after age 40. Ovarian lesions also decrease reserve. Although older age is a risk factor for decreased ovarian reserve, age and decreased ovarian reserve are each independent predictors of infertility and thus of a poorer response to fertility treatment.

Diagnosis

• FSH and estradiol levels, sometimes after stimulation with clomiphene

Testing for decreased ovarian reserve is considered for women who are ≥ 35, who have had ovarian surgery, or who have responded poorly to treatments such as ovarian stimulation with exogenous gonadotropins. Follicle-stimulating hormone (FSH) levels > 10 mIU/mL or estradiol levels of < 80 pg/mL on day 3 of the menstrual cycle suggest the diagnosis. Diagnosis can also be made by giving the woman clomiphene 100 mg po once/day on days 5 to 9 of the menstrual cycle (clomiphene citrate challenge test). A dramatic increase in FSH and estradiol levels from day 3 to day 10 of the cycle indicates decreased reserve.

Treatment

If women are > 42 or ovarian reserve is decreased, assisted reproduction using donor oocytes may be necessary.

Ovulatory Dysfunction

Ovulatory dysfunction is abnormal, irregular, or absent ovulation. Menses are often irregular or absent. Diagnosis is often possible by history or can be confirmed by measurement of hormone levels or serial pelvic ultrasonography. Treatment is usually induction of ovulation with clomiphene or other drugs.

Etiology

Chronic ovulatory dysfunction in premenopausal women is most commonly caused by polycystic ovary syndrome (PCOS—see p. 2514) but has many other causes, including hyperprolactinemia, hypothalamic dysfunction (eg, hypothalamic amenorrhea), and other disorders that cause anovulatory amenorrhea (see Table 246-1 on p. 2502).

Symptoms and Signs

Ovulatory dysfunction is suspected if menses are absent, irregular, or not preceded by symptoms, such as breast tenderness, lower abdominal bloating, or moodiness.

Diagnosis

• Basal body temperature monitoring

• Measurement of urinary or serum hormones or ultrasonography

Measuring morning body temperature daily can help determine whether and when ovulation is occurring (see p. 2587). However, this method is often inaccurate and has an error margin of 2 days. More accurate methods include home testing kits, which detect an increase in urinary luteinizing hormone (LH) excretion 24 to 36 h before ovulation (requiring daily testing for several days around midcycle, usually beginning about or after cycle day 9), and pelvic ultrasonography, which is used to monitor ovarian follicle diameter and rupture (and should begin in the late follicular phase as well). Also, serum progesterone levels of ≥ 3 ng/mL (≥ 9.75 nmol/L) or elevated levels of one of its urinary metabolites, pregnanediol glucuronide (measured, if possible, 1 wk before onset of the next menstrual period), indicate that ovulation has occurred.

Intermittent or absent ovulation should prompt evaluation for disorders of the pituitary, hypothalamus, or ovaries (eg, PCOS).

Treatment

• Clomiphene

• Possibly metformin if body mass index is ≥ 35

• Gonadotropins if clomiphene is ineffective

Ovulation can usually be induced with drugs. Commonly, chronic anovulation that is not due to hyperprolactinemia is initially treated with the antiestrogen clomiphene citrate. Clomiphene is most effective when the cause is PCOS. First, uterine bleeding, unless it has occurred spontaneously, is induced with medroxyprogesterone acetate 5 to 10 mg po once/day for 5 to 10 days. Clomiphene 50 mg po once/day is started between the 3rd and 5th day after bleeding begins; it is continued for 5 days. Ovulation usually occurs 5 to 10 days (mean 7 days) after the last day of clomiphene; if ovulation occurs, menses follows within 35 days of the induced bleeding episode. The daily dose can be increased by up to 50 mg every 2 cycles to a maximum of 200 mg/dose as needed to induce ovulation. Treatment is continued as needed for up to 4 ovulatory cycles. Ovulation occurs in 75 to 80% of women treated with clomiphene, but the pregnancy rate is only about 40 to 50%.

Adverse effects of clomiphene include vasomotor flushes (10%), abdominal distention (6%), breast tenderness (2%), nausea (3%), visual symptoms (1 to 2%), and headaches (1 to 2%). Multifetal pregnancy (primarily twins) occurs in about 5%, and ovarian hyperstimulation syndrome occurs in ≤ 1%. Ovarian cysts are common. A previously suggested association between clomiphene taken for > 12 cycles and ovarian cancer has not been confirmed.

For women with PCOS, metformin (750 to 1000 mg po bid) may be a useful adjunct in inducing ovulation, particularly if the patient is insulin resistant, as many patients with PCOS are. However, clomiphene alone is more effective than metformin and is just as effective as metformin and clomiphene together. Metformin may be useful for women with a body mass index > 35 and should be considered for women with PCOS and glucose intolerance.

For all women with ovulatory dysfunction that does not respond to clomiphene, human gonadotropins (ie, preparations that contain purified or recombinant follicle-stimulating hormone [FSH] and variable amounts of LH) can be used. Several IM and sc preparations with similar efficacy are available; they typically contain 75 IU of FSH activity with or without LH activity. They are usually given once/day, beginning on the 3rd to 5th day after induced or spontaneous bleeding; ideally, they stimulate maturation of 1 to 3

follicles, determined ultrasonographically, within 7 to 14 days. Ovulation is induced with human chorionic gonadotropin (hCG) 5,000 to 10,000 IU IM after follicle maturation; criteria for induction may vary, but typically, at least one follicle should be > 16 mm in diameter. However, ovulation is not induced if women are at high risk of multifetal pregnancy or ovarian hyperstimulation syndrome. Risk factors for these problems include presence of > 3 follicles > 16 mm in diameter and preovulatory serum estradiol levels > 1500 pg/mL (or possibly > 1000 pg/mL) in women with several small ovarian follicles. When exogenous gonadotropins are used appropriately, > 95% of women treated with them ovulate, but the pregnancy rate is only 50 to 75%.

After gonadotropin therapy, 10 to 30% of successful pregnancies are multiple. Ovarian hyperstimulation syndrome occurs in 10 to 20% of patients; ovaries can become massively enlarged, and intravascular fluid volume shifts into the peritoneal space, causing potentially life-threatening ascites and hypovolemia.

Underlying disorders (eg, hyperprolactinemia—see p. 772) are treated. If the cause is hypothalamic amenorrhea, gonadorelin acetate, a synthetic gonadotropin-releasing hormone (GnRH) given as a pulsatile IV infusion, can induce ovulation. Doses of 2.5 to 5.0 µg boluses (pulse doses) regularly q 60 to 90 min are most effective. Gonadorelin acetate is unlikely to cause multifetal pregnancy. Because gonadorelin is no longer available in the US, clomiphene citrate is the first drug used to treat hypothalamic amenorrhea, followed by exogenous gonadotropins, if ovulation induction is unsuccessful.

Tubal Dysfunction and Pelvic Lesions

Tubal dysfunction is fallopian tube obstruction or epithelial dysfunction that impairs zygote motility; pelvic lesions are structural abnormalities that can impede fertilization or implantation.

Etiology

Tubal dysfunction can result from

- Pelvic inflammatory disease
- Use of an intrauterine device (a rare cause of pelvic infection)
- Ruptured appendix
- Lower abdominal surgery leading to pelvic adhesions
- Inflammatory disorders (eg, TB)
- Ectopic pregnancy

Pelvic lesions that can impede fertility include

- Intrauterine adhesions (Asherman's syndrome)
- Fibroids obstructing the fallopian tubes or distorting the uterine cavity
- Certain malformations
- Pelvic adhesions

Endometriosis can cause tubal, uterine, or other lesions that impair fertility.

Diagnosis

- Hysterosalpingography
- Sometimes laparoscopy or sonohysterography

All infertility evaluations include assessment of the fallopian tubes. Most often, hysterosalpingography (fluoroscopic imaging of the uterus and fallopian tubes after injection of a radiopaque agent into the uterus) is done 2 to 5 days after cessation of menstrual flow. Hysterosalpingography rarely indicates tubal patency falsely but indicates tubal obstruction falsely in about 15% of cases. This test can also detect some pelvic and intrauterine lesions. For unexplained reasons, fertility appears to be enhanced after hysterosalpingography if the test result is normal. Thus, if hysterosalpingography results are normal, additional diagnostic tests of tubal function can be delayed for several cycles.

Tubal lesions can be further evaluated with laparoscopy. Intrauterine and tubal lesions can be detected or further evaluated by sonohysterography (injection of isotonic fluid through the cervix into the uterus during ultrasonography) or hysteroscopy. Diagnosis and treatment are often done simultaneously during laparoscopy or hysteroscopy.

Treatment

• Laparoscopy or hysteroscopy to restore patency

During laparoscopy, pelvic adhesions can be lysed, or pelvic endometriosis can be fulgurated or ablated by laser. During hysteroscopy, adhesions can be lysed, and submucous fibroids and intrauterine polyps can be removed. Success rates are low, so assisted reproductive techniques are often necessary.

Unexplained Infertility

Infertility is considered unexplained when semen in the man and ovulation and fallopian tubes in the woman are normal.

When infertility remains unexplained after initial evaluation, empiric treatments are instituted.

Controlled ovarian hyperstimulation (COH) can be used to make pregnancy more likely and to achieve it sooner. This procedure stimulates development of multiple follicles; the goal is to induce ovulation of > 1 oocyte (superovulation). However, COH may result in multifetal pregnancy, which has increased risks and morbidity. COH involves the following:

• Giving clomiphene, with human chorionic gonadotropin (hCG) to trigger ovulation, for up to 3 menstrual cycles

• Intrauterine insemination within 2 days of hCG administration

• If pregnancy does not result, other assisted reproductive techniques

Alternatively, before trying assisted reproduction, some clinicians use gonadotropins (preparations that contain purified or recombinant follicle-stimulating hormone and variable amounts of luteinizing hormone), followed by hCG as for ovulatory dysfunction, then intrauterine insemination within 2 days of hCG administration. A progestin may be needed during the luteal phase to maximize the chance of implantation. Gonadotropin dosage depends on the patient's age and ovarian reserve.

The pregnancy rate is the same (about 65%) whether in vitro fertilization is used immediately after unsuccessful treatment with clomiphene plus hCG or whether gonadotropins with intrauterine insemination are used next before trying in vitro fertilization. However, when in vitro fertilization is done immediately after treatment with clomiphene plus hCG, women become pregnant more quickly.

Assisted Reproductive Techniques

Assisted reproductive techniques (ARTs) involve manipulation of sperm and ova in vitro with the goal of producing an embryo.

ARTs may result in multifetal pregnancy, but risk is less than that with controlled ovarian hyperstimulation.

If risk of genetic defects is high, the embryo can often be tested for defects before transfer and implantation (preimplantation genetic diagnosis).

In women < 35, > 43% of ART cycles result in pregnancy, and almost 87% of the pregnancies end in live births in the US (2005 data). The pregnancy rate decreases with increasing age; for women aged 41 to 42, the pregnancy rate is 17.5%, and only about 60% of these pregnancies end in live births. Use of donor oocytes is usually recommended for women > 42.

In vitro fertilization (IVF): IVF can be used to treat infertility due to oligospermia, sperm antibodies, tubal dysfunction, or endometriosis as well as unexplained infertility. The procedure involves the following:

- **Controlled ovarian hyperstimulation:** Clomiphene plus gonadotropins or gonadotropins alone can be used. A gonadotropin-releasing hormone (GnRH) agonist or antagonist is often given to prevent premature ovulation. After sufficient follicular growth, human chorionic gonadotropin (hCG) is given to induce final follicular maturation and ovulation.

- **Oocyte retrieval:** About 34 h after hCG is given, oocytes are retrieved by direct needle puncture of the follicle, usually transvaginally with ultrasound guidance or less commonly laparoscopically.

- **Fertilization:** The oocytes are inseminated in vitro. The semen sample is typically washed several times with tissue culture medium and concentrated for motile sperm, which are then added.

- **Embryo culture:** After sperm are added, the oocytes are cultured for about 2 to 5 days.

- **Embryo transfer:** Only 1 or a few of the resulting embryos are transferred to the uterine cavity, minimizing the chance of a multi-fetal pregnancy, the greatest risk of IVF. The number of embryos transferred is determined by the woman's age and likelihood of response to IVF. Other embryos may be frozen in liquid nitrogen for transfer in a subsequent cycle.

Gamete intrafallopian tube transfer (GIFT): GIFT is an alternative to IVF but is used infrequently, typically for women with unexplained infertility or with normal tubal function plus endometriosis. Multiple oocytes and sperm are obtained as for IVF but are transferred—transvaginally with ultrasound guidance or laparoscopically—to the distal fallopian tubes, where fertilization occurs. Live birth rates per cycle are about 25 to 35% at most infertility centers.

Intracytoplasmic sperm injection: This technique is useful when other techniques are not successful or are unlikely to be so or when a severe sperm disorder is present. Oocytes are obtained as for IVF. A single sperm is injected into each oocyte to avoid fertilization by abnormal sperm. The embryo is then cultured and transferred as for IVF. In 2005, about 60% of all ART cycles in the US involved intracytoplasmic sperm injection.

Other techniques: A combination of IVF and GIFT, zygote intrafallopian tube transfer, use of donor oocytes, and transfer of frozen embryos to a surrogate mother are sometimes used. Some of these techniques raise moral and ethical issues (eg, rightful parentage in surrogate motherhood, selective reduction of the number of implanted embryos if multi-fetal pregnancy results).

Chapter 259. Prenatal Genetic Counseling and Evaluation

Introduction

(See also Ch. 341)

Prenatal genetic counseling is provided for all prospective parents, ideally before conception, to assess risk factors for congenital disorders. (Certain precautions to help prevent birth defects (eg, avoiding teratogens, taking supplemental folate—see p. 2608.) are recommended for all women who are planning to become pregnant.) Parents with risk factors are advised about possible outcomes and options for evaluation. If testing identifies a disorder, reproductive options are discussed.

Preconception options include

• Contraception

• Artificial insemination if the man is a carrier

• Oocyte donation if the woman is a carrier

Postconception options include

• Pregnancy termination

• Sometimes treatment (eg, dexamethasone to prevent virilization in a female fetus with 21-hydroxylase deficiency)

Information presented at genetic counseling should be as simple, nondirective, and jargon-free as possible to help anxious couples understand it. Frequent repetition may be necessary. Couples should be given time alone to formulate questions. Couples can be told about information that is available on the Internet (www.modimes.org) for many common problems (eg, advanced maternal age, recurrent spontaneous abortions, previous offspring with neural tube defects, previous offspring with trisomy). Many couples (eg, those with known or suspected risk factors) benefit from referral to genetic specialists for presentation of information and testing options.

Risk factors: Some risk of genetic abnormality exists in all pregnancies. Among live births, incidence is

• 0.5% for numeric or structural chromosomal disorders

• 1% for single-gene (mendelian) disorders

• 1% for multiple-gene (polygenic) disorders

Among stillbirths, rates of abnormalities are higher. Most malformations involving a single organ system (eg, neural tube defects, most congenital heart defects) result from polygenic or multifactorial (ie, also influenced by environmental factors) inheritance.

Risk of having a fetus with a chromosomal disorder is increased for most couples who have had a previous fetus or infant with a chromosomal disorder (recognized or missed), except for a few specific types (eg, 45,X; triploidy; de novo chromosomal rearrangements). Chromosomal disorders are more likely to be present in the following:

• Fetuses that spontaneously abort during the 1st trimester (50 to 60%)

• Fetuses with a major malformation (30%)

• Stillborns (5%)

Rarely, a parent has a chromosomal disorder that increases risk of a chromosomal disorder in the fetus. Asymptomatic parental chromosomal disorders (eg, balanced abnormalities such as certain translocations and inversions) may not be suspected. A balanced parental chromosomal rearrangement should be suspected if couples have had recurrent spontaneous abortions, infertility, or a child with a malformation.

For unclear reasons, risk of a fetal chromosomal disorder increases as maternal age increases. Among live births, the rate is about

- 0.2% at age 20
- 0.5% at age 35
- 1.5% at age 40
- 14% at age 49

Most chromosomal disorders due to older maternal age involve an extra chromosome (trisomy), particularly trisomy 21 (Down syndrome). Paternal age > 50 increases risk of some spontaneous dominant mutations, such as achondroplasia, in offspring.

An autosomal dominant disorder is suspected if there is a family history in more than one generation; autosomal disorders affect males and females equally. If one parent has an autosomal dominant disorder, risk is 50% that the disorder will be transmitted to an offspring.

For an autosomal recessive disorder to be expressed, an offspring must receive a mutant gene for that disorder from both parents. Parents may be heterozygous (carriers) and, if so, are usually clinically normal. If both parents are carriers, offspring (male or female) are at a 25% risk of being homozygous for the mutant gene and thus affected, 50% are likely to be heterozygous, and 25% are likely to be genetically normal. If only siblings and no other relatives are affected, an autosomal recessive disorder should be suspected. Likelihood that both parents carry the same autosomal recessive trait is increased if they are consanguineous.

Because females have 2 X chromosomes and males have only one, X-linked recessive disorders are expressed in all males who carry the mutation. Such disorders are usually transmitted through clinically normal, heterozygous (carrier) females. Thus, for each son of a carrier female, risk of having the disorder is 50%, and for each daughter, risk of being a carrier is 50%. Affected males do not transmit the gene to their sons, but they transmit it to all their daughters, who thus are carriers. Unaffected males do not transmit the gene.

Genetic Evaluation

Genetic evaluation is part of routine prenatal care and is ideally done before conception. The extent of genetic evaluation a woman chooses is related to how the woman weighs factors such as

- The probability of a fetal abnormality based on risk factors and the results of any previous testing
- The probability of a complication from invasive fetal testing
- The importance of knowing the results (eg, would the pregnancy be terminated if an abnormality was diagnosed, would not knowing the results cause anxiety)

For these reasons, the decision is individual, and recommendations often cannot be generalized to all women, even those with similar risk.

A screening history is part of the evaluation. The history is summarized as a pedigree (see Fig. 341-1 on p. 3375). Information should include the health status and presence of genetic disorders or carrier status of both parents, of 1st-degree relatives (parents, siblings, offspring), and of 2nd-degree relatives (aunts, uncles, grandparents), as well as ethnic and racial background and consanguineous

matings. Outcomes of previous pregnancies are noted. If genetic disorders are suspected, relevant medical records must be reviewed.

Genetic screening tests are best done before conception. Tests are offered to parents at risk of being asymptomatic carriers for certain common mendelian disorders (see Table 259-1). Diagnostic tests for specific abnormalities are offered to parents when appropriate (see Table 259-2).

Pregnant women should be offered screening using multiple maternal serum markers (α-fetoprotein, β-human chorionic gonadotropin [β-hCG], estriol, inhibin A—see p. 2604) to detect neural tube defects, Down syndrome (and other chromosomal abnormalities), and some other birth defects. This screening is done at 15 to 20 wk of pregnancy.

Fetal genetic diagnostic tests: These tests are usually done via chorionic villus sampling, amniocentesis, or, rarely, percutaneous umbilical blood sampling. They can detect all trisomies, many other chromosomal abnormalities, and several hundred mendelian abnormalities. They are usually recommended if risk of a fetal chromosomal abnormality is increased (see Table 259-2). Fetal genetic diagnostic tests, unlike screening tests, are usually invasive and involve fetal risk. Thus, in the past, these tests were not routinely recommended for women without risk factors. However, because fetal genetic diagnostic tests are now more widely available and safety has improved, offering fetal genetic testing to all pregnant women, regardless of risk, is recommended.

[**Table 259-1.** Genetic Screening for Some Ethnic Groups]

Preimplantation diagnosis is not commonly used because the procedure requires technical expertise and is expensive.

Procedures

All procedures used to diagnose genetic disorders, except ultrasonography, are invasive and involve slight fetal risk. If testing detects a serious abnormality, the pregnancy can be terminated, or in some cases, a disorder can be treated (eg, dexamethasone to prevent virilization in a female fetus with 21-hydroxylase deficiency). Even if neither of these possibilities is anticipated, some women prefer to know of fetal abnormalities before birth.

Ultrasonography

Some experts recommend ultrasonography routinely for all pregnant women. Others use ultrasonography only for specific indications, such as checking for suspected genetic

[**Table 259-2.** Indications for Fetal Genetic Diagnostic Tests]

or obstetric abnormalities or helping interpret abnormal maternal serum marker levels. If ultrasonography is done by skilled operators, sensitivity for major congenital malformations is high. However, some conditions (eg, oligohydramnios, maternal obesity, fetal position) interfere with obtaining optimal images. Ultrasonography is noninvasive and has no known risks to the woman or fetus.

Basic ultrasonography is done to

- Confirm gestational age
- Determine fetal viability
- Detect a multifetal pregnancy
- During the 2nd or 3rd trimester, possibly identify major malformations in the fetal intracranial structures, spine, heart, bladder, kidneys, stomach, thorax, abdominal wall, long bones, and umbilical cord

Although ultrasonography provides only structural information, some structural abnormalities strongly suggest genetic abnormalities. Multiple malformations may suggest a chromosomal disorder.

Targeted ultrasonography, with high-resolution ultrasonography equipment, is available at certain referral centers and provides more detailed images than basic ultrasonography. This test may be indicated for couples with a family history of a congenital malformation (eg, congenital heart defects, cleft lip and palate, pyloric stenosis), particularly one that may be treated effectively before birth (eg, posterior urethral valves with megacystis) or at delivery (eg, diaphragmatic hernia). High-resolution ultrasonography may also be used if maternal serum marker levels are abnormal. High-resolution ultrasonography may allow detection of the following:

• Renal malformations (eg, renal agenesis [Potter's syndrome], polycystic kidney disease)

• Lethal forms of short-limbed skeletal dysplasias (eg, thanatophoric skeletal dysplasia, achondrogenesis)

• Gut malformations (eg, obstruction)

• Diaphragmatic hernia

• Microcephalus

• Hydrocephalus

During the 2nd trimester, identifying structures that are statistically associated with increased risk of fetal chromosomal abnormalities helps refine risk estimate.

Amniocentesis

In amniocentesis, a needle is inserted transabdominally, using ultrasonographic guidance, into the amniotic sac to withdraw amniotic fluid and fetal cells for testing, including measurement of chemical markers (eg, α-fetoprotein, acetylcholinesterase). The safest time for amniocentesis is after 14 wk gestation. Immediately before amniocentesis, ultrasonography is done to assess fetal cardiac motion and determine gestational age, placental position, amniotic fluid location, and fetal number. If the mother has Rh-negative blood and is unsensitized, Rh_0(D) immune globulin 300 µg is given after the procedure to reduce the likelihood of sensitization (see p. 2666).

Amniocentesis has traditionally been offered to pregnant women > 35 because their risk of having an infant with Down syndrome or another chromosomal abnormality is increased. However, with the widespread availability and improved safety of amniocentesis, the American College of Obstetricians and Gynecologists recommends all pregnant women be offered amniocentesis to assess the presence of fetal chromosomal disorders.

Occasionally, the amniotic fluid obtained is bloody. Usually, the blood does not affect amniotic cell growth and is maternal; however, if the blood is fetal, it may falsely elevate amniotic fluid α-fetoprotein level. Dark red or brown fluid indicates previous intra-amniotic bleeding and an increased risk of fetal loss. Green fluid, which usually results from meconium staining, does not appear to indicate increased risk of fetal loss.

Amniocentesis rarely results in significant maternal morbidity (eg, symptomatic amnionitis). With experienced operators, risk of fetal loss is about 0.1 to 0.2%. Vaginal spotting or amniotic fluid leakage, usually self-limited, occurs in 1 to 2% of women tested. Amniocentesis done before 14 wk gestation, particularly before 13 wk, results in a higher rate of fetal loss and an increased risk of talipes equinovarus (clubbed feet).

Chorionic Villus Sampling

In chorionic villus sampling (CVS), chorionic villi are aspirated into a syringe and cultured. CVS provides the same information about fetal genetic and chromosomal status as amniocentesis and has similar

accuracy. However, CVS is done between 10 wk gestation and the end of the 1st trimester and thus provides earlier results. Therefore, if needed, pregnancy may be terminated earlier (and more safely and simply), or if results are normal, parental anxiety may be relieved earlier. Unlike amniocentesis, amniotic fluid is not obtained at the time of CVS, and α-fetoprotein cannot be measured. Thus, women who have CVS should be offered maternal screening for serum α-fetoprotein at 16 to 18 wk to assess risk of fetal neural tube defects (see p. 2603).

Depending on placental location (identified by ultrasonography), CVS can be done by passing a catheter through the cervix or by inserting a needle through the woman's abdominal wall. After CVS, Rh_0(D) immune globulin 300 µg is given to Rh-negative unsensitized women.

Errors in diagnosis due to maternal cell contamination are rare. Detection of certain chromosomal abnormalities (eg, tetraploidy) may not reflect true fetal status but rather mosaicism confined to the placenta. Confined placental mosaicism is detected in about 1% of CVS specimens. Consultation with experts familiar with these abnormalities is advised. Rarely, subsequent amniocentesis is required to obtain additional information.

Rate of fetal loss due to CVS is similar to that of amniocentesis (ie, about 0.2%). Transverse limb defects and oromandibular-limb hypogenesis have been attributed to CVS but are exceedingly rare if CVS is done after 10 wk gestation by an experienced operator.

Percutaneous Umbilical Blood Sampling

Fetal blood samples can be obtained by percutaneous puncture of the umbilical cord vein (funipuncture) using ultrasound guidance. Chromosome analysis can be completed in 48 to 72 h. For this reason, percutaneous umbilical blood sampling (PUBS) was formerly often done when results were needed rapidly. This test was especially useful late in the 3rd trimester, particularly if fetal abnormalities were first suspected at that time. Now, genetic analysis of amniotic fluid cells or chorionic villi via interphase fluorescent in situ hybridization (FISH) allows preliminary diagnosis (or exclusion) of more common chromosomal abnormalities within 24 to 48 h, and PUBS is rarely done for genetic indications.

Procedure-related fetal loss rate with PUBS is about 1%.

Preimplantation Diagnosis

Genetic diagnosis is sometimes possible before implantation when in vitro fertilization is done; polar bodies from oocytes, blastomeres from 6- to 8-cell embryos, or a trophectoderm sample from the blastocyst is used. These tests are available only in specialized centers and are used primarily for couples with a high risk of certain mendelian disorders (eg, cystic fibrosis) or chromosomal abnormalities. Newer techniques may reduce costs and make such tests more widely available. Preimplantation genetic diagnosis to screen embryos from older women does not appear to increase the chance of successful pregnancy.

Noninvasive Maternal Screening Strategies

Noninvasive maternal screening, unlike invasive testing, has no risk of test-related complications. By more precisely assessing the risk of fetal abnormalities, particularly for women at otherwise low risk, noninvasive maternal screening can help women decide whether to have invasive testing. Noninvasive maternal screening for fetal chromosomal abnormalities should be offered to all pregnant women who have not already decided to have amniocentesis or CVS. However, if CVS is to be done, maternal serum screening should still be offered for detection of fetal neural tube defects.

Normal values vary with gestational age. Corrections for maternal weight, diabetes mellitus, race, and other factors may be necessary. Screening can be done during the 1st trimester, 2nd trimester, or both (called sequential or integrated screening). Any of the 3 approaches are acceptable. Regardless of which is done, maternal levels of α-fetoprotein should be measured during the 2nd trimester.

1st-Trimester Screening

First-trimester combined screening includes measurement of

• Maternal serum β-hCG (total or free)

• Pregnancy-associated plasma protein A (PAPP-A)

• Fetal nuchal translucency (by ultrasonography)

Fetal Down syndrome is typically associated with high levels of β-hCG, low levels of PAPP-A, and presence of enlarged fetal nuchal translucency (NT). Although an enlarged NT is associated with increase in risk for fetal Down syndrome, no threshold NT value is considered diagnostic. In large prospective US trials involving women of various ages, overall sensitivity for detection of Down syndrome was about 85%, with a false-positive rate of 5%. Specialized ultrasound training and adherence to rigorous quality-assurance monitoring of NT measurements are necessary to achieve this level of screening accuracy. First-trimester screening is being used increasingly in the US, particularly in large centers. It provides information early so that a definitive diagnosis can be made with CVS. An important advantage of 1st-trimester screening is that termination of pregnancy is safer during the 1st rather than the 2nd trimester.

2nd-Trimester Screening

Second-trimester screening may include the multiple marker screening approach, which includes

• Maternal levels of serum α-fetoprotein (MSAFP): MSAFP may be used independently as a screen for neural tube defects only, not for risk of Down syndrome. An elevated level suggests open spina bifida, anencephaly, abdominal wall defects, increased risk of pregnancy complications (eg, spontaneous abortion, abruptio placentae), or, occasionally, twins or multifetal pregnancy. Unexplained elevated MSAFP may be associated with increased risk of later pregnancy complications, such as stillbirth or intrauterine growth retardation.

• Maternal levels of β-hCG, unconjugated estriol, α-fetoprotein, and sometimes inhibin A: This screening may be used as an alternative or adjunct to 1st-trimester screening.

Second-trimester multiple marker screening is used to help assess the risk of Down syndrome, trisomy 18, and a few rarer single-gene syndromes (eg, Smith-Lemli-Opitz syndrome). Maternal serum tests are widely available, but detection rates for Down syndrome are not as high as those obtained with 1st-trimester screening. Also, termination of pregnancy is riskier in the 2nd trimester than in the 1st trimester.

Second-trimester screening may also include

• Targed ultrasonography

Maternal serum screening for neural tube defects: An elevated level of MSAFP may indicate a fetal malformation such as open spina bifida. Results are most accurate when the initial sample is obtained between 16 and 18 wk gestation, although screening can be done from about 15 to 20 wk. Designating a cutoff value to determine whether further testing is warranted involves weighing the risk of missed abnormalities against the risk of complications from unnecessary testing. Usually, a cutoff value in the 95th to 98th percentile or 2.0 to 2.5 times the normal pregnancy median (multiples of the median, or MOM) is used. This value is about 80% sensitive for open spina bifida and 90% sensitive for anencephaly. Closed spina bifida is usually not detected. Amniocentesis is eventually required in 1 to 2% of women originally screened. Lower cutoff values of MSAFP increase sensitivity but decrease specificity, resulting in more amniocenteses.

Ultrasonography is the next step if further testing is warranted. Targeted ultrasonography (see below) with or without amniocentesis is done if no explanation can be determined with basic ultrasonography. Ultrasonography can confirm gestational age (which may be underestimated) or detect multifetal pregnancy, fetal death, or congenital malformations. In some women, ultrasonography cannot identify a

cause for elevated α-fetoprotein levels. Some experts believe that if high-resolution ultrasonography done by an experienced operator is normal, further testing is unnecessary. However, because this test occasionally misses neural tube defects, many experts recommend further testing by amniocentesis regardless of ultrasonography results.

Amniocentesis with measurement of α-fetoprotein and acetylcholinesterase levels in amniotic fluid is done if further testing is needed. Elevated α-fetoprotein in amniotic fluid suggests

- A neural tube defect
- Another malformation (eg, omphalocele, congenital nephrosis, cystic hygroma, gastroschisis, upper GI atresia)
- Contamination of the sample with fetal blood

Presence of acetylcholinesterase in amniotic fluid suggests a neural tube defect or another malformation. Elevated α-fetoprotein plus presence of acetylcholinesterase in amniotic fluid is virtually 100% sensitive for anencephaly and 90 to 95% sensitive for open spina bifida. Abnormal amniotic fluid markers indicate that a malformation is likely even if high-resolution ultrasonography (which can detect most of these malformations) does not detect a malformation, and parents should be informed.

Maternal serum screening for chromosomal abnormalities: During the 2nd trimester, the most common approach to screening is with multiple serum markers. These markers, adjusted for gestational age, are used mainly to refine estimates of Down syndrome risk beyond that associated with maternal age. With triple screening (ie, α-fetoprotein, hCG, and unconjugated estriol), sensitivity for Down syndrome is about 65 to 70%, with a false-positive rate of about 5%.

Quad screening is triple screening plus measurement of inhibin A. Quad screening increases sensitivity to about 80%, with a 5% false-positive rate.

If maternal serum screening suggests Down syndrome, ultrasonography is done to confirm gestational age, and risk is recalculated if the presumed gestational age is incorrect. If the original sample was drawn too early, another one must be drawn at the appropriate time. Amniocentesis is offered particularly if risk exceeds a specific prespecified threshold (usually 1 in 270, which is about the same as risk when maternal age is > 35).

Triple screening can also assess risk of trisomy 18, indicated by low levels of all 3 serum markers. Sensitivity for trisomy 18 is 60 to 70%; the false-positive rate is about 0.5%. Combining ultrasonography and serum screening increases sensitivity to about 80%.

Targeted ultrasonography: Targeted ultrasonography is offered at some perinatal centers and is used to assess risk for chromosomal abnormalities by searching for structural features associated with fetal aneuploidy (so-called soft markers). However, no structural finding is diagnostic for a given chromosomal abnormality, and all soft markers may also be seen in fetuses that are chromosomally normal. Nonetheless, the discovery of such a marker may lead to offering the woman amniocentesis to confirm or exclude a chromosomal abnormality. If a major structural malformation is present, a fetal chromosomal abnormality is more likely. Disadvantages include unnecessary anxiety if a soft marker is detected and unnecessary amniocentesis. Several experienced centers report high sensitivity, but whether a normal ultrasound indicates a substantially reduced risk of fetal chromosomal abnormalities is unclear.

Sequential 1st- and 2nd-Trimester Screening

Noninvasive 1st-trimester and 2nd-trimester quad screening can be combined sequentially, with invasive fetal genetic testing withheld until results of 2nd-trimester screening are available—whether 1st-trimester test results are abnormal or not. Sequential screening followed by amniocentesis for high-risk patterns increases sensitivity for Down syndrome to 95%, with a false-positive rate of only 5%.

A variation of sequential screening, called contingent sequential screening, is based on the level of risk

indicated by 1st-trimester screening:

- High risk: Invasive testing is offered without doing 2nd-trimester screening.
- Intermediate risk: 2nd-trimester screening is offered.
- Low risk (eg, < 1 in 1500): 2nd-trimester screening for Down syndrome is not offered because the 1st-trimester risk is so low.

Chapter 260. Conception and Prenatal Development

Introduction

For conception (fertilization), a live sperm must unite with an ovum in a fallopian tube with normally functioning epithelium. Conception occurs just after ovulation, about 14 days after a menstrual period. At ovulation, cervical mucus becomes less viscid, facilitating rapid movement of sperm to the ovum, usually near the fimbriated end of the tube. Sperm may remain alive in the vagina for about 3 days after intercourse.

The fertilized egg (zygote) divides repeatedly as it travels to the implantation site in the endometrium (usually near the fundus) over a period of 5 to 8 days. By the time of implantation, the zygote has become a layer of cells around a cavity, called a blastocyst. The blastocyst wall is 1 cell thick except for the embryonic pole, which is 3 or 4 cells thick. The embryonic pole, which becomes the embryo, implants first.

Amniotic sac and placenta: Within 1 or 2 days of implantation, a layer of cells (trophoblast cells) develops around the blastocyst. The progenitor villous trophoblast cell, the stem cell of the placenta, develops along 2 cell lines:

- Nonproliferative extravillous trophoblast: These cells penetrate the endometrium, facilitating implantation and anchoring of the placenta.

- Syncytiotrophoblast: These cells produce chorionic gonadotropin by day 10 and other trophic hormones shortly thereafter.

An inner layer (amnion) and outer layer (chorion) of membranes develop from the trophoblast; these membranes form the amniotic sac (see Fig. 260-1), which contains the conceptus (term used for derivatives of the zygote at any stage). When the sac is formed and the blastocyst cavity closes (by about 10 days), the conceptus is considered an embryo. The amniotic sac fills with fluid and expands with the growing embryo, filling the endometrial cavity by about 12 wk after conception; then, the amniotic sac is the only cavity remaining in the uterus.

Trophoblast cells develop into those that form the placenta. The extravillous trophoblast forms villi, which penetrate the uterus. The syncytiotrophoblast covers the villi. The

[**Fig. 260-1.** Placenta and embryo at about 11 4/7 wk gestation.]

syncytiotrophoblast synthesizes trophic hormones and provides arterial and venous exchange between the circulation of the conceptus and that of the mother.

The placenta is fully formed by wk 18 to 20 but continues to grow, weighing about 500 g by term.

Embryo: Around day 10, 3 germ layers (ectoderm, mesoderm, endoderm) are usually distinct in the embryo. Then the primitive streak, which becomes the neural tube, begins to develop. Around day 16, the cephalad portion of the mesoderm thickens, forming a central channel that develops into the heart and great vessels. The heart begins to pump plasma around day 20, and on the next day, fetal RBCs, which are immature and nucleated, appear. Fetal RBCs are soon replaced by mature RBCs, and blood vessels develop throughout the embryo. Eventually, the umbilical artery and vein develop, connecting the embryonic vessels with the placenta.

Most organs form between 21 and 57 days after fertilization (between 5 and 10 wk gestation); however, the CNS continues to develop throughout pregnancy. Susceptibility to malformations induced by teratogens is highest when organs are forming.

Chapter 261. Approach to the Pregnant Woman and Prenatal Care

Introduction

Pregnant women require routine prenatal care to help ensure their health and the health of the fetus. Also, evaluation is often required for symptoms and signs of illness. Common symptoms that are often pregnancy-related include vaginal bleeding, pelvic pain, vomiting, and lower-extremity edema (for specific obstetric disorders, see Ch. 265; for nonobstetric disorders in pregnant women, see Ch. 263).

Ideally, women who are planning to become pregnant should see a physician before conception, so that they can be counseled about pregnancy risks and ways to reduce them. The initial routine prenatal visit should occur between 6 and 8 wk gestation. Follow-up visits should occur at about 4-wk intervals until 28 wk, at 2-wk intervals from 28 to 36 wk, and weekly thereafter until delivery. Prenatal care includes screening for disorders, taking measures to reduce fetal and maternal risks, and counseling.

History

During the initial visit, clinicians should obtain a full medical history, including

- Previous and current disorders
- Drug use (therapeutic, social, and illicit)
- Risk factors for complications of pregnancy (see Table 264-1)
- Obstetric history, with the outcome of all previous pregnancies, including maternal and fetal complications (eg, gestational diabetes, preeclampsia, congenital malformations, stillbirth)

Family history should include all chronic disorders in family members to identify possible hereditary disorders (see p. 2599).

During subsequent visits, queries focus on interim developments, particularly vaginal bleeding or fluid discharge, headache, changes in vision, edema of face or fingers, and changes in frequency or intensity of fetal movement.

Gravidity and parity: Gravidity is the number of confirmed pregnancies; a pregnant woman is a gravida. Parity is the number of deliveries after 20 wk. Multifetal pregnancy is counted as one in terms of gravidity and parity. Abortus is the number of pregnancy losses (abortions) before 20 wk regardless of cause (eg, spontaneous, therapeutic, or elective abortion; ectopic pregnancy). Sum of parity and abortus equals gravidity.

Parity is often recorded as 4 numbers:

- Number of term deliveries (after 37 wk)
- Number of premature deliveries (> 20 and < 37 wk)
- Number of abortions
- Number of living children

Thus, a woman who is pregnant and has had one term delivery, one set of twins born at 32 wk, and 2 abortions is gravida 5, para 1-1-2-3.

Physical Examination

A full general examination, including height and weight, is done first.

In the initial obstetric examination, speculum and bimanual pelvic examination is done

• To check for lesions or discharge

• To note the color and consistency of the cervix

• To obtain cervical samples for testing

Also, fetal heart rate and, in patients presenting later in pregnancy, lie of the fetus are assessed (see Fig. 262-1 on p. 2629).

Pelvic capacity can be estimated clinically by evaluating various measurements with the middle finger during bimanual examination. If the distance from the underside of the pubic symphysis to the sacral promontory is > 11.5 cm, the pelvic inlet is almost certainly adequate. Normally, distance between the ischial spines is ≥ 9 cm, length of the sacrospinous ligaments is 4 to ≥ 5 cm, and the subpubic arch is ≥ 90°.

During subsequent visits, BP and weight assessment is important. Obstetric examination focuses on uterine size, fundal height (in cm above the symphysis pubis), fetal heart rate and activity, and maternal diet, weight gain, and overall well-being. Speculum and bimanual examination is usually not needed unless vaginal discharge or bleeding, leakage of fluid, or pain is present.

Testing

Laboratory testing: For diagnosis of pregnancy, see p. 2623. Initial laboratory evaluation is thorough; some components are repeated during follow-up visits (see Table 261-1).

If a woman has Rh-negative blood, she may be at risk of developing $Rh_0(D)$ antibodies (see Pretransfusion Testing on p. 1037), and the fetus may be at risk of developing erythroblastosis fetalis. $Rh_0(D)$ antibody levels should be measured in pregnant women at

[**Table 261-1.** Components of Routine Prenatal Evaluation]

18 to 20 wk and again at about 26 to 28 wk. Additional measures may be necessary to prevent development of maternal Rh antibodies (see Erythroblastosis Fetalis on p. 2665).

Generally, women are routinely screened for gestational diabetes between 24 and 28 wk using a 50-g, 1-h glucose tolerance test (see p. 2654). If women have risk factors for gestational diabetes, they are screened during the 1st trimester. Risk factors include gestational diabetes or a macrosomic neonate (weight > 4500 g at birth) in a previous pregnancy, unexplained fetal losses, a family history of diabetes in close relatives, a history of persistent glucosuria, and a body mass index (BMI) > 30 kg/m^2.

Ultrasonography: Most obstetricians recommend at least one ultrasound examination during each pregnancy, ideally between 16 and 20 wk, when estimated delivery date (EDD) can still be confirmed fairly accurately and when placental location and fetal anatomy can be evaluated. Estimates of gestational age are based on measurements of fetal head circumference, biparietal diameter, abdominal circumference, and femur length. Measurement of fetal crown-rump length during the 1st trimester is particularly accurate in predicting EDD: to within about 5 days when measurements are made at < 12 wk gestation and to within about 7 days at 12 to 15 wk. Ultrasonography during the 3rd trimester is accurate for predicting EDD to within about 2 to 3 wk.

Specific indications for ultrasonography include

• Investigation of abnormalities during the 1st trimester

- Need for detailed assessment of fetal anatomy
- Detection of multifetal pregnancy, hydatidiform mole, polyhydramnios, placenta previa, or ectopic pregnancy
- Determination of placental location, fetal position and size, and size of the uterus in relation to given gestational dates (too small or too large)

Ultrasonography is also used for needle guidance during chorionic villus sampling, amniocentesis, and fetal transfusion. High-resolution ultrasonography includes techniques that maximize sensitivity for detecting fetal malformations.

If ultrasonography is needed during the 1st trimester (eg, to evaluate pain, bleeding, or viability of pregnancy), use of an endovaginal transducer maximizes diagnostic accuracy; evidence of an intrauterine pregnancy (gestational sac or fetal pole) can be seen as early as 4 to 5 wk and is seen at 7 to 8 wk in > 95% of cases. With real-time ultrasonography, fetal movements and heart motion can be directly observed as early as 5 to 6 wk.

Other imaging: Conventional x-rays can induce spontaneous abortion or congenital malformations, particularly during early pregnancy. Risk is low (up to about 1/million) with each x-ray of an extremity or of the neck, head, or chest if the uterus is shielded. Risk is higher with abdominal, pelvic, and lower back x-rays. Thus, for all women of childbearing age, an imaging test with less ionizing radiation (eg, ultrasonography) should be substituted when possible, or if x-rays are needed, the uterus should be shielded (because pregnancy is possible). Medically necessary x-rays or other imaging should not be postponed because of pregnancy. However, elective x-rays are postponed until after pregnancy.

Treatment

Problems identified during evaluation are managed. Women are counseled about exercise and diet, and nutritional supplements are prescribed. What to avoid, what to expect, and when to obtain further evaluation are explained. Couples are encouraged to attend childbirth classes.

Diet and supplements: To provide nutrition for the fetus, most women require about 250 kcal extra daily; most should come from protein. If maternal weight gain is excessive (> 1.4 kg/mo during the early months) or inadequate (< 0.9 kg/mo), diet must be modified further. Weight-loss dieting during pregnancy is not recommended, even for morbidly obese women.

Most pregnant women need a daily oral iron supplement of ferrous sulfate 300 mg or ferrous gluconate 450 mg, which may be better tolerated. Woman with anemia should take the supplements bid. All women should be given oral prenatal vitamins that contain folate 400 µg (0.4 mg), taken once/day; folate reduces risk of neural tube defects. For women who have had a fetus or an infant with a neural tube defect, the recommended daily dose is 4000 µg (4 mg).

Physical activity: Pregnant women can continue to do moderate physical activities and exercise but should take care not to injure the abdomen. Sexual intercourse can be continued throughout pregnancy unless vaginal bleeding, pain, leakage of amniotic fluid, or uterine contractions occur.

Travel: The safest time to travel during pregnancy is between 14 and 28 wk, but there is no absolute contraindication to travel at any time during pregnancy. Pregnant women should wear seat belts regardless of gestational age and type of vehicle. Travel on airplanes is safe until 36 wk gestation. On long flights, pregnant patients should walk or stretch every 2 to 3 h to prevent venous stasis.

Immunizations: Vaccines for measles, mumps, rubella, and varicella should not be used during pregnancy (see p. 2626). The hepatitis B vaccine can be safely used if indicated, and the influenza vaccine is strongly recommended for women who are pregnant or postpartum during influenza season.

Pregnant women with Rh-negative blood and thus at risk of developing Rh_0(D) antibodies are given Rh_0(D) immune globulin 300 µg IM after any significant vaginal bleeding or other sign of placental

hemorrhage or separation (abruptio placentae), after a spontaneous or therapeutic abortion, after amniocentesis or chorionic villus sampling, prophylactically at 28 wk, and, if the neonate has Rh_0(D)-positive blood, after delivery.

Modifiable risk factors: Women should not use alcohol and tobacco and should avoid exposure to secondhand smoke. They should also avoid exposure to chemicals or paint fumes, direct handling of cat litter (due to risk of toxoplasmosis), prolonged temperature elevation (eg, in a hot tub or sauna), and exposure to people with active viral infections (eg, rubella, parvovirus infection [fifth disease], varicella).

Women with substance abuse problems should be monitored by a specialist in high-risk pregnancy.

Drugs and vitamins that are not medically indicated should be discouraged (see Drugs in Pregnancy on p. 2625).

Symptoms requiring evaluation: Women should be advised to seek evaluation for unusual headaches, visual disturbances, pelvic pain or cramping, vaginal bleeding, rupture of membranes, extreme swelling of the hands or face, diminished urine volume, any prolonged illness or infection, or persistent symptoms of labor. Multiparous women with a history of rapid labor should notify the physician at the first symptom of labor.

Pelvic Pain During Early Pregnancy

Pelvic pain is common during early pregnancy and may accompany serious or minor disorders. Some conditions causing pelvic pain also cause vaginal bleeding. In some of these disorders (eg, ruptured ectopic pregnancy, ruptured hemorrhagic corpus luteum cyst), bleeding may be severe, sometimes leading to hemorrhagic shock.

Causes of upper and generalized abdominal pain are similar to those in nonpregnant patients.

Etiology

Causes of pelvic pain during early pregnancy (see Table 261-2) may be

- Obstetric
- Gynecologic, nonobstetric
- Nongynecologic

Sometimes no particular disorder is identified.

The most common obstetric cause is

- Spontaneous abortion (threatened, inevitable, incomplete, complete, septic, or missed)

The most common serious obstetric cause is

- Ruptured ectopic pregnancy

Nonobstetric gynecologic causes include adnexal torsion, which is more common during pregnancy because during pregnancy, the corpus luteum causes the ovaries to enlarge, increasing the risk of the ovary twisting around the pedicle.

Common nongynecologic causes include various common GI and GU disorders:

- Viral gastroenteritis

- Irritable bowel syndrome
- Appendicitis
- Inflammatory bowel disease
- UTI
- Nephrolithiasis

Pelvic pain during late pregnancy may result from labor or one of the many nonobstetric causes of pelvic pain.

Evaluation

Evaluation should exclude potentially serious treatable causes (eg, ruptured or un-ruptured ectopic pregnancy, septic abortion, appendicitis).

History: History of present illness should include the patient's gravidity and parity as well as the pain's onset (sudden or gradual), location (localized or diffuse), and character (crampy or colicky). A history of illicitly attempted termination of pregnancy suggests septic abortion, but absence of this history does not exclude this diagnosis.

Review of systems should seek GU and GI symptoms that suggest a cause. Important GU symptoms include vaginal bleeding (ectopic pregnancy or abortion); syncope or near syncope (ectopic pregnancy); urinary frequency, urgency, or dysuria (UTI); and vaginal discharge and history of unprotected intercourse (pelvic inflammatory disease).

[Table 261-2. Some Causes of Pelvic Pain During Early Pregnancy]

Important GI symptoms include diarrhea (gastroenteritis, inflammatory bowel disease, or irritable bowel syndrome), vomiting (due to many disorders, including gastroenteritis and bowel obstruction), and obstipation (bowel obstruction, irritable bowel, or a functional disorder).

Past medical history should seek disorders known to cause pelvic pain (eg, inflammatory bowel disease, irritable bowel syndrome, nephrolithiasis, ectopic pregnancy, spontaneous abortion). Risk factors for these disorders should be identified.

Risk factors for ectopic pregnancy include

- History of sexually transmitted disease or pelvic inflammatory disease
- Cigarette smoking
- Use of intrauterine device
- Age > 35
- Previous abdominal surgery (especially tubal surgery)
- Use of fertility drugs or assisted reproductive techniques
- Previous ectopic pregnancy (the most important)
- Multiple sex partners
- Douching

Risk factors for spontaneous abortion include

• Age > 35

• History of spontaneous abortion

• Cigarette smoking

• Drugs (eg, cocaine, alcohol, high doses of caffeine)

• Uterine abnormalities (eg, leiomyoma, adhesions)

Risk factors for bowel obstruction include

• Previous abdominal surgery

• Hernia

Physical examination: Physical examination begins with a review of vital signs, particularly for fever and signs of hypovolemia (hypotension, tachycardia).

Evaluation focuses on abdominal and pelvic examinations. The abdomen is palpated for tenderness, peritoneal signs (rebound, rigidity, guarding), and uterine size and is percussed for tympany. Fetal heart sounds are checked using a Doppler probe.

Pelvic examination includes inspection of the cervix for discharge, dilation, and bleeding. Discharge, if present, should be sampled and sent for culture. Any blood or clots in the vaginal vault are gently removed. Bimanual examination should check for cervical motion tenderness, adnexal masses or tenderness, and uterine size.

Red flags: The following findings are of particular concern:

• Hemodynamic instability (hypotension, tachycardia, or both)

• Syncope or near syncope

• Peritoneal signs (rebound, rigidity, guarding)

• Fever, chills, and purulent vaginal discharge

• Vaginal bleeding

Interpretation of findings: Certain findings suggest causes of pelvic pain but are not always diagnostic (see Table 261-2).

For all women who present with pelvic pain during early pregnancy, the most serious cause—ectopic pregnancy—must be excluded, regardless of any other findings. Nonobstetric causes of pelvic pain (eg, acute appendicitis) must always be considered and investigated as in nonpregnant women.

As in any patient, findings of peritoneal irritation (eg, focal tenderness, guarding, rebound, rigidity) are a concern. Common causes include appendicitis, ruptured ectopic pregnancy, and, less often, ruptured ovarian cyst. However, absence of peritoneal irritation does not rule out such disorders, and index of suspicion must be high.

Vaginal bleeding accompanying the pain suggests spontaneous abortion or ectopic pregnancy. An open cervical os or tissue passed through the cervix strongly suggests an inevitable, incomplete, or complete abortion. The presence of fever, chills, and a purulent vaginal discharge suggests a septic abortion (particularly in patients with a history of instrumentation of the uterus or illicitly attempted termination of

pregnancy). Pelvic inflammatory disease is rare during pregnancy but may occur.

Testing: If an obstetric cause of pelvic pain is suspected, quantitative measurement of β-hCG, CBC, blood type, and Rh typing should be done. If the patient is hemodynamically unstable (with hypotension, persistent tachycardia, or both), blood should be cross-matched, and fibrinogen level, fibrin split products, and PT/PTT are determined.

Pelvic ultrasonography is done to confirm an intrauterine pregnancy. However, ultrasonography can and should be deferred in the hemodynamically unstable patient with a positive pregnancy test, given the very high likelihood of either ectopic pregnancy or spontaneous abortion with hemorrhage. Both transabdominal and transvaginal ultrasonography should be used as necessary. If the uterus is empty and tissue has not been passed, ectopic pregnancy is suspected. If Doppler ultrasonography shows that blood flow to the adnexa is absent or decreased, adnexal (ovarian) torsion is suspected. However, this finding is not always present because spontaneous detorsion can occur.

Treatment

Treatment is directed at the cause. If ectopic pregnancy is confirmed and is not ruptured, methotrexate can often be considered, or surgical salpingotomy or salpingectomy may be done. If the ectopic pregnancy is ruptured or leaking, treatment is immediate laparoscopy or laparotomy.

Treatment of spontaneous abortions depends on the type of abortion and the patient's hemodynamic stability. Threatened abortions are treated conservatively with oral analgesics. Inevitable, incomplete, or missed abortions are treated medically with misoprostol or surgically with uterine evacuation via D & C. Septic abortions are treated with uterine evacuation plus IV antibiotics.

Women who have Rh-negative blood should be given Rh_0(D) immune globulin if they have vaginal bleeding or an ectopic pregnancy.

Ruptured corpus luteum cysts and degeneration of a uterine fibroid are treated conservatively with oral analgesics.

Treatment of adnexal torsion is surgical: manual detorsion if the ovary is viable; oophorectomy or salpingectomy if the ovary is infarcted and nonviable.

Key Points

- Clinicians should always be alert for ectopic pregnancy.
- Nonobstetric causes should be considered; acute abdomen may develop during pregnancy.
- If no clear nonobstetric cause is identified, ultrasonography is usually necessary.
- A septic abortion is suspected when there is a history of recent uterine instrumentation or induced abortion.
- If vaginal bleeding occurred, Rh status is determined, and all women with Rh-negative blood are given Rh_0(D) immune globulin.

Vaginal Bleeding During Early Pregnancy

Vaginal bleeding occurs in 20 to 30% of confirmed pregnancies during the first 20 wk of gestation; about half of these cases end in spontaneous abortion. Vaginal bleeding is also associated with other adverse pregnancy outcomes such as low birth weight, preterm birth, stillbirth, and perinatal death.

Etiology

Obstetric or nonobstetric disorders may cause vaginal bleeding during early pregnancy (see

Table 261-3).

The most dangerous cause is

• Ruptured ectopic pregnancy

The most common cause is

• Spontaneous abortion (threatened, inevitable, incomplete, complete, septic, missed)

[**Table 261-3.** Some Causes of Vaginal Bleeding During Early Pregnancy]

Evaluation

A pregnant woman with vaginal bleeding must be evaluated promptly.

Ectopic pregnancy or other causes of copious vaginal bleeding (eg, inevitable abortion, ruptured hemorrhagic corpus luteum cyst) can lead to hemorrhagic shock. IV access should be established early during evaluation in case such complications occur.

History: History of present illness should include the patient's gravidity (number of confirmed pregnancies), parity (number of deliveries after 20 wk), and number of abortions (spontaneous or induced); description and amount of bleeding, including how many pads were soaked and whether clots or tissue were passed; and presence or absence of pain. If pain is present, onset, location, duration, and character should be determined.

Review of symptoms should note fever, chills, abdominal or pelvic pain, vaginal discharge, and neurologic symptoms such as dizziness, light-headedness, syncope, or near syncope.

Past medical history should include risk factors for ectopic pregnancy and spontaneous abortion (see p. 2611).

Physical examination: Physical examination includes review of vital signs for fever and signs of hypovolemia (tachycardia, hypotension).

Evaluation focuses on abdominal and pelvic examinations. The abdomen is palpated for tenderness, peritoneal signs (rebound, rigidity, guarding), and uterine size. Fetal heart sounds should be checked with a Doppler ultrasound probe.

Pelvic examination includes inspection of external genitals, speculum examination, and bimanual examination. Blood or products of conception in the vaginal vault, if present, are removed; products of conception are sent to a laboratory for confirmation. The cervix should be inspected for discharge, dilation, lesions, polyps, and tissue in the os. If the pregnancy is < 14 wk, the cervical os may be gently probed (but no more than fingertip depth) using ringed forceps to determine the integrity of the internal cervical os. If the pregnancy is ≥ 14 wk, the cervix should not be probed because the vascular placenta may tear, especially if it covers the internal os (placenta previa). Bimanual examination should check for cervical motion tenderness, adnexal masses or tenderness, and uterine size.

Red flags: The following findings are of particular concern:

• Hemodynamic instability (hypotension, tachycardia, or both)

• Orthostatic changes in pulse or BP

• Syncope or near syncope

• Peritoneal signs (rebound, rigidity, guarding)

• Fever, chills, and mucopurulent vaginal discharge

Interpretation of findings: Clinical findings help suggest a cause but are rarely diagnostic (see Table 261-3). However, a dilated cervix plus passage of fetal tissue and crampy abdominal pain strongly suggests spontaneous abortion, and septic abortion is usually apparent from the circumstances and signs of severe infection (fever, toxic appearance, purulent or bloody discharge). Even if these classic manifestations are not present, threatened or missed abortion is possible, and the most serious cause—ruptured ectopic pregnancy—must be excluded. Although the classic description of ectopic pregnancy includes severe pain, peritoneal signs, and a tender adnexal mass, ectopic pregnancy can manifest in many ways and should always be considered, even when bleeding appears scant and pain appears minimal.

Testing: A self-diagnosed pregnancy is verified with a urine test. For women with a documented pregnancy, several tests are done:

• Quantitative β-hCG level

• Blood typing and Rh testing

• Usually ultrasonography

Rh testing is done to determine whether Rh_0(D) immune globulin is needed to prevent maternal sensitization. If bleeding is substantial, testing should also include CBC and either type and screen (for abnormal antibodies) or cross-matching. For major hemorrhage or shock, PT/PTT is also determined.

Transvaginal pelvic ultrasonography is done to confirm an intrauterine pregnancy unless products of conception have been obtained intact (indicating completed abortion). If patients are in shock or bleeding is substantial, ultrasonography should be done at the bedside. The quantitative β-hCG level helps interpret ultrasound results. If the level is ≥ 1500 mIU/mL and ultrasonography does not confirm an intrauterine pregnancy (a live or dead fetus), ectopic pregnancy is likely. If the level is < 1500 mIU/mL and no intrauterine pregnancy is seen, intrauterine pregnancy is still possible.

If the patient is stable and clinical suspicion for ectopic pregnancy is low, serial β-hCG levels may be done on an outpatient basis. Normally, the level doubles every 1.4 to 2.1 days up to 41 days gestation; in ectopic pregnancy (and in abortions), levels may be lower than expected by dates and usually do not double as rapidly. If clinical suspicion for ectopic pregnancy is moderate or high (eg, because of substantial blood loss, adnexal tenderness, or both), diagnostic uterine evacuation or D & C and possibly diagnostic laparoscopy should be done.

Ultrasonography can also help identify a ruptured corpus luteum cyst and gestational trophoblastic disease. It can show products of conception in the uterus, which are present in patients with incomplete, septic, or missed abortion.

Treatment

Treatment is directed at the underlying disorder:

• Ruptured ectopic pregnancy: Immediate laparoscopy or laparotomy

• Unruptured ectopic pregnancy: Methotrexate or salpingotomy or salpingectomy via laparoscopy or laparotomy

• Threatened abortion: Expectant management for hemodynamically stable patients

• Inevitable, incomplete, or missed abortions: D & C or uterine evacuation

• Septic abortion: IV antibiotics and urgent uterine evacuation if retained products of conception are identified during ultrasonography

• Complete abortion: Obstetric follow-up

Key Points

• Clinicians should always be alert for ectopic pregnancy; symptoms can be mild or severe.

• Spontaneous abortion is the most common cause of bleeding during early pregnancy.

• Rh testing is required for all women who present with vaginal bleeding during early pregnancy to determine whether Rh_0(D) immune globulin is needed.

Nausea and Vomiting During Early Pregnancy

Nausea and vomiting affect up to 80% of pregnant women. Symptoms are most common and most severe during the 1st trimester. Although common usage refers to morning sickness, nausea, vomiting, or both typically may occur at any point during the day. Symptoms vary from mild to severe (hyperemesis gravidarum).

Hyperemesis gravidarum is persistent, severe pregnancy-induced vomiting that causes significant dehydration, often with electrolyte abnormalities, ketosis, and weight loss (see p. 2667).

Pathophysiology

The pathophysiology of nausea and vomiting during early pregnancy is unknown, although metabolic, endocrine, GI, and psychologic factors probably all play a role. Estrogen may contribute because estrogen levels are elevated in patients with hyperemesis gravidarum.

Etiology

The most common causes of uncomplicated nausea and vomiting during early pregnancy (see Table 261-4) are

• Morning sickness (most common)

• Hyperemesis gravidarum

• Gastroenteritis

Occasionally, prenatal vitamin preparations with iron cause nausea. Rarely, severe, persistent vomiting results from a hydatidiform mole.

[**Table 261-4.** Some Causes of Nausea and Vomiting During Early Pregnancy]

Vomiting can also result from many nonobstetric disorders. Common causes of acute abdomen (eg, appendicitis, cholecystitis) may occur during pregnancy and may be accompanied by vomiting, but the chief complaint is typically pain rather than vomiting. Similarly, some CNS disorders (eg, migraine, CNS hemorrhage, increased intracranial pressure) may be accompanied by vomiting, but headache or other neurologic symptoms are typically the chief complaint.

Evaluation

Evaluation aims to exclude serious or life-threatening causes of nausea and vomiting. Morning sickness (uncomplicated nausea and vomiting) and hyperemesis gravidarum are diagnoses of exclusion.

History: History of present illness should particularly note the following:

• Onset and duration of vomiting

• Exacerbating and relieving factors

• Type (eg, bloody, watery, bilious) and amount of emesis

• Frequency (intermittent or persistent)

Important associated symptoms include diarrhea, constipation, and abdominal pain. If pain is present, the location, radiation, and severity should be queried. The examiner should also ask what social effects the symptoms have had on the patient and her family (eg, whether she is able to work or to care for her children).

Review of systems should seek symptoms of nonobstetric causes of nausea and vomiting, including fever or chills, particularly if accompanied by flank pain or voiding symptoms (UTI or pyelonephritis), and neurologic symptoms such as headache, weakness, focal deficits, and confusion (migraine or CNS hemorrhage).

Past medical history includes questions about morning sickness or hyperemesis in past pregnancies. Past surgical history should include questions about any prior abdominal surgery, which would predispose a patient to mechanical bowel obstruction.

Drugs taken by the patient are reviewed for drugs that could contribute (eg, iron-containing compounds, hormonal therapy) and for safety during pregnancy.

Physical examination: Examination begins with review of vital signs for fever, tachycardia, and abnormal BP (too low or too high).

A general assessment is done to look for signs of toxicity (eg, lethargy, confusion, agitation). A complete physical examination, including pelvic examination, is done to check for findings suggesting serious or potentially life-threatening causes of nausea and vomiting (see Table 261-5).

Red flags: The following findings are of particular concern:

• Abdominal pain

• Signs of dehydration (eg, orthostatic hypotension, tachycardia)

[**Table 261-5.** Relevant Physical Examination Findings in a Pregnant Patient with Vomiting]

• Fever

• Bloody or bilious emesis

• No fetal motion or heart sounds

• Abnormal neurologic examination

• Persistent or worsening symptoms

Interpretation of findings: Distinguishing pregnancy-related vomiting from vomiting due to other causes is important. Clinical manifestations help (see Table 261-4).

Vomiting is less likely to be due to pregnancy if it begins after the 1st trimester or is accompanied by abdominal pain, diarrhea, or both. Abdominal tenderness may suggest acute abdomen. Meningismus, neurologic abnormalities, or both suggest a neurologic cause.

Vomiting is more likely to be due to pregnancy if it begins during the 1st trimester, it lasts or recurs over

several days to weeks, abdominal pain is absent, and there are no symptoms or signs involving other organ systems.

If vomiting appears to be pregnancy-related and is severe (ie, frequent, prolonged, accompanied by dehydration), hyperemesis gravidarum and hydatidiform mole should be considered.

Testing: Patients with significant vomiting, signs of dehydration, or both usually require testing. If hyperemesis gravidarum is suspected, urine ketones are measured; if symptoms are particularly severe or persistent, serum electrolytes are measured. If fetal heart sounds are not clearly audible or detected by fetal Doppler, pelvic ultrasonography should be done to rule out hydatidiform mole. Other tests are done based on clinically suspected nonobstetric disorders (see Table 261-4).

Treatment

Pregnancy-induced vomiting may be relieved by drinking or eating frequently (5 or 6 small meals/day), but only bland foods (eg, crackers, soft drinks, BRAT diet [bananas, rice, apple-sauce, dry toast]) should be eaten. Eating before rising may help. If dehydration (eg, due to hyperemesis gravidarum) is suspected, 1 to 2 L of normal saline or Ringer's lactate is given IV, and any identified electrolyte abnormalities are corrected.

Certain drugs (see Table 261-6) can be used to relieve nausea and vomiting during the 1st trimester without evidence of adverse effects on the fetus.

Vitamin B_6 is used as monotherapy; other drugs are added if symptoms are not relieved.

Ginger (eg, ginger capsules 250 mg po tid or qid, ginger lollipops), acupuncture, motion sickness bands, and hypnosis may help, as may switching from prenatal vitamins to a children's chewable vitamin with folate.

[**Table 261-6.** Suggested Drugs for Nausea and Vomiting During Early Pregnancy]

Key Points

• Vomiting during pregnancy is usually self-limited and responds to dietary modification.

• Hyperemesis gravidarum is less common but is severe, leading to dehydration, ketosis, and weight loss.

• Nonobstetric causes should be considered.

Lower-Extremity Edema During Late Pregnancy

Edema is common during late pregnancy. It typically involves the lower extremities but occasionally appears as swelling or puffiness in the face or hands.

Etiology

The most common cause of edema in pregnancy is

• Physiologic edema

Physiologic edema results from hormone-induced Na retention. Edema may also occur when the enlarged uterus intermittently compresses the inferior vena cava during recumbency, obstructing outflow from both femoral veins.

Pathologic causes of edema are less common but often dangerous. They include deep venous thrombosis (DVT) and preeclampsia (see Table 261-7). DVT is more common during pregnancy because pregnancy is a hypercoagulable state,

and women may be less mobile. Preeclampsia results from pregnancy-induced hypertension; however, not all women with

[Table 261-7. Some Causes of Edema During Late Pregnancy]

preeclampsia develop edema. When extensive, cellulitis, which usually causes focal erythema, may resemble general edema.

Evaluation

Evaluation aims to exclude DVT and preeclampsia. Physiologic edema is a diagnosis of exclusion.

History: History of present illness should include symptom onset and duration, exacerbating and relieving factors (physiologic edema is reduced by lying in the left lateral decubitus position), and risk factors for DVT and preeclampsia. Risk factors for DVT include

- Venous insufficiency
- Trauma
- Hypercoagulability disorder
- Thrombotic disorders
- Cigarette smoking
- Immobility
- Cancer

Risk factors for preeclampsia include

- Chronic hypertension
- Personal or family history of preeclampsia
- Age < 17 or > 35
- First pregnancy
- Multifetal pregnancy
- Diabetes
- Vascular disorders
- Hydatidiform mole
- Abnormal maternal serum screening results

Review of symptoms should seek symptoms of possible causes, including nausea and vomiting, abdominal pain, and jaundice (preeclampsia); pain, redness, or warmth in an extremity (DVT or cellulitis); dyspnea (pulmonary edema or preeclampsia); sudden increase in weight or edema of the hands and face (preeclampsia); and headache, confusion, mental status changes, blurry vision, or seizures (preeclampsia).

Past medical history should include history of DVT, pulmonary embolism, preeclampsia, and hypertension.

Physical examination: Examination begins with review of vital signs, particularly BP.

Areas of edema are evaluated for distribution (ie, whether bilateral and symmetric or unilateral) and presence of redness, warmth, and tenderness.

General examination focuses on systems that may show findings of preeclampsia. Eye examination includes testing visual fields for deficits, and funduscopic examination should check for papilledema.

Cardiovascular examination includes auscultation of the heart and lungs for evidence of fluid overload (eg, audible S_3 or S_4 heart sounds, tachypnea, rales, crackles) and inspection of neck veins for jugular venous distention. The abdomen should be palpated for tenderness, especially in the epigastric or right upper quadrant region. Neurologic examination should assess mental status for confusion and seek focal neurologic deficits.

Red flags: The following findings are of particular concern:

• BP ≥ 140/90 mm Hg

• Unilateral leg or calf warmth, redness, or tenderness, with or without fever

• Hypertension and any systemic symptoms or signs, particularly mental status changes

Interpretation of findings: Although edema is common during pregnancy, considering and ruling out the most dangerous causes (preeclampsia and DVT) are important:

• If BP is > 140/90 mm Hg, preeclampsia should be considered.

• If edema involves only one leg, particularly when redness, warmth, and tenderness are present, DVT and cellulitis should be considered.

• Bilateral leg edema suggests a physiologic process or preeclampsia as the cause.

Clinical findings help suggest a cause (see Table 261-7). Additional findings may suggest preeclampsia (see Table 261-8).

Testing: If preeclampsia is suspected, urine protein is measured; hypertension plus proteinuria indicates preeclampsia. Urine dipstick testing is used routinely, but if diagnosis is unclear, urine protein may be measured in a 24-h collection. Many laboratories can more rapidly assess urine protein by measuring and calculating the urine protein:urine creatinine ratio.

If DVT is suspected, lower-extremity duplex ultrasonography is done.

Treatment

Specific causes are treated.

Physiologic edema can be reduced by intermittently lying on the left side (which moves the uterus off the inferior vena cava), by intermittently elevating the lower extremities, and by wearing elastic compression stockings.

Key Points

• Edema is common and usually benign (physiologic) during late pregnancy.

• Physiologic edema is reduced by lying in the left lateral decubitus position, elevating the lower extremities, and using compression stockings.

[Table 261-8. Some Findings that Suggest Preeclampsia]

• Hypertension and proteinuria indicate preeclampsia.

• Unilateral leg edema, redness, warmth, and tenderness require evaluation for DVT.

Vaginal Bleeding During Late Pregnancy

Bleeding during late pregnancy (≥ 20 wk gestation, but before birth) occurs in 3 to 4% of pregnancies.

Pathophysiology

Some disorders can cause substantial blood loss, occasionally enough to cause hemorrhagic shock or disseminated intravascular coagulation.

Etiology

The most common cause of bleeding during late pregnancy is

• Bloody show of labor

Bloody show heralds onset of labor, is scant and mixed with mucus, and results from tearing of small veins as the cervix dilates and effaces at the start of labor.

More serious but less common causes (see Table 261-9) include

• Abruptio placentae (placental abruption)

• Placenta previa

• Vasa previa

• Uterine rupture (rare)

Abruptio placentae is premature separation of a normally implanted placenta from the uterine wall. The mechanism is unclear, but it is probably a late consequence of chronic uteroplacental vascular insufficiency. Some cases follow trauma (eg, assault, motor vehicle crash). Because some or most of the bleeding may be concealed between the placenta and uterine wall, the amount of external (ie, vaginal) bleeding does not necessarily reflect the extent of blood loss or placental separation. Abruptio placentae is the most common life-threatening cause of bleeding during late pregnancy, accounting for about 30% of cases. It may occur at any time but is most common during the 3rd trimester.

Placenta previa is abnormal implantation of the placenta over or near the internal cervical os. It results from various risk factors. Bleeding may be spontaneous or triggered by digital examination or by onset of labor. Placenta previa accounts for about 20% of bleeding during late pregnancy and is most common during the 3rd trimester.

In **vasa previa**, the fetal blood vessels connecting the cord and placenta overlie the internal cervical os and are in front of the fetal presenting part. Usually, this abnormal connection occurs when vessels from the cord run through part of the chorionic membrane rather than directly into the placenta (velamentous insertion). The mechanical forces of labor can disrupt these small blood vessels, causing them to rupture. Because of the relatively small fetal blood volume, even a small blood loss due to vasa previa can represent catastrophic hemorrhage for the fetus and cause fetal death.

Uterine rupture may occur during labor—almost always in women who have had scarring of the uterus (eg, due to cesarean delivery, uterine surgery, or uterine infection)—or after severe abdominal trauma.

[Table 261-9. Some Causes of Bleeding During Late Pregnancy]

Evaluation

The evaluation aims to exclude potentially serious causes of bleeding (abruptio placentae, placenta previa, vasa previa, uterine rupture). Bloody show of labor and abruptio placentae are diagnoses of exclusion.

History: History of present illness should include the patient's gravidity (number of confirmed pregnancies), parity (number of deliveries after 20 wk), and number of abortions (spontaneous or induced); duration of bleeding; and amount and color (bright red vs dark) of blood. Important associated symptoms include abdominal pain and rupture of membranes. Clinicians should note whether these symptoms are present or not and describe them (eg, whether pain is intermittent and crampy, as in labor, or constant and severe, suggesting abruptio placentae or uterine rupture).

Review of systems should elicit any history of syncope or near syncope (suggesting major hemorrhage).

Past medical history should note risk factors for major causes of bleeding (see Table 261-10), particularly previous cesarean delivery. Clinicians should determine whether patients have a history of hypertension, cigarette smoking, in vitro fertilization, or any illicit drug use (particularly cocaine).

Physical examination: Examination starts with review of vital signs, particularly BP, for signs of hypovolemia. Fetal heart rate is assessed, and continuous fetal monitoring is started if possible.

The abdomen is palpated for uterine size, tenderness, and tonicity (normal, increased, or decreased).

A digital cervical examination is contraindicated when bleeding occurs during late pregnancy until ultrasonography confirms normal placental and vessel location (and excludes placenta previa and vasa previa). Careful speculum examination can be done. If ultrasonography is normal, clinicians may proceed with a digital examination to determine cervical dilation and effacement.

Red flags: The following findings are of particular concern:

- Hypotension
- Tense, tender uterus
- Fetal distress (loss of heart sounds, bradycardia, variable or late decelerations detected during monitoring)
- Cessation of labor and atonic uterus

Interpretation of findings: If more than a few drops of blood are observed or there are

[Table 261-10. Some Risk Factors for Major Causes of Bleeding During Late Pregnancy]

signs of fetal distress, the more serious causes must be ruled out: abruptio placentae, placenta previa, vasa previa, and uterine rupture. However, some patients with abruptio placentae or uterine rupture have minimal visible bleeding despite major intra-abdominal or intrauterine hemorrhage.

Clinical findings help suggest a cause (see also Table 261-9). Light bleeding with mucus suggests bloody show of labor. Sudden, painless bleeding with bright red blood suggests placenta previa or vasa previa. Dark red clotted blood suggests abruptio placentae or uterine rupture. A tense, contracted, tender uterus suggests abruptio placentae; an atonic or abnormally shaped uterus with abdominal tenderness suggests uterine rupture.

Testing: The tests should include the following:

• Ultrasonography

• CBC and type and screen

• Possibly Kleihauer-Betke testing

All women with bleeding during late pregnancy require transvaginal ultrasonography, done at the bedside if the patient is unstable. A normal placenta and normal cord and vessel insertion exclude placenta previa and vasa previa. Although ultrasonography sometimes shows abruptio placentae, this test is not sufficiently reliable to distinguish abruptio placentae from uterine rupture. These diagnoses are made clinically, based on risk factors and examination findings (a tense uterus is more common in abruptio placentae; loss of tone is more common in rupture). Rupture is confirmed during laparotomy.

In addition, CBC and type and screen (blood typing and screening for abnormal antibodies) should be done. If bleeding is severe, if moderate to severe abruptio placentae is suspected, or if maternal hypotension is present, several units of blood are cross-matched and tests for disseminated intravascular coagulation (PT/PTT, fibrinogen level, D-dimer level) are done.

The Kleihauer-Betke test can be done to measure the amount of fetal blood in the maternal circulation and determine the need for additional doses of Rh_0(D) immune globulin to prevent maternal sensitization.

Treatment

Treatment is aimed at the specific cause. Patients with signs of hypovolemia require IV fluid resuscitation, starting with 20 mL/kg of normal saline solution. Blood transfusion should be considered for patients not responding to 2 L of saline.

Key Points

• All patients require IV access for fluid or blood resuscitation, as well as continuous maternal and fetal monitoring.

• A digital cervical examination is contraindicated in evaluation of bleeding during late pregnancy until placenta previa and vasa previa are excluded.

• In abruptio placentae, vaginal bleeding may be absent if blood is concealed between the placenta and uterine wall.

• Uterine rupture is suspected in women with a history of cesarean delivery or other uterine surgery.

• Vaginal bleeding may be mild despite maternal hypotension.

Chapter 262. Normal Pregnancy, Labor, and Delivery

Introduction

The earliest sign of pregnancy and the reason most pregnant women initially see a physician is missing a menstrual period. For sexually active women who are of reproductive age and have regular periods, missing a period for ≥ 1 wk is presumptive evidence of pregnancy.

Pregnancy is considered to last 266 days from the time of conception or 280 days from the first day of the last menstrual period if periods occur regularly every 28 days. Delivery date is estimated based on the last menstrual period. Delivery up to 2 wk earlier or later than the estimated date is normal.

Symptoms and Signs

Pregnancy may cause breasts to be engorged because of increased levels of estrogen (primarily) and progesterone—an extension of premenstrual breast engorgement. Nausea, occasionally with vomiting, may occur because of increased secretion of estrogen and the β subunit of human chorionic gonadotropin (β-hCG) by syncytial cells of the placenta, beginning 10 days after fertilization (see p. 2605). The corpus luteum in the ovary, stimulated by β-hCG, continues secreting large amounts of estrogen and progesterone to maintain the pregnancy. Many women become fatigued at this time, and a few women notice abdominal bloating very early. Women usually begin to feel fetal movement between 16 and 20 wk.

Pelvic examination findings include a softer cervix and an irregularly softened, enlarged uterus. The cervix usually becomes bluish to purple, probably because blood supply to the uterus is increased. Around 12 wk gestation, the uterus extends above the true pelvis into the abdomen; at 20 wk, it reaches the umbilicus; and by 36 wk, the upper pole almost reaches the xiphoid process.

Diagnosis

Usually urine and occasionally blood tests are used to confirm or exclude pregnancy; results are usually accurate several days before a missed menstrual period and often as early as several days after conception. Levels of β-hCG, which correlate with gestational age in normal pregnancies, can be used to determine whether a fetus is growing normally. The best approach is to compare 2 serum β-hCG values, obtained 48 to 72 h apart and measured by the same laboratory. In a normal single pregnancy, β-hCG levels double about every 1.4 to 2.1 days during the first 60 days (7.5 wk), then begin to decrease between 10 and 18 wk. Regular doubling of the β-hCG level during the 1st trimester strongly suggests normal growth.

Other accepted signs of pregnancy include the following:

- Presence of a gestational sac in the uterus, seen with ultrasonography typically at about 4 to 5 wk and typically corresponding to a serum β-hCG level of about 1500 mIU/mL (a yolk sac can usually be seen in the gestational sac by 5 wk)
- Fetal heart motion, seen with real-time ultrasonography as early as 5 to 6 wk
- Fetal heart sounds, heard with Doppler ultrasonography as early as 8 to 10 wk if the uterus is accessible abdominally
- Fetal movements felt by the examining physician after 20 wk

Physiology of Pregnancy

Pregnancy causes physiologic changes in all maternal organ systems; most return to normal after delivery. In general, the changes are more dramatic in multifetal than in single pregnancies.

Cardiovascular: Cardiac output (CO) increases 30 to 50%, beginning by 6 wk gestation and peaking

between 16 and 28 wk (usually at about 24 wk). It remains near peak levels until after 30 wk. Then, CO becomes sensitive to body position. Positions that cause the enlarging uterus to obstruct the vena cava the most (eg, the recumbent position) cause CO to decrease the most. On average, CO usually decreases slightly from 30 wk until labor begins. During labor, CO increases another 30%. After delivery, the uterus contracts, and CO drops rapidly to about 15 to 25% above normal, then gradually decreases (mostly over the next 3 to 4 wk) until it reaches the prepregnancy level at about 6 wk postpartum.

The increase in CO during pregnancy is due mainly to demands of the uteroplacental circulation; volume of the uteroplacental circulation increases markedly, and circulation within the intervillous space acts partly as an arteriovenous shunt. As the placenta and fetus develop, blood flow to the uterus must increase to about 1 L/min (20% of normal CO) at term. Increased needs of the skin (to regulate temperature) and kidneys (to excrete fetal wastes) account for some of the increased CO.

To increase CO, heart rate increases from the normal 70 to as high as 90 beats/min, and stroke volume increases. During the 2nd trimester, BP usually drops (and pulse pressure widens), even though CO and renin and angiotensin levels increase, because uteroplacental circulation expands (the placental intervillous space develops) and systemic vascular resistance decreases. Resistance decreases because blood viscosity and sensitivity to angiotensin decrease. During the 3rd trimester, BP may return to normal. With twins, CO increases more and diastolic BP is lower at 20 wk than with a single fetus.

Exercise increases CO, heart rate, O_2 consumption, and respiratory volume/min more during pregnancy than at other times. The hyperdynamic circulation of pregnancy increases frequency of functional murmurs and accentuates heart sounds. X-ray or ECG may show the heart displaced into a horizontal position, rotating to the left, with increased transverse diameter. Premature atrial and ventricular beats are common during pregnancy. All these changes are normal and should not be erroneously diagnosed as a heart disorder; they can usually be managed with reassurance alone. However, paroxysms of atrial tachycardia occur more frequently in pregnant women and may require prophylactic digitalization or other antiarrhythmic drugs. Pregnancy does not affect the indications for or safety of cardioversion.

Hematologic: Total blood volume increases proportionally with CO, but the increase in plasma volume is greater (close to 50%, usually by about 1600 mL for a total of 5200 mL) than that in RBC mass (about 25%); thus, Hb is lowered by dilution, from about 13.3 to 12.1 g/dL. This dilutional anemia decreases blood viscosity. With twins, total maternal blood volume increases more (closer to 60%).

WBC count increases slightly to 9,000 to 12,000/µL. Marked leukocytosis (≥ 20,000/µL) occurs during labor and the first few days postpartum.

Iron requirements increase by a total of about 1 g during the entire pregnancy and are higher during the 2nd half of pregnancy—6 to 7 mg/day. The fetus and placenta use about 300 mg of iron, and the increased maternal RBC mass requires an additional 500 mg. Excretion accounts for 200 mg. Iron supplements are needed to prevent a further decrease in Hb levels because the amount absorbed from the diet and recruited from iron stores (average total of 300 to 500 mg) is usually insufficient to meet the demands of pregnancy.

Urinary: Changes in renal function roughly parallel those in cardiac function. GFR increases 30 to 50%, peaks between 16 and 24 wk gestation, and remains at that level until nearly term, when it may decrease slightly because uterine pressure on the vena cava often causes venous stasis in the lower extremities. Renal plasma flow increases in proportion to GFR. As a result, BUN decreases, usually to < 10 mg/dL (< 3.6 mmol urea/L), and creatinine levels decrease proportionally to 0.5 to 0.7 mg/dL (44 to 62 µmol/L). Marked dilation of the ureters (hydroureter) is caused by hormonal influences (predominantly progesterone) and by backup due to pressure from the enlarged uterus on the ureters, which can also cause hydronephrosis. Postpartum, the urinary collecting system may take as long as 12 wk to return to normal.

Postural changes affect renal function more during pregnancy than at other times; ie, the supine position increases renal function more, and upright positions decrease renal function more. Renal function also markedly increases in the lateral position; this position relieves the pressure that the enlarged uterus puts on the great vessels when pregnant women are supine. This positional increase in renal function is one

reason pregnant women need to urinate frequently when trying to sleep.

Respiratory: Lung function changes partly because progesterone increases and partly because the enlarging uterus interferes with lung expansion. Progesterone signals the brain to lower CO_2 levels. To lower CO_2 levels, tidal and minute volume and respiratory rate increase, thus increasing plasma pH. O_2 consumption increases by about 20% to meet the increased metabolic needs of the fetus, placenta, and several maternal organs. Inspiratory and expiratory reserve, residual volume and capacity, and plasma PCO_2 decrease. Vital capacity and plasma PO_2 do not change. Thoracic circumference increases by about 10 cm. Considerable hyperemia and edema of the respiratory tract occur. Occasionally, symptomatic nasopharyngeal obstruction and nasal stuffiness occur, eustachian tubes are transiently blocked, and tone and quality of voice change. Mild dyspnea during exertion is common, and deep respirations are more frequent.

GI and hepatobiliary: As pregnancy progresses, pressure from the enlarging uterus on the rectum and lower portion of the colon may cause constipation. GI motility decreases because elevated progesterone levels relax smooth muscle. Heartburn and belching are common, possibly resulting from delayed gastric emptying and gastroesophageal reflux due to relaxation of the lower esophageal sphincter and diaphragmatic hiatus. HCl production decreases; thus, peptic ulcer disease is uncommon during pregnancy, and preexisting ulcers often become less severe.

Incidence of gallbladder disorders increases somewhat. Pregnancy subtly affects hepatic function, especially bile transport. Routine liver function test values are normal, except for alkaline phosphatase levels, which increase progressively during the 3rd trimester and may be 2 to 3 times normal at term; the increase is due to placental production of this enzyme rather than hepatic dysfunction.

Endocrine: Pregnancy alters the function of most endocrine glands, partly because the placenta produces hormones and partly because most hormones circulate in protein-bound forms and protein binding increases during pregnancy.

The placenta produces a hormone (similar to thyroid-stimulating hormone) that stimulates the thyroid, causing hyperplasia, increased vascularity, and moderate enlargement. Estrogen stimulates hepatocytes, causing increased thyroid-binding globulin levels; thus, although total thyroxine levels may increase, levels of free thyroid hormones remain normal. Effects of thyroid hormone tend to increase and may resemble hyperthyroidism, with tachycardia, palpitations, excessive perspiration, and emotional instability. However, true hyperthyroidism occurs in only 0.08% of pregnancies.

The placenta produces corticotropin-releasing hormone (CRH), which stimulates maternal ACTH production. Increased ACTH levels increase levels of adrenal hormones, especially aldosterone and cortisol, and thus contribute to edema. Increased production of corticosteroids and increased placental production of progesterone lead to insulin resistance and an increased need for insulin, as does the stress of pregnancy and possibly the increased level of human placental lactogen. Insulinase, produced by the placenta, may also increase insulin requirements, so that many women with gestational diabetes develop more overt forms of diabetes (see pp. 866 and 2638).

The placenta produces melanocyte-stimulating hormone (MSH), which increases skin pigmentation late in pregnancy. The placenta also produces the β subunit of human chorionic gonadotropin (β-hCG), a trophic hormone that, like follicle-stimulating and luteinizing hormones, maintains the corpus luteum and thereby prevents ovulation.

The pituitary gland enlarges by about 135% during pregnancy. The maternal plasma prolactin level increases by 10-fold. Increased prolactin is related to an increase in thyrotropin-releasing hormone production, stimulated by estrogen. The primary function of increased prolactin is to ensure lactation. The level returns to normal postpartum, even in women who breastfeed.

Dermatologic: Increased levels of estrogens, progesterone, and MSH contribute to pigmentary changes, although exact pathogenesis is unknown. These changes include melasma (mask of pregnancy), which is a blotchy, brownish pigment over the forehead and malar eminences; darkening of the mammary areolae,

axilla, and genitals; and linea nigra, a dark line that appears down the midabdomen. Melasma due to pregnancy usually regresses within a year.

Incidence of spider angiomas, usually only above the waist, and thin-walled, dilated capillaries, especially in the lower legs, increases.

Drugs in Pregnancy

The most commonly used drugs include anti-emetics, antacids, antihistamines, analgesics, antimicrobials, diuretics, hypnotics, tranquilizers, and social and illicit drugs.

The FDA classifies drugs into 5 categories of safety for use during pregnancy (see Table 262-1). However, few well-controlled studies of therapeutic drugs have been conducted in pregnant women. Most information about drug safety during pregnancy is derived from animal studies and uncontrolled studies in people (eg, postmarketing reports). During pregnancy, drugs are often required to treat certain disorders (see Table 264-2 on p. 2656). Despite widespread concern about drug safety, exposure to therapeutic drugs accounts for only 2 to 3% of all fetal congenital malformations; most malformations result from genetic, environmental, or unknown causes.

Not all maternal drugs cross the placenta to the fetus. Those that do can have a direct toxic or teratogenic effect (for known and suspected teratogens, see Table 262-2). Those that do not cross the placenta may still harm the fetus by constricting placental vessels and thus impairing gas and nutrient exchange, by producing severe uterine hypertonia resulting in anoxic injury, or by altering maternal physiology (eg, causing hypotension).

[**Table 262-1.** FDA Categories of Drug Safety During Pregnancy]

Drugs diffuse across the placenta similarly to the way they cross other epithelial barriers (see p. 3172). Whether and how quickly a drug crosses the placenta depend on the drug's molecular weight, extent of its binding to another substance (eg, carrier protein), area available for exchange across the villi, and amount of drug metabolized by the placenta. Most drugs with a molecular weight < 500 daltons readily cross the placenta and enter fetal circulation. Substances with a high molecular weight (eg, protein-bound drugs) usually do not cross the placenta. The exception is immune globulin G, which is occasionally used to treat disorders such as fetal alloimmune thrombocytopenia. Generally, equilibration between maternal blood and fetal tissues takes at least 40 min.

A drug's effect on the fetus is determined largely by fetal age at exposure, drug potency, and drug dosage. Fetal age affects the type of drug effect:

- **Before the 20th day after fertilization:** Drugs given at this time may have an all-or-nothing effect, killing the embryo or not affecting it at all. Teratogenesis is not likely during this stage.

- **During organogenesis (between 20 and 56 days after fertilization):** Teratogenesis is most likely at this stage. Drugs reaching the embryo at this stage may result in abortion, a sublethal gross anatomic defect (true teratogenic effect), or covert embryopathy (a permanent subtle metabolic or functional defect that may manifest later in life), or the drugs may have no measurable effect.

- **After organogensis (in the 2nd and 3rd trimesters):** Teratogenesis is unlikely, but drugs may alter growth and function of normally formed fetal organs and tissues.

Vaccines: Immunization is as effective in women who are pregnant as in those who are not. Influenza vaccine is recommended for all pregnant women in the 2nd or 3rd trimester during influenza season. Other vaccines should be reserved for situations in which the woman or fetus is at significant risk of exposure to a hazardous infection and risk of adverse effects from the vaccine is low. Vaccinations for cholera, hepatitis A and B, measles, mumps, plague, poliomyelitis, rabies, tetanus-diphtheria, typhoid, and yellow fever may be given during pregnancy if risk of infection is substantial.

Live-virus vaccines should not be given to women who are or may be pregnant. Rubella vaccine, an attenuated live-virus vaccine, may cause subclinical placental and fetal infection. However, no defects in neonates have been attributed to rubella vaccine, and women vaccinated inadvertently during early pregnancy need not be advised to terminate pregnancy based solely on theoretical risk from the vaccine. Varicella is another attenuated live-virus vaccine that can potentially infect the fetus; risk is highest between 13 wk and

[Table 262-2. Known or Suspected Teratogens]

22 wk gestation. This vaccine is contraindicated during pregnancy.

Vitamin A: In the amount typically present in prenatal vitamins (5000 IU/day), vitamin A has not been associated with teratogenic risk. However, doses > 10,000 IU/day during early pregnancy may increase risk of congenital malformations.

Social and illicit drugs: Cigarette smoking and use of alcohol during pregnancy can cause significant problems in fetuses and neonates (see p. 2655).

Although marijuana's main metabolite can cross the placenta, recreational use of this drug does not appear to consistently increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities.

Many mothers of children with congenital heart defects used amphetamines during pregnancy, suggesting a possible teratogenic association.

Women who used cocaine during pregnancy have had perinatal complications, including abruptio placentae and stillbirth; however, no consistent teratogenic effects have been shown.

Whether consuming large amounts of caffeine can increase risk of perinatal complications is unclear. Consuming caffeine in small amounts (eg, 1 cup of coffee/day) appears to pose little or no risk to the fetus, but some data, which did not account for tobacco or alcohol use, suggest that consuming large amounts (> 7 cups of coffee/day) increases risk of stillbirths, preterm deliveries, low birth weight, and spontaneous abortions. Decaffeinated beverages theoretically pose little risk to the fetus.

Use of the dietary sugar substitute aspartame during pregnancy is often questioned. The most common metabolite of aspartame, phenylalanine, is concentrated in the fetus by active placental transport; toxic levels may cause intellectual disability (mental retardation). However, when ingestion is within the usual range, fetal phenylalanine levels are far below toxic levels. Thus, moderate ingestion of aspartame (eg, no more than 1 liter of diet soda per day) during pregnancy appears to pose little risk of fetal toxicity. However, in pregnant women with phenylketonuria (see p. 3011), intake of phenylalanine and thus aspartame is prohibited.

Management of Normal Labor

Labor consists of a series of rhythmic, involuntary, progressive contractions of the uterus that cause effacement (thinning and shortening) and dilation of the uterine cervix. The stimulus for labor is unknown, but digitally manipulating or mechanically stretching the cervix during examination enhances uterine contractile activity, most likely by stimulating release of oxytocin by the posterior pituitary gland. Normal labor usually begins within 2 wk (before or after) the estimated delivery date. In a first pregnancy, labor usually lasts 12 to 18 h on average; subsequent labors are often shorter, averaging 6 to 8 h. Management of complications during labor requires additional measures (see p. 2676).

Beginning of labor: Bloody show (a small amount of blood with mucous discharge from the cervix) may precede onset of labor by as much as 72 h. Bloody show can be differentiated from abnormal 3rd-trimester vaginal bleeding because the amount is small, bloody show is typically mixed with mucus, and the pain due to abruptio placentae (premature separation) is absent. In most pregnant women, previous ultrasonography has been done and ruled out placenta previa. However, if ultrasonography has not ruled out placenta previa and vaginal bleeding occurs, placenta previa is assumed to be present until it is ruled

out. Digital vaginal examination is contraindicated, and ultrasonography is done as soon as possible.

Labor begins with irregular uterine contractions of varying intensity; they apparently soften (ripen) the cervix, which begins to efface and dilate. As labor progresses, contractions increase in duration, intensity, and frequency.

Stages of labor: There are 3 stages of labor.

The 1st stage—from onset of labor to full dilation of the cervix (about 10 cm)—has 2 phases, latent and active.

During the latent phase, irregular contractions become progressively better coordinated, discomfort is minimal, and the cervix effaces and dilates to 4 cm. The latent phase is difficult to time precisely, and duration varies, averaging 8 h in nulliparas and 5 h in multiparas; duration is considered abnormal if it lasts > 20 h in nulliparas or > 12 h in multiparas.

During the active phase, the cervix becomes fully dilated, and the presenting part descends well into the midpelvis. On average, the active phase lasts 5 to 7 h in nulliparas and 2 to 4 h in multiparas. The cervix should dilate 1.2 cm/h in nulliparas and 1.5 cm/h in multiparas. Pelvic examinations are done every 2 to 3 h to evaluate labor progress. Lack of progress in dilation and descent of the presenting part may indicate dystocia (fetopelvic disproportion). If the membranes have not spontaneously ruptured, some clinicians routinely use amniotomy (artificial rupture of membranes) during the active phase. As a result, labor may progress more rapidly, and meconium-stained amniotic fluid may be detected earlier. Amniotomy during this stage may be necessary for specific indications, such as facilitating internal fetal monitoring to confirm fetal well-being. Amniotomy should be avoided in women with HIV infection or hepatitis B or C, so that the fetus is not exposed to these organisms.

Maternal heart rate and BP and fetal heart rate should be checked continuously by electronic monitoring or intermittently by auscultation during the 1st stage of labor (see p. 2630). Women may begin to feel the urge to bear down as the presenting part descends into the pelvis. However, they should be discouraged from bearing down until the cervix is fully dilated so that they do not tear the cervix or waste energy.

The 2nd stage is the time from full cervical dilation to delivery of the fetus. On average, it lasts 2 h in nulliparas (median 50 min) and 1 h in multiparas (median 20 min). It may last another hour or more if conduction (epidural) analgesia or intense opioid sedation is used. For spontaneous delivery, women must supplement uterine contractions by expulsively bearing down. In the 2nd stage, women should be attended constantly, and fetal heart sounds should be checked continuously or after every contraction. Contractions may be monitored by palpation or electronically.

The 3rd stage of labor begins after delivery of the infant and ends with delivery of the placenta.

Rupture of membranes: Occasionally, the membranes (amniotic and chorionic sac) rupture before labor begins, and amniotic fluid leaks through the cervix and vagina. Rupture of membranes at any stage before the onset of labor is called premature rupture of membranes (PROM—see p. 2682). Some women with PROM feel a gush of fluid from the vagina, followed by steady leaking. Further confirmation is not needed if during examination, fluid is seen leaking from the cervix.

Confirmation of more subtle cases may require testing. For example, the pH of vaginal fluid may be tested with Nitrazine paper, which turns deep blue at a pH > 6.5 (pH of amniotic fluid: 7.0 to 7.6); false-positive results can occur if vaginal fluid contains blood or semen or if certain infections are present. A sample of the secretions from the posterior vaginal fornix or cervix may be obtained, placed on a slide, air dried, and viewed microscopically for ferning. Ferning (crystallization of NaCl in a palm leaf pattern in amniotic fluid) usually confirms rupture of membranes. If rupture is still unconfirmed, ultrasonography showing oligohydramnios (deficient amniotic fluid) provides further evidence suggesting rupture. Rarely, amniocentesis with instillation of dye is done to confirm rupture; dye detected in the vagina or on a tampon confirms rupture.

When a woman's membranes rupture, she should contact her physician immediately. About 80 to 90% of

women with PROM at term and about 50% of women with PROM preterm go into labor spontaneously within 24 h; > 90% of women with PROM go into labor within 2 wk. The earlier the membranes rupture before 37 wk, the longer the delay between rupture and labor onset. If membranes rupture at term but labor does not start within several hours, labor is typically induced to lower risk of maternal and fetal infection.

Birthing options: Most women prefer hospital delivery, and most health care practitioners recommend it because unexpected maternal and fetal complications may occur during labor and delivery or postpartum, even in women without risk factors. About 30% of hospital deliveries involve an obstetric complication (eg, laceration, postpartum hemorrhage). Other complications include abruptio placentae, nonreassuring fetal heart rate pattern, shoulder dystocia, need for emergency cesarean delivery, and neonatal depression or abnormality. Nonetheless, many women want a more homelike environment for delivery; in response, some hospitals provide birthing facilities with fewer formalities and rigid regulations but with emergency equipment and personnel available. Birthing centers may be freestanding or located in hospitals; care at either site is similar or identical. In some hospitals, certified nurse-midwives provide much of the care for low-risk pregnancies. Midwives work with a physician, who is continuously available for consultation and operative deliveries (eg, by forceps, vacuum extractor, or cesarean). All birthing options should be discussed.

For many women, presence of the father or another support person during labor is helpful and should be encouraged. Moral support, encouragement, and expressions of affection decrease anxiety and make labor less frightening and unpleasant. Childbirth education classes can prepare parents for a normal or complicated labor and delivery. Sharing the stresses of labor and the sight and sound of their own child tends to create strong bonds between the parents and between parents and child. The parents should be fully informed of any complications.

Admission: Typically, pregnant women are advised to go to the hospital if they believe their membranes have ruptured or if they are experiencing contractions lasting at least 30 sec and occurring regularly at intervals of about ≤ 6 min. Within an hour after presentation at a hospital, whether a woman is in labor can usually be determined based on occurrence of regular and sustained painful uterine contractions, bloody show, membrane rupture, and complete cervical effacement. If these criteria are not met, false labor may be tentatively diagnosed, and the pregnant woman is typically observed for a time and, if labor does not begin within several hours, is sent home.

When pregnant women are admitted, their BP, heart and respiratory rates, temperature, and weight are recorded, and presence or absence of edema is noted. A urine specimen is collected for protein and glucose analysis, and blood is drawn for a CBC and blood typing. A physical examination is done. While examining the abdomen, the clinician estimates size, position, and presentation of the fetus, using Leopold's maneuvers (see Fig. 262-1). The clinician notes the presence and rate of fetal heart sounds, as well as location for auscultation. Preliminary estimates of the strength, frequency, and duration of contractions are also recorded. A helpful mnemonic device for evaluation is the 3 Ps: powers (contraction strength, frequency, and duration), passage (pelvic measurements), and passenger (eg, fetal size, position, heart rate pattern).

If labor is active and the pregnancy is at term, a clinician examines the vagina with 2 fingers of a gloved hand to evaluate progress of labor. If bleeding (particularly if heavy) is present, the examination is delayed until placental location is confirmed by ultrasonography. If bleeding results from placenta previa, vaginal examination can initiate severe hemorrhage. If labor is not active but membranes are ruptured, a speculum examination is done initially

[**Fig. 262-1.** Leopold maneuver.]

to document cervical dilation and effacement and to estimate station (location of the presenting part); however, digital examinations are delayed until the active phase of labor or problems (eg, decreased fetal heart sounds) occur. If the membranes have ruptured, any fetal meconium (producing greenish-brown discoloration) should be noted because it may be a sign of fetal stress. If labor is preterm (< 37 wk) or has not begun, only a sterile speculum examination should be done, and a culture should be taken for

gonococci, chlamydiae, and group B streptococci.

Cervical dilation is recorded in centimeters as the diameter of a circle; 10 cm is considered complete. Effacement is estimated in percentages, from 0 to 100%. Because effacement involves cervical shortening as well as thinning, it may be recorded in centimeters using the normal, uneffaced average cervical length of 3.5 to 4.0 cm as a guide.

Station is expressed in centimeters above or below the level of the maternal ischial spines. Level with the ischial spines corresponds to 0 station; levels above (+) or below (-) the spines are recorded in cm increments. Fetal lie, position, and presentation are noted. Lie describes the relationship of the long axis of the fetus to that of the mother (longitudinal, oblique, transverse); presentation describes the part of the fetus at the cervical opening (eg, breech, vertex, shoulder). Position describes the relationship of the presenting part to the maternal pelvis (eg, occiput left anterior [OLA] for cephalic, sacrum right posterior [SRP] for breech).

Preparation for delivery: Women are admitted to the labor suite for frequent observation until delivery. If labor is active, they should receive little or nothing by mouth to prevent possible vomiting and aspiration during delivery or in case emergency delivery with general anesthesia is necessary. Enemas and shaving or clipping of vulvar hair are no longer indicated. An IV infusion of Ringer's lactate may be started, preferably using a large-bore indwelling catheter inserted into a vein in the hand or forearm. During a normal labor of 6 to 10 h, women should be given 500 to 1000 mL of this solution. The infusion prevents dehydration during labor and subsequent hemoconcentration and maintains an adequate circulating blood volume. The catheter also provides immediate access for drugs or blood if needed. Fluid preloading is valuable if epidural or spinal anesthesia is planned.

Analgesia: Analgesics may be given during labor as needed, but as little as possible should be given because they cross the placenta and may depress the neonate's breathing. Neonatal toxicity can occur because after the umbilical cord is cut, the neonate, whose metabolic and excretory processes are immature, clears the transferred drug much more slowly, by liver metabolism or by urinary excretion. Preparation for and education about childbirth lessen anxiety, markedly decreasing the need for analgesics.

Physicians are increasingly offering epidural injection (providing regional anesthesia) as the first choice for analgesia during labor. Typically, a local anesthetic (eg, 0.2% ropivacaine, 0.125% bupivacaine) is continuously infused, often with an opioid (eg, fentanyl, sufentanil), into the lumbar epidural space. Initially, the anesthetic is given cautiously to avoid masking the awareness of pressure that helps stimulate pushing and to avoid motor block; both effects can slow labor.

If epidural injection is inadequate or if IV administration is preferred, fentanyl (100 µg), meperidine (up to 25 mg), or morphine sulfate (up to 10 mg) given IV q 60 to 90 min is commonly used. These opioids provide good analgesia with only a small total dose. If toxicity results, respiration is supported, and naloxone 0.01 mg/kg can be given IM, IV, sc, or endotracheally to the neonate as a specific antagonist. Naloxone may be repeated in 1 to 2 min as needed based on the neonate's response. Clinicians should check the neonate 1 to 2 h after the initial dosing with naloxone because the effects of the earlier dose abate. If fentanyl, meperidine, or morphine provides insufficient analgesia, an additional dose of the opioid or another analgesic method should be used rather than the so-called synergistic drugs (eg, promethazine), which have no antidote. (These drugs are actually additive, not synergistic.) Synergistic drugs are still sometimes used because they lessen nausea due to the opioid; doses should be small.

Fetal Monitoring

Fetal status must be monitored during labor. The main parameters are fetal heart rate (HR) and fetal HR variability, particularly as it relates to uterine contractions and maternal movement. Several patterns are recognized. One is considered normal and reassuring; the others are considered abnormal and nonreassuring. A normal pattern is a baseline HR with the following characteristics:

• 120 to 160 beats/min

- Varies by 6 to 25 beats with movement or contractions (normal HR variability)
- Accelerates appropriately for gestational age
- Does not decelerate during contractions

Patterns that indicate possible nonreassuring fetal heart status include the following:

- Late decelerations: HR gradually decreases and returns to baseline with contractions, but the decrease begins late, and most of it occurs (and HR is slowest) after contractions peak.
- Variable decelerations: HR decreases abruptly by ≥ 15 beats/min; the decrease may or may not occur simultaneously with contractions and varies in onset, depth, and duration (≥ 15 sec but < 2 min).
- Tachycardia
- Severe bradycardia: HR is ≤ 110 beats/min.
- Loss of normal HR variability

Nonreassuring patterns require more intensive monitoring.

Monitoring can be manual and intermittent, using a fetoscope for auscultation of fetal HR. However, in the US, electronic fetal HR monitoring (external or internal) has become standard of care for high-risk pregnancies, and many clinicians use it for all pregnancies. Although this practice has been lifesaving, its value is debated, partly because many apparent abnormalities are false positives, leading to unnecessary cesarean deliveries. Rate of cesarean delivery is higher among women monitored electronically than among those monitored by auscultation. Fetal pulse oximetry is being studied as a way to confirm abnormal or equivocal results of electronic monitoring; fetal oxygenation may help determine whether a cesarean delivery is needed. For oximetry, an internal sensor must be placed inside the uterus and against the fetal skin to ensure an accurate reading of fetal oxygenation. However, fetal pulse oximetry does not appear to change the rate of cesarean delivery from that based on results of fetal HR monitoring alone.

If manual auscultation of fetal HR is used, it must be done throughout labor according to specific guidelines, and one-on-one nursing care is needed. For low-risk pregnancies with normal labor, fetal HR must be checked after each contraction or at least every 30 min during the 1st stage of labor and every 15 min during the 2nd stage. For high-risk pregnancies, fetal HR must be checked every 15 min during the 1st stage and every 3 to 5 min during the 2nd stage. Listening for at least 1 to 2 min beginning at a contraction's peak is recommended to check for late deceleration. Periodic auscultation has a lower false-positive rate for abnormalities and incidence of intervention than continuous electronic monitoring, and it provides opportunities for more personal contact with women during labor. However, following the standard guidelines for auscultation is often difficult and may not be cost-effective. Also, unless done accurately, auscultation may not detect abnormalities.

For external electronic fetal HR monitoring, devices are applied to the maternal abdomen to record fetal heart sounds and uterine contractions. For internal monitoring, amniotic membranes must be ruptured. Then, leads are inserted through the cervix; an electrode is attached to the fetal scalp to monitor HR, and a catheter is placed in the uterine cavity to measure intrauterine pressure. Usually, external and internal monitoring are similarly reliable. External devices are used for women in normal labor; internal methods are used when external monitoring does not supply enough information about fetal well-being or uterine contraction intensity (eg, if the external sensor is not functioning correctly).

External electronic fetal monitoring can be used during labor or electively to continuously record fetal HR and correlate it with fetal movements (called a nonstress test). A nonstress test is interpreted as nonreassuring if no accelerations occur during a 40-min period. External monitoring can be used similarly with a contraction stress test; fetal movements and HR are monitored during contractions induced by oxytocin (oxytocin challenge test) or breast stimulation or during spontaneous contractions. Nonstress

and contraction stress tests are frequently used to monitor complicated or high-risk pregnancies (eg, complicated by maternal diabetes or hypertension or by prior stillbirth or fetal growth restriction).

If a problem (eg, fetal HR decelerations, lack of normal HR variability) is detected during labor, intrauterine fetal resuscitation is tried; women may be given O_2 via a tight non-rebreather face mask or rapid IV fluid infusion or may be positioned laterally. If fetal heart pattern does not improve in a reasonable period and delivery is not imminent, urgent cesarean delivery is needed.

Management of Normal Delivery

Many obstetric units now use a combined labor, delivery, recovery, and postpartum (LDRP) room, so that the woman, father or other support person, and neonate remain in the same room throughout their stay. Some units use a traditional labor room and separate delivery suite, to which the woman is transferred when delivery is imminent. The support person should be offered the opportunity to accompany her. In the delivery room, the perineum is washed and draped, and the neonate is delivered. After delivery, the woman may remain there or be transferred to a postpartum unit. Management of complications during delivery requires additional measures (see p. 2676).

Anesthesia

Options include regional, local, and general anesthesia. Local anesthetics and opioids are commonly used. These drugs pass through the placenta; thus, during the hour before delivery, such drugs should be given in small doses to avoid toxicity (eg, CNS depression, bradycardia) in the neonate. Opioids used alone do not provide adequate analgesia and so are most often used with anesthetics.

Regional anesthesia: Several methods are available.

Lumbar epidural injection of a local anesthetic (see p. 2630) is the most commonly used method. Epidural injection is being increasingly used for delivery, including cesarean, and has essentially replaced pudendal and paracervical blocks. The local anesthetics often used for epidural injection (eg, bupivacaine) have a longer duration of action and slower onset than those used for pudendal block (eg, lidocaine).

Other methods include caudal injection (into the sacral canal), which is rarely used, and spinal injection (into the paraspinal subarachnoid space). Spinal injection may be used for cesarean delivery, but it is used less often for vaginal deliveries because it is short-lasting (preventing its use during labor) and has a small risk of spinal headache afterward. When spinal injection is used, patients must be constantly attended, and vital signs must be checked every 5 min to detect and treat possible hypotension.

Local anesthesia: Methods include pudendal block, perineal infiltration, and paracervical block.

Pudendal block, rarely used because epidural injections are used instead, involves injecting a local anesthetic through the vaginal wall so that the anesthetic bathes the pudendal nerve as it crosses the ischial spine. This block anesthetizes the lower vagina, perineum, and posterior vulva; the anterior vulva, innervated by lumbar dermatomes, is not anesthetized. Pudendal block is a safe, simple method for uncomplicated spontaneous vaginal deliveries if women wish to bear down and push or if labor is advanced and there is no time for epidural injection.

Infiltration of the perineum with an anesthetic is commonly used, although this method is not as effective as a well-administered pudendal block.

Paracervical block is rarely appropriate for delivery because incidence of fetal bradycardia is > 15%. It is used mainly for 1st- or early 2nd-trimester abortions. The technique involves injecting 5 to 10 mL of 1% lidocaine at the 3 and 9 o'clock positions; the analgesic response is short-lasting.

General anesthesia: Because potent and volatile inhalation drugs (eg, isoflurane) can cause marked depression in mother and fetus, general anesthesia is not recommended for routine delivery. Rarely, nitrous oxide 40% with O_2 may be used for analgesia during vaginal delivery as long as verbal contact

with the woman is maintained. Thiopental, a hypnotic, is commonly given IV with other drugs (eg, succinylcholine, nitrous oxide plus O_2) for induction of general anesthesia during cesarean delivery; used alone, thiopental provides inadequate analgesia. With thiopental, induction is rapid and recovery is prompt. It becomes concentrated in the fetal liver, preventing levels from becoming high in the CNS; high levels in the CNS may cause neonatal depression. Increased interest in preparation for childbirth has reduced the need for general anesthesia except for cesarean delivery.

Delivery Procedures

A vaginal examination is done to determine position and station of the fetal head; the head is usually the presenting part (see Fig. 262-2). When effacement is complete and the cervix is fully dilated, the woman is told to bear down and strain with each contraction to move the head through the pelvis and progressively dilate the vaginal introitus so that more and more of the head appears. When about 3 or 4 cm of the head is visible during a contraction in nulliparas (somewhat less in multiparas), the following maneuvers can facilitate delivery and reduce risk of perineal laceration.

- The clinician, if right-handed, places the left palm over the infant's head during a contraction to control and, if necessary, slightly slow progress.

- Simultaneously, the clinician places the curved fingers of the right hand against the dilating perineum, through which the infant's brow or chin is felt.

- To advance the head, the clinician can wrap a hand in a towel and, with curved fingers, apply pressure against the underside of the brow or chin (modified Ritgen maneuver).

[**Fig. 262-2.** Sequence of events in delivery for vertex presentations.]

Thus, the clinician controls the progress of the head to effect a slow, safe delivery.

Forceps or a vacuum extractor (see p. 2676) is often used for vaginal delivery when the 2nd stage of labor is likely to be prolonged (eg, because the mother is too exhausted to bear down adequately or because regional epidural anesthesia precludes vigorous bearing down). If anesthesia is local (pudendal block or infiltration of the perineum), forceps or a vacuum extractor is usually not needed unless complications develop; local anesthesia may not interfere with bearing down. Indications for forceps and vacuum extractor are essentially the same.

An **episiotomy** is not routine and is done only if the perineum does not stretch adequately and is obstructing delivery, usually only for first deliveries at term. A local anesthetic can be infiltrated if epidural analgesia is inadequate. Episiotomy prevents excessive stretching and possible tearing of the perineal tissues, including anterior tears. The incision is easier to repair than a tear.

The most common type is a midline incision made from the midpoint of the fourchette directly back toward the rectum. Extension into the rectal sphincter or rectum is a risk, but if recognized promptly, the extension can be repaired successfully and heals well. Tears or extensions into the rectum can usually be prevented by keeping the infant's head well flexed until the occipital prominence passes under the symphysis pubis.

Another type of episiotomy is a mediolateral incision made from the midpoint of the fourchette at a 45° angle laterally on either side. This type usually does not extend into the sphincter or rectum, but it causes greater postoperative pain and takes longer to heal than midline episiotomy. Thus, for episiotomy, a midline cut is preferred. However, use of episiotomy is decreasing because extension or tearing into the sphincter or rectum is a concern. Episioproctotomy (intentionally cutting into the rectum) is not recommended because rectovaginal fistula is a risk.

When the head is delivered, the clinician determines whether the umbilical cord is wrapped around the neck. If it is, the clinician should try to unwrap the cord; if the cord cannot be rapidly removed this way, the cord may be clamped and cut.

After delivery of the head, the infant's body rotates so that the shoulders are in an anteroposterior position; gentle downward pressure on the head delivers the anterior shoulder under the symphysis. The head is gently lifted, the posterior shoulder slides over the perineum, and the rest of the body follows without difficulty. The nose, mouth, and pharynx are aspirated with a bulb syringe to remove mucus and fluids and help start respirations. The cord should be double-clamped and cut between the clamps, and a plastic cord clip should be applied about 2 to 3 cm distal from the cord insertion on the infant. If fetal or neonatal compromise is suspected, a segment of umbilical cord is double-clamped so that arterial blood gas analysis can be done. An arterial pH > 7.l5 to 7.20 is considered normal. The infant is thoroughly dried, then placed on the mother's abdomen or, if resuscitation is needed, in a warmed resuscitation bassinet.

Placenta: After delivery of the infant, the clinician places a hand gently on the abdomen over the uterine fundus to detect contractions; placental separation usually occurs during the 1st or 2nd contraction, often with a gush of blood from behind the separating placenta. The mother can usually help deliver the placenta by bearing down. If she cannot and if substantial bleeding occurs, the placenta can usually be evacuated (expressed) by placing a hand on the abdomen and exerting firm downward (caudal) pressure on the uterus; this procedure is done only if the uterus feels firm because pressure on a flaccid uterus can cause it to invert. If this procedure is not effective, the clinician holds the umbilical cord taut while placing the other hand on the abdomen and pushing upward (cephalad) on the firm uterus, away from the placenta; traction on the umbilical cord is avoided because it may invert the uterus. If the placenta has not been delivered within 45 to 60 min of delivery, manual removal may be necessary; the clinician inserts an entire hand into the uterine cavity, separating the placenta from its attachment, then extracts the placenta. In such cases, an abnormally adherent placenta (placenta accreta—see p. 2669) should be suspected.

The placenta should be examined for completeness because fragments left in the uterus can cause hemorrhage or infection later. If the placenta is incomplete, the uterine cavity should be explored manually. Some obstetricians routinely explore the uterus after each delivery. However, exploration is uncomfortable and is not routinely recommended. Immediately after delivery of the placenta, an oxytocic drug (oxytocin 10 units IM or as an infusion of 20 units/1000 mL saline at 125 mL/h) is given to help the uterus contract firmly. Oxytocin should not be given as an IV bolus because cardiac arrhythmia may occur.

Postdelivery: The cervix and vagina are inspected for lacerations, which, if present, are repaired, as is episiotomy if done. Then if the mother and infant are recovering normally, they can begin bonding. Many mothers wish to begin breastfeeding soon after delivery, and this activity should be encouraged. Mother, infant, and father should remain together in a warm, private area for an hour or more to enhance parent-infant bonding. Then, the infant may be taken to the nursery or left with the mother depending on her wishes.

For the first hour after delivery, the mother should be observed closely to make sure the uterus is contracting (detected by palpation during abdominal examination) and to check for bleeding, BP abnormalities, and general well-being. The time from delivery of the placenta to 4 h postpartum has been called the 4th stage of labor; most complications, especially hemorrhage (see p. 2680), occur at this time, and frequent observation is mandatory.

Chapter 263. Pregnancy Complicated by Disease

Introduction

Nonobstetric disorders often complicate pregnancy; management sometimes differs from that for nonpregnant patients. Coordination of care between the obstetrician and medical specialist often helps.

Anemia in Pregnancy

Normally during pregnancy, erythroid hyperplasia of the marrow occurs, and RBC mass increases. However, a disproportionate increase in plasma volume results in hemodilution (hydremia of pregnancy): Hct decreases from between 38 and 45% in healthy women who are not pregnant to about 34% during late single pregnancy and to 30% during late multifetal pregnancy. Thus during pregnancy, anemia is defined as Hb < 10 g/dL (Hct < 30%). If Hb is < 11.5 g/dL at the onset of pregnancy, women may be treated prophylactically because subsequent hemodilution usually reduces Hb to < 10 g/dL. Despite hemodilution, O_2-carrying capacity remains normal throughout pregnancy. Hct normally increases immediately after birth.

Anemia occurs in up to one third of women during the 3rd trimester. The most common causes are iron deficiency and folate deficiency.

Symptoms and Signs

Early symptoms are usually nonexistent or nonspecific (eg, fatigue, weakness, light-headedness, mild dyspnea during exertion). Other symptoms and signs may include pallor and, if anemia is severe, tachycardia or hypotension. Anemia increases risk of preterm delivery and postpartum maternal infections.

Diagnosis

Diagnosis begins with CBC; usually, if women have anemia, subsequent testing is based on whether the MCV is low (< 79 fL) or high (> 100 fL):

- For microcytic anemias: Evaluation includes testing for iron deficiency (measuring serum ferritin) and hemoglobinopathies (using hemoglobin electrophoresis). If these tests are nondiagnostic and there is no response to empiric treatment, consultation with a hematologist is usually warranted.

- For macrocytic anemias: Evaluation includes serum folate and B_{12} levels.

Treatment

Treatment is directed at reversing the anemia. Transfusion is usually indicated for any anemia if severe constitutional symptoms (eg, light-headedness, weakness, fatigue) or cardiopulmonary symptoms or signs (eg, dyspnea, tachycardia, tachypnea) are present; the decision is not based on the Hct.

Iron Deficiency Anemia

About 95% of anemia cases during pregnancy are due to iron deficiency (see p. 924). The cause is usually inadequate dietary intake (especially in adolescent girls), a previous pregnancy, or the normal recurrent loss of iron in menstrual blood (which approximates the amount normally ingested each month and thus prevents iron stores from building up).

Diagnosis

Typically, Hct is ≤ 30%, and MCV is < 79 fL. Decreased serum iron and ferritin and increased serum transferrin levels confirm the diagnosis.

Treatment

• Ferrous sulfate 325 mg po once/day

One 325-mg ferrous sulfate tablet taken mid-morning is usually effective. Higher or more frequent doses increase GI adverse effects, especially constipation, and one dose blocks absorption of the next dose, thereby reducing percentage intake. About 20% of pregnant women do not absorb enough supplemental oral iron; a few of them require parenteral therapy, usually iron dextran 100 mg IM every other day for a total of ≥ 1000 mg over 3 wk. Hct or Hb is measured weekly to determine response. If iron supplements are ineffective, concomitant folate deficiency should be suspected.

Neonates of mothers with iron deficiency anemia usually have a normal Hct but decreased total iron stores and a need for early dietary iron supplements.

Prevention

Although the practice is controversial, iron supplements (usually ferrous sulfate 325 mg po once/day) are usually given routinely to pregnant women to prevent depletion of body iron stores and prevent the anemia that may result from abnormal bleeding or a subsequent pregnancy.

Folate Deficiency Anemia

Folate deficiency (see pp. 29 and 932) increases risk of neural tube defects and possibly fetal alcohol syndrome. Deficiency occurs in 0.5 to 1.5% of pregnant women; macrocytic, megaloblastic anemia is present if deficiency is moderate or severe. Rarely, severe anemia and glossitis occur.

Diagnosis

Folate deficiency is suspected if CBC shows anemia with macrocytic indices or high RBC distribution width (RDW). Low serum folate levels confirm the diagnosis.

Treatment

Treatment is folate 1 mg po bid. Severe megaloblastic anemia may warrant bone marrow examination and further treatment in a hospital.

Prevention

For prevention, all pregnant women are given folate 0.4 mg po once/day. Women who have had a fetus with spina bifida should take 4.0 mg once/day, starting before conception.

Hemoglobinopathies

(See also Sidebar 106-1 on p. 943)

During pregnancy, hemoglobinopathies, particularly sickle cell disease, Hb S-C disease, β-thalassemia disease, and α-thalassemia, can worsen maternal and perinatal outcomes (for genetic screening, see Table 259-1 on p. 2600).

Preexisting **sickle cell disease,** particularly if severe, increases risk of maternal infection (most often, pneumonia, UTIs, and endometritis), pregnancy-induced hypertension, heart failure, and pulmonary infarction. Fetal growth restriction, preterm delivery, and low birth weight are common. Anemia almost always becomes more severe as pregnancy progresses. Sickle cell trait increases the risk of UTIs but is not associated with severe pregnancy-related complications.

Treatment of sickle cell disease during pregnancy is complex. Painful crises should be treated aggressively. Prophylactic exchange transfusions to keep Hb A at ≥ 60% reduce risk of hemolytic crises and pulmonary complications, but they are not routinely recommended because they increase risk of

transfusion reactions, hepatitis, HIV transmission, and blood group isoimmunization. Prophylactic transfusion does not appear to decrease perinatal risk. Therapeutic transfusion is indicated for the following:

• Symptomatic anemia

• Heart failure

• Severe bacterial infection

• Severe complications of labor and delivery (eg, bleeding, sepsis)

Hb S-C disease may first cause symptoms during pregnancy. The disease increases risk of pulmonary infarction by occasionally causing bony spicule embolization. Effects on the fetus are uncommon but, if they occur, often include fetal growth restriction.

Sickle cell-β-thalassemia is similar to Hb S-C disease but is less common and more benign.

α-Thalassemia does not cause maternal morbidity, but if the fetus is homozygous, hydrops and fetal death occur during the 2nd or early 3rd trimester.

Asthma in Pregnancy

The effect of pregnancy on asthma varies; deterioration is slightly more common than improvement, but most pregnant women do not have severe attacks. The effect of asthma on pregnancy also varies, but risk of preterm delivery and fetal growth restriction is increased.

Treatment

Pregnancy does not usually change treatment of asthma (see p. 1873). Inhaled bronchodilators and corticosteroid inhalers are first-line maintenance therapy. Theophylline is no longer recommended routinely during pregnancy. For an acute exacerbation, in addition to bronchodilators, methylprednisolone 60 mg IV q 6 h for 24 to 48 h may be used, followed by oral prednisone in a tapering dose.

Autoimmune Disorders in Pregnancy

Autoimmune disorders are 5 times more common among women, and incidence tends to peak during reproductive years. Thus, these disorders commonly occur in pregnant women.

Systemic lupus erythematosus: SLE (see p. 305) may first appear during pregnancy; women who have had an unexplained 2ndtrimester stillbirth, a fetus with growth restriction, preterm delivery, or recurrent spontaneous abortions are often later diagnosed with SLE.

The course of preexisting SLE during pregnancy cannot be predicted, but SLE may worsen, particularly immediately postpartum. Complications may include fetal growth restriction, preterm delivery due to preeclampsia, and congenital heart block due to maternal antibodies that cross the placenta. Significant preexisting renal or cardiac complications increase risk of maternal morbidity and mortality. Diffuse nephritis, hypertension, or the presence of circulating antiphospholipid antibodies (usually anticardiolipin antibody or lupus anticoagulant) increases risk of perinatal mortality. Women with antiphospholipid antibodies also have an increased risk of maternal thromboembolic disorders. Neonates may have anemia, thrombocytopenia, or leukopenia; these disorders tend to resolve during the first weeks after birth when maternal antibodies disappear.

Treatment may require prednisone; the lowest possible dose is used. However, 10 to 60 mg po once/day is often needed. Women with antiphospholipid antibodies are also often treated with aspirin (81 mg po once/day) and prophylactic heparin (5,000 to 10,000 units bid sc). For women with severe, refractory SLE, the need to continue immunosuppressants (eg, hydroxychloroquine) during pregnancy is reviewed individually.

Rheumatoid arthritis: RA (see p. 332) may begin during pregnancy or, even more often, during the postpartum period. Preexisting RA generally abates temporarily during pregnancy. The fetus is not specifically affected, but delivery may be difficult if the woman's hip joints or lumbar spine is affected. If a woman develops an RA flare during pregnancy, first-line treatment usually begins with prednisone. For refractory cases, other immunosuppressants may be required.

Myasthenia gravis: Myasthenia gravis (see p. 1793) varies in its course during pregnancy. Frequent acute myasthenic episodes may require increasing doses of anticholinesterase drugs (eg, neostigmine), which may cause symptoms of cholinergic excess (eg, abdominal pain, diarrhea, vomiting, increasing weakness); atropine may then be required. Sometimes myasthenia becomes refractory to standard therapy and requires corticosteroids or immunosuppressants. During labor, women may need assisted ventilation and are extremely sensitive to drugs that depress respiration (eg, sedatives, opioids, Mg sulfate). Because the IgG responsible for myasthenia crosses the placenta, transient myasthenia occurs in 20% of neonates, even more if mothers have not had a thymectomy.

Immune thrombocytopenic purpura (ITP): ITP (see p. 958), mediated by maternal anti-platelet IgG, tends to worsen during pregnancy and increases risk of maternal morbidity. Corticosteroids reduce IgG levels and cause remission in most women, but improvement is sustained in only 50%. Immunosuppressive therapy and plasmapheresis further reduce IgG, increasing platelet counts. Rarely, splenectomy is required for refractory cases; it is best done during the 2nd trimester, when it causes sustained remission in about 80%. IV immune globulin increases platelet count significantly but briefly, so that labor can be induced in women with low platelet counts. Platelet transfusions are indicated only when cesarean delivery is required and maternal platelet counts are < 50,000/µL.

Although antiplatelet IgG can cross the placenta, it only very rarely causes fetal or neonatal thrombocytopenia. Maternal anti-platelet antibody levels (measured by direct or indirect assay) cannot predict fetal involvement. Percutaneous umbilical blood sampling can be diagnostic. If fetal platelet count is < 50,000/µL, intracranial bleeding can occur during labor or vaginal delivery; cesarean delivery is necessary.

Cancer in Pregnancy

(See also Ch. 256.)

Pregnancy should not delay treatment of cancer. Treatment is similar to that in nonpregnant women except for rectal and gynecologic cancers.

Because embryonic tissues grow rapidly and have a high DNA turnover rate, they resemble cancer tissues and are thus very vulnerable to antineoplastic drugs. Many antimetabolites and alkylating drugs (eg, busulfan, chlorambucil, cyclophosphamide, 6-mercaptopurine, methotrexate) can cause fetal abnormalities. Methotrexate is particularly problematic; use during the 1st trimester increases risk of spontaneous abortion and, if the pregnancy continues, multiple congenital malformations. Although pregnancy often concludes successfully despite cancer treatment, risk of fetal injury due to treatment leads some women to choose abortion.

Rectal cancer: Rectal cancers may require hysterectomy to ensure complete tumor removal. Cesarean delivery may be done as early as 28 wk, followed by hysterectomy so that the infant can be saved and aggressive cancer treatment started.

Cervical cancer: Pregnancy does not appear to worsen cervical cancer. Cervical cancer can develop during pregnancy, and an abnormal Papanicolaou (Pap) test should not be attributed to pregnancy. Abnormal Pap tests are followed by colposcopy and directed biopsies when indicated. Usually, conization can be avoided. If biopsy shows mild dysplasia, normal delivery is possible, and follow-up evaluation can start 6 wk postpartum. Severe dysplasia or carcinoma in situ warrants further evaluation during pregnancy; colposcopy is usually accurate, but sometimes biopsy is necessary.

For carcinoma in situ (Federation of Gynecology and Obstetrics [FIGO] stage 0—see

Table 256-7 on p. 2578) and microinvasive cancer (stage IA1), treatment is often deferred until after delivery because conservative options may be possible then.

If invasive cancer (FIGO stage IA2 or higher) is diagnosed during early pregnancy, immediate therapy appropriate for the cancer is traditionally recommended. If invasive cancer is diagnosed after 20 wk and if the woman accepts the unquantified increase in risk, treatment can be deferred until into the 3rd trimester (eg, 32 wk) to maximize fetal maturity but not delay treatment too long. When hysterectomy is delayed until delivery, some experts recommend that it be done immediately after delivery. Others recommend delaying hysterectomy until 6 wk postpartum because risks due to hysterectomy are thought to be much greater at delivery because of the increased blood supply to the pelvic organs at that time.

In certain cancers, chemotherapy may induce tumor regression, allowing the fetus to mature to a viable stage before definitive treatment (surgery or radiation therapy). Delivery is usually cesarean, but vaginal delivery, although controversial, may be as safe.

Other gynecologic cancers: After 12 wk gestation, ovarian cancer is easily missed; then, the ovaries, with the uterus, rise out of the pelvis and are no longer easily palpable. If very advanced, ovarian cancer during pregnancy may be fatal before completion of the pregnancy. Affected women require bilateral oophorectomy as soon as possible. Endometrial and fallopian tube cancers rarely occur during pregnancy.

Leukemia and Hodgkin lymphoma: These disorders (see Chs. 117 and 118) are uncommon during pregnancy. Antineoplastic drugs typically used increase risk of fetal loss and congenital malformations. Because leukemias can become fatal rapidly, treatment is given as soon as possible, without any significant delay to allow the fetus to mature. If Hodgkin lymphoma is confined to above the diaphragm, radiation therapy may be used; the abdomen must be shielded. If lymphoma is below the diaphragm, abortion may be recommended.

Breast cancer: Breast engorgement during pregnancy may make recognizing breast cancer difficult. Any solid or cystic breast mass should be evaluated (see Ch. 255).

Diabetes Mellitus in Pregnancy

(See also Ch. 99)

Pregnancy aggravates preexisting type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes but does not appear to exacerbate diabetic retinopathy, nephropathy, or neuropathy.

Gestational diabetes (diabetes that begins during pregnancy) can develop in overweight, hyperinsulinemic, insulin-resistant women or in thin, relatively insulin-deficient women. Gestational diabetes occurs in 1 to 3% of all pregnancies, but the rate may be much higher in certain groups (eg, Mexican Americans, American Indians, Asians, Indians, Pacific Islanders).

Diabetes during pregnancy increases fetal and maternal morbidity and mortality. Neonates are at risk of respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, and hyperviscosity. Poor control of preexisting or gestational diabetes during organogenesis (up to about 10 wk gestation) increases risk of major congenital malformations and spontaneous abortion. Poor control of diabetes later in pregnancy increases risk of fetal macrosomia (usually defined as fetal weight > 4000 or > 4500 g at birth), preeclampsia, and spontaneous abortion. However, gestational diabetes can result in fetal macrosomia even if blood glucose is kept nearly normal.

Treatment

• Close monitoring

• Tight control of blood glucose

• Management of complications

Preconception counseling and optimal control of diabetes before, during, and after pregnancy minimize maternal and fetal risks, including congenital malformations. Because malformations may develop before pregnancy is diagnosed, the need for constant, strict control of glucose levels is stressed to women who have diabetes and who are considering pregnancy (or who are not using contraception).

Most experts recommend that all pregnant women be screened for gestational diabetes (see p. 2608). A glucose tolerance test is usually recommended, but the diagnosis can probably be made by a fasting plasma glucose of > 126 mg/dL or a random plasma glucose > 200 mg/dL.

To minimize risks, clinicians should do all of the following:

• Involve a diabetes team (eg, physicians, nurses, nutritionists, social workers) and a pediatrician

• Promptly diagnose and treat complications of pregnancy, no matter how trivial

• Plan for delivery and have an experienced pediatrician present

• Ensure that neonatal intensive care is available

In regional perinatal centers, specialists in management of diabetic complications are available.

During pregnancy: Treatment can vary, but some general management guidelines are useful (see Tables 263-1, 263-2, and 263-3).

[**Table 263-1.** Management of Type 1 Diabetes Mellitus* During Pregnancy]

Women with type 1 or 2 should monitor their blood glucose levels at home. During pregnancy, normal fasting blood glucose levels are about 76 mg/dL (4.2 mmol/L); treatment aims to keep fasting blood glucose levels at < 95 mg/dL (< 5.3 mmol/L) and 2-h postprandial levels at ≤ 120 mg/dL (≤ 6.6 mmol/L). The goals are no wide blood glucose fluctuations and glycosylated Hb (Hb A_{1C}) levels kept at < 8%.

[**Table 263-2.** Management of Type 2 Diabetes Mellitus* During Pregnancy]

Insulin is the traditional drug of choice because it cannot cross the placenta and provides more predictable glucose control; it is used for types 1 and 2 diabetes and for some women with gestational diabetes. Human insulin is used if possible because it minimizes antibody formation. Insulin antibodies cross the placenta, but their effect on the fetus is unknown. In some women with long-standing type 1 diabetes, hypoglycemia does not trigger the normal release of counterregulatory hormones (catecholamines, glucagon, cortisol, and growth hormone); thus, too much insulin can trigger hypoglycemic coma without premonitory symptoms. All pregnant women with type 1 should have glucagon kits and be instructed (as should family members) in giving glucagon if severe hypoglycemia (indicated by unconsciousness, confusion, or blood glucose levels < 40 mg/dL [< 2.2 mmol/L]) occurs.

Oral hypoglycemic drugs (eg, glyburide) are being increasingly used to manage diabetes in pregnant women because of the ease of administration (pills compared to injections), low cost, and single daily dosing. Several studies have shown that glyburide is safe during pregnancy and that it provides control equivalent to that of insulin for women with gestational diabetes. For women with type II diabetes before pregnancy, data for use of oral drugs during pregnancy are scant; insulin is most often preferred. Oral hypoglycemics taken during pregnancy may be continued postpartum during breastfeeding, but the infant should be closely monitored for signs of hypoglycemia.

Management of complications: Although diabetic retinopathy, nephropathy, and mild neuropathy are not contraindications to pregnancy, they require preconception counseling and close management before and during pregnancy.

Retinopathy requires that an ophthalmologic examination be done every trimester. If proliferative retinopathy is noted at the first prenatal visit, photocoagulation should be used as soon as possible to prevent progressive deterioration.

Nephropathy, particularly in women with renal transplants, predisposes to pregnancy-induced

[**Table 263-3.** Management of Gestational Diabetes During Pregnancy]

hypertension. Risk of preterm delivery is higher if maternal renal function is impaired or if transplantation was recent. Prognosis is best if delivery occurs ≥ 2 yr after transplantation.

Congenital malformations of major organs are predicted by elevated Hb A_{1c} levels at conception and during the first 8 wk of pregnancy. If the level is ≥ 8.5% during the 1st trimester, risk of congenital malformations is significantly increased, and targeted ultrasonography and fetal echocardiography are done during the 2nd trimester to check for malformations. If women with type 2 diabetes take oral hypoglycemic drugs during the 1st trimester, fetal risk of congenital malformations is unknown (see Table 264-2).

Labor and delivery: Certain precautions are required to ensure an optimal outcome.

Timing of delivery depends on fetal well-being. Women are told to count fetal movements during a 60-min period daily (fetal kick count) and to report any sudden decreases to the obstetrician immediately. Nonstress testing (see p. 2630) is begun at 32 wk and, if results are nonreassuring, is followed by a biophysical profile (measurement of amniotic fluid and fetal muscle tone, movement, and breathing pattern). These tests and similar noninvasive prenatal fetal monitoring tests (called antenatal testing) are initiated earlier if women have severe hypertension or a renal disorder or if fetal growth restriction is suspected. Amniocentesis to assess fetal lung maturity is often necessary for women with the following:

- Obstetric complications in past pregnancies
- Elective delivery before 39 wk
- Inadequate prenatal care
- Uncertain delivery date
- Poor glucose control

Type of delivery is usually spontaneous vaginal delivery at term. If labor does not begin spontaneously by 38 to 40 wk, induction is necessary because of the increasing risk of stillbirth and shoulder dystocia. Dysfunctional labor, fetopelvic disproportion, or risk of shoulder dystocia may make cesarean delivery necessary.

Blood glucose levels are best controlled during labor and delivery by a continuous low-dose insulin infusion. If induction is planned, women eat their usual diet the day before and take their usual insulin dose. On the morning of labor induction, breakfast and insulin are withheld, baseline fasting plasma glucose is measured, and an IV infusion of 5% dextrose in 0.45% saline solution is started at 125 mL/h, using an infusion pump. Initial insulin infusion rate is determined by capillary glucose level. Insulin dose is determined as followed:

- Initially: 0 units for a capillary level of < 80 mg/dL (< 4.4 mmol/L) or 0.5 units/h for a level of 80 to 100 mg/dL (4.4 to 5.5 mmol/L)
- Thereafter: Increased by 0.5 units/h for each 40-mg/dL (2.2-mmol/L) increase in glucose level over 100 mg/dL up to 2.5 units/h for levels > 220 mg/dL (> 12.2 mmol/L)
- Every hour during labor: Measurement of glucose level at bedside and adjustment of dose to keep the level at 70 to 120 mg/dL (3.8 to 6.6 mmol/L)

• If the glucose level is significantly elevated: Possibly additional bolus doses

For spontaneous labor, the procedure is the same, except that if intermediate-acting insulin was taken in the previous 12 h, the insulin dose is decreased. For women who have fever, infection, or other complications and for obese women who have type 2 and have required > 100 units of insulin/day before pregnancy, the insulin dose is increased.

Postpartum: After delivery, loss of the placenta, which synthesizes large amounts of insulin antagonist hormones throughout pregnancy, decreases the insulin requirement immediately. Thus, women with gestational diabetes and many of those with type 2 require no insulin postpartum. For women with type 1, insulin requirements decrease dramatically but then gradually increase after about 72 h.

During the first 6 wk postpartum, the goal is tight glucose control. Glucose levels are checked before meals and at bedtime. Breast-feeding is not contraindicated but may result in hypoglycemia if oral hypoglycemics are taken. Women who have had gestational diabetes should have a 2-h oral glucose tolerance test with 75 g of glucose at 6 to 12 wk postpartum to determine whether diabetes has resolved.

Fever in Pregnancy

A temperature > 39.5° C (> 103° F) during the 1st trimester increases risk of spontaneous abortion and fetal brain or spinal cord defects. Fever late in pregnancy increases risk of preterm labor.

Treatment is directed at the cause, but anti-pyretics are indicated to decrease maternal temperature. In women with severe hyperthermia, cooling blankets may be used.

Fibroids in Pregnancy

Fibroids may increase risk of preterm labor, abnormal fetal presentation, placenta previa, and recurrent spontaneous abortions. Rarely, fibroids partially obstruct the birth canal.

Preconception evaluation is recommended for women who have very large fibroids or who have fibroids and have had a spontaneous abortion.

Heart Disorders in Pregnancy

Heart disorders account for about 10% of maternal obstetric deaths. In the US, because incidence of rheumatic heart disease has markedly declined, most heart problems during pregnancy result from congenital heart disease. Pregnancy is inadvisable for women with certain high-risk disorders (eg, pulmonary hypertension, severe valvular disorders, prior postpartum cardiomyopathy).

Pathophysiology

Pregnancy stresses the cardiovascular system, often worsening known heart disorders; mild heart disorders may first become evident during pregnancy. Stresses include decreased Hb and increased blood volume, stroke volume, and eventually heart rate. Cardiac output increases by 30 to 50%. These changes become maximal between 28 and 34 wk gestation. During labor, cardiac output increases about 20% with each uterine contraction; other stresses include straining during the 2nd stage of labor and the increase in venous blood returning to the heart from the contracting uterus. Cardiovascular stresses do not return to prepregnancy levels until several weeks after delivery.

Symptoms and Signs

Findings resembling heart failure (eg, mild dyspnea, systolic murmurs, jugular venous distention, tachycardia, dependent edema, mild cardiomegaly seen on chest x-ray—see p. 2118) typically occur during normal pregnancy or may result from a heart disorder. Diastolic or presystolic murmurs are more specific for heart disorders.

Heart failure can cause premature labor or arrhythmias. Risk of maternal or fetal death correlates with New York Heart Association functional classification, which is based on the amount of physical activity that causes symptoms of heart failure. Risk is not increased if symptoms

• Do not occur during exertion (class I)

• Occur only during significant exertion (class II)

Risk is increased if symptoms

• Occur during mild exertion (class III)

• Occur during minimal or no exertion (class IV)

Diagnosis

Diagnosis is usually based on clinical evaluation and echocardiography.

Treatment

• Avoidance of warfarin, ACE inhibitors, aldosterone antagonists, and certain anti-arrhythmics (eg, amiodarone)

• For NYHA class III or IV, activity restriction and possible bed rest after 20 wk

• Most other usual treatments for heart failure and arrhythmias

Frequent prenatal visits, ample rest, avoidance of excessive weight gain and stress, and treatment of anemia are required. An anesthesiologist familiar with heart disorders in pregnancy should attend the labor. During labor, pain and anxiety are treated aggressively to minimize tachycardia. Women are closely monitored immediately postpartum and are followed for several weeks postpartum by a cardiologist.

Before women with NYHA class III or IV status conceive, the disorder should be optimally treated medically and, if indicated (eg, if due to a valvular heart disorder), treated surgically.

Some women with a heart disorder and poor cardiac function require digoxin 0.25 mg po once/day plus bed rest, beginning at 20 wk. Cardiac glycosides (eg, digoxin, digitoxin) cross the placenta, but neonates (and children) are relatively resistant to their toxicity. Women with class IV heart failure may be advised to obtain early therapeutic abortion. ACE inhibitors are contraindicated because they may cause fetal renal damage. Aldosterone antagonists (spironolactone, eplerenone) should be avoided because they may cause feminization of a male fetus. Other treatments for heart failure (eg, diuretics, nitrates, inotropes) may be continued during pregnancy depending on disease severity and fetal risk, as determined by a cardiologist and a perinatologist.

Arrhythmias: Atrial fibrillation may accompany cardiomyopathy or valvular lesions. Rate control is usually similar to that in nonpregnant patients, with β-blockers, Ca channel blockers, or digoxin (see p. 2147). Certain antiarrhythmics (eg, amiodarone) should be avoided. In pregnant patients with new-onset atrial fibrillation or hemodynamic instability, cardioversion may be used to restore sinus rhythm. Anticoagulation may be required because the relative hypercoagulability during pregnancy makes atrial thrombi (and subsequent systemic or pulmonary embolization) more likely. Neither standard heparin nor low molecular weight heparins cross the placenta, but low molecular weight heparins may have less risk of thrombocytopenia. Warfarin crosses the placenta and may cause fetal abnormalities (see Table 264-2 on p. 2656), particularly during the 1st trimester. Warfarin use during the last month of pregnancy has risks. Rapid reversal of warfarin's anticoagulant effects may be difficult and may be required because of fetal or neonatal intracranial hemorrhage resulting from birth trauma or because of maternal bleeding (eg, resulting from trauma or emergency cesarean delivery).

Management of acute supraventricular or ventricular tachycardia is the same as for non-pregnant

patients.

Endocarditis prophylaxis: For pregnant patients with a structural heart disorder, indications and use of endocarditis prophylaxis for nonobstetric events are the same as those for nonpregnant patients (see p. 2199). Although rate of bacteremia with uncomplicated vaginal or caesarean delivery is low and routine prophylaxis is not recommended by the American College of Cardiology, many obstetricians give patients with valvular disease prophylactic antibiotics shortly before and after delivery.

Valvular Stenosis and Insufficiency

During pregnancy, stenosis and regurgitation (insufficiency) most often affect the mitral and aortic valves. Pregnancy amplifies the murmurs of mitral and aortic stenosis but diminishes those of mitral and aortic regurgitation. During pregnancy, mild mitral or aortic regurgitation is usually easy to tolerate; stenosis is more difficult to tolerate and predisposes to maternal and fetal complications. Mitral stenosis is especially dangerous; the tachycardia, increased blood volume, and increased cardiac output during pregnancy interact with this disorder to rapidly increase pulmonary capillary pressure, causing pulmonary edema. Atrial fibrillation is also common.

Treatment

Ideally, valvular disorders are diagnosed and treated medically before conception; surgical correction is often recommended for severe disorders. Prophylactic antibiotics are required in certain situations (see p. 2643).

Mitral stenosis: Patients must be closely observed throughout pregnancy because mitral stenosis may rapidly become more severe. If required, valvotomy is relatively safe during pregnancy; however, open heart surgery increases fetal risk. During labor, conduction anesthesia (eg, epidural or spinal nerve block by a local anesthetic) is usually preferred.

Aortic stenosis: During labor, local anesthesia is preferred, but if necessary, general anesthesia is used. Conduction anesthesia should be avoided because it decreases filling pressures (preload), which may already be decreased by aortic stenosis. Straining, which can suddenly reduce filling pressures and impair cardiac output, is discouraged during the 2nd stage of labor; operative vaginal delivery may be preferred, if feasible. Cesarean delivery is done if indicated (see p. 2678).

Other Heart Disorders

Mitral valve prolapse: This disorder occurs more frequently in younger women and tends to be familial. Mitral valve prolapse is usually an isolated abnormality but may cause some degree of mitral regurgitation or be accompanied by Marfan syndrome or an atrial septal defect.

Women with mitral valve prolapse generally tolerate pregnancy well. The relative increase in ventricular size during normal pregnancy reduces the discrepancy between the disproportionately large mitral valve and the ventricle.

Patients with mitral regurgitation may require prophylactic antibiotics during delivery. β-Blockers are indicated for recurrent arrhythmias. Rarely, thrombi and systemic emboli develop and require anticoagulation.

Congenital heart disease: For most asymptomatic patients, risk is not increased during pregnancy. However, patients with Eisenmenger's syndrome (now rare), primary pulmonary hypertension, or perhaps isolated pulmonary stenosis are predisposed, for unknown reasons, to sudden death during labor, during the postpartum period (the 6 wk after delivery), or after abortion at > 20 wk gestation. Thus, pregnancy is inadvisable. If these patients become pregnant, they should be closely monitored with a pulmonary artery catheter and an arterial line during delivery. For patients with intracardiac shunts, the goal is to prevent right-to-left shunting by maintaining peripheral vascular resistance and by minimizing pulmonary vascular resistance.

Patients with Marfan syndrome are at increased risk of aortic dissection and rupture of aortic aneurysms during pregnancy. Bed rest, avoidance of Valsalva maneuvers, and measurement of aortic diameter with echocardiography are required.

Peripartum cardiomyopathy: Heart failure with no identifiable cause (eg, MI, valvular disorder) can develop between the last month of pregnancy and 5 mo postpartum in patients without a previous heart disorder. Risk factors include multiparity, age ≥ 30, multifetal pregnancy, and preeclampsia. The 5-yr mortality rate is 50%. Recurrence is likely in subsequent pregnancies, particularly in patients with residual cardiac dysfunction; future pregnancies are therefore not recommended. Treatment is as for heart failure (see p. 2643).

Hepatic Disorders in Pregnancy

Jaundice (see p. 212) may result from nonobstetric or obstetric conditions. Nonobstetric causes include drugs, acute cholecystitis, and biliary obstruction by gallstones. Gallstones appear to be more common during pregnancy, probably because bile lithogenicity is increased and gallbladder contractility is impaired. Obstetric causes include hyperemesis gravidarum (usually causing mild jaundice) and septic abortion; both cause hepatocellular injury and hemolysis.

Acute viral hepatitis: The most common cause of jaundice during pregnancy is acute viral hepatitis. It may predispose to preterm delivery but does not appear to be teratogenic. Acute viral hepatitis is generally mild, but hepatitis E, common in underdeveloped countries, may be severe. Hepatitis B virus may be transmitted to the neonate immediately after delivery or, less often, to the fetus transplacentally. Transmission is particularly likely if women are e-antigen-positive and are chronic carriers of hepatitis B surface antigen (HBsAg) or if they contract hepatitis during the 3rd trimester. Affected neonates are more likely to develop subclinical hepatic dysfunction and become carriers than to develop clinical hepatitis. All pregnant women are tested for HBsAg to determine whether precautions against vertical transmission are needed (for prenatal prophylaxis with immune globulin and vaccination for neonates exposed to hepatitis B virus, see p. 2826).

Chronic active hepatitis: Chronic active hepatitis, especially with cirrhosis, impairs fertility. When pregnancy occurs, risk of spontaneous abortion and prematurity is increased, but risk of maternal mortality is not. Corticosteroids given for chronic active hepatitis can be continued during pregnancy because fetal risks due to corticosteroids have not been proved to exceed those due to maternal chronic active hepatitis. Azathioprine and other immunosuppressants, despite fetal risks, are sometimes indicated for severe disease.

Cholestasis (pruritus) of pregnancy: This relatively common disorder apparently results from idiosyncratic exaggeration of normal bile stasis due to hormonal changes. Intense pruritus, the earliest symptom, develops during the 2nd or 3rd trimester; dark urine and jaundice sometimes follow. Acute pain and systemic symptoms are absent. The disorder usually resolves after delivery but tends to recur with each pregnancy or with use of oral contraceptives.

For severe pruritus, oral cholestyramine 4 to 6 g bid or 3 to 4 g tid is usually effective. Bleeding due to hypoprothrombinemia occasionally develops but is readily reversed by vitamin K (phytonadione) 5 to 10 mg IM once/day for 2 to 3 days.

Fatty liver of pregnancy: This rare, poorly understood disorder occurs near term, sometimes with preeclampsia. Symptoms include acute nausea and vomiting, abdominal discomfort, and jaundice, followed in severe cases by rapidly progressive hepatocellular failure. Maternal and fetal mortality rates are high in severe cases.

Clinical and laboratory findings resemble those of fulminant viral hepatitis except that aminotransferase levels may be < 500 units/L and hyperuricemia may be present.

Diagnosis is based on clinical criteria, liver function tests, hepatitis serologic tests, and liver biopsy. Biopsy shows diffuse small droplets of fat in hepatocytes, usually with minimal apparent necrosis, but in some cases, findings are indistinguishable from viral hepatitis.

Depending on gestational age, prompt delivery or termination of pregnancy is usually advised, although whether either alters maternal outcome is unclear. Survivors recover completely and have no recurrences. A seemingly identical disorder may develop at any stage of pregnancy if high doses of tetracyclines are given IV.

Preeclampsia: Severe preeclampsia (see p. 2670) can cause liver problems with hepatic fibrin deposition, necrosis, and hemorrhage that can result in abdominal pain, nausea, vomiting, and mild jaundice. Subcapsular hematoma with intra-abdominal hemorrhage occasionally occurs, most often in women with preeclampsia that progresses to the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Rarely, the hematoma causes the liver to rupture spontaneously; rupture is life threatening, and pathogenesis is unknown.

Chronic hepatic disorders: Pregnancy may temporarily worsen cholestasis in primary biliary cirrhosis and other chronic cholestatic disorders, and the increased plasma volume during the 3rd trimester slightly increases risk of variceal hemorrhage in women with cirrhosis. However, pregnancy usually does not harm women with a chronic hepatic disorder. Cesarean delivery is reserved for the usual obstetric indications.

Hypertension in Pregnancy

(See also Ch. 208.)

Hypertension (BP ≥ 140/90 mm Hg) during pregnancy can be classified as one of the following:

- **Chronic:** BP is high before pregnancy or before 20 wk gestation. Chronic hypertension complicates about 1 to 5% of all pregnancies.

- **Gestational:** Hypertension develops after 20 wk gestation (typically after 37 wk) and remits by 6 wk postpartum; it occurs in about 5 to 10% of pregnancies, more commonly in multifetal pregnancy.

Both types of hypertension increase risk of preeclampsia, eclampsia (see p. 2670), and other causes of maternal mortality or morbidity, including hypertensive encephalopathy, stroke, renal failure, left ventricular failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Risk of fetal mortality or morbidity increases because of decreased uteroplacental blood flow, which can cause vasospasm, growth restriction, hypoxia, and abruptio placentae. Outcomes are worse if hypertension is severe (BP > 180/100 mm Hg) or accompanied by renal insufficiency (eg, creatinine clearance < 60 mL/min, serum creatinine > 2 mg/dL [> 180 µmol/L]).

Diagnosis

BP is measured routinely at prenatal visits. If severe hypertension occurs for the first time in pregnant women who do not have a multi-fetal pregnancy or gestational trophoblastic disease, tests to rule out renal artery stenosis, coarctation of the aorta, Cushing's syndrome, SLE, and pheochromocytoma should be considered (see p. 2068).

Treatment

- For mild hypertension, conservative measures followed by antihypertensives if needed

- Methyldopa, β-blockers, or Ca channel blockers tried first

- Avoidance of ACE inhibitors, aldosterone antagonists, and thiazides

- For moderate or severe hypertension, anti-hypertensive therapy, close monitoring, and, if condition worsens, possibly termination of pregnancy or delivery, depending on gestational age

Treatment of mild to moderate hypertension without renal insufficiency during pregnancy is controversial;

the issues are whether treatment improves outcome and whether the risks of drug treatment outweigh risks of untreated disease. Because the uteroplacental circulation is maximally dilated and cannot autoregulate, decreasing maternal BP with drugs may abruptly decrease uteroplacental blood flow. Diuretics reduce effective maternal circulating blood volume; consistent reduction increases risk of fetal growth restriction. However, hypertension with renal insufficiency is treated even if hypertension is mild or moderate.

Recommendations for chronic and gestational hypertension are similar and depend on severity. However, chronic hypertension may be more severe, and the BP ranges in gestational diabetes often do not require treatment.

If hypertension is mild (140/90 to 150/100 mm Hg) and if BP is labile, reduced physical activity may decrease BP and improve fetal growth, making perinatal risks similar to those for women without hypertension. However, if these conservative measures do not decrease BP, many experts recommend drug therapy.

If hypertension is moderate (150/100 to 180/110 mm Hg), drug therapy is indicated. Women who are taking methyldopa, a β-blocker, a Ca channel blocker, or a combination before pregnancy may continue these drugs. However, ACE inhibitors and diuretics should be stopped once pregnancy is confirmed. Women must be taught to self-monitor BP and should have renal function testing every trimester. Fetal growth is monitored with monthly ultrasound examinations; antenatal testing begins at 32 wk. Delivery should be accomplished at 38 to 39 wk but may be done earlier if severe preeclampsia or fetal growth restriction is detected or if fetal testing is non-reassuring.

If hypertension is severe (≥ 180/110 mm Hg), immediate evaluation, including BUN and serum creatinine, creatinine clearance, 24-h urinary protein level, and funduscopy, is indicated. Risk of complications —maternal (progression of end-organ dysfunction or preeclampsia) and fetal (prematurity, growth restriction, stillbirth)—is increased significantly. If continuation of pregnancy is strongly desired despite the risk, several antihypertensives are often required. Hospitalization is also often required for much of the latter part of pregnancy. If the woman's condition worsens, pregnancy termination may be recommended.

Drugs: First-line drugs for hypertension during pregnancy include methyldopa, β-blockers, and Ca channel blockers. Initial methyldopa dose is 250 mg po bid, increased as needed to 2 g/day or sometimes more unless excessive somnolence, depression, and symptomatic orthostatic hypotension occur. The most commonly used β-blocker is labetalol (a β-blocker with some α_1-blocking effects), which can be used alone or with methyldopa when the maximum daily dose of methyldopa has been reached. Usual dose of labetalol is 100 mg bid to tid, increased as needed to a total daily dose of 2400 mg. Adverse effects of β-blockers include increased risk of fetal growth restriction, decreased maternal energy levels, and maternal depression. Extended-release nifedipine, a Ca-channel blocker, may be preferred because it is given once/day (initial dose of 30 to 60 mg); adverse effects include headaches and pretibial edema.

Several classes of antihypertensives are usually avoided during pregnancy:

- **ACE inhibitors** are contraindicated because risk of fetal urinary tract abnormalities is increased.

- **Thiazide diuretics** can adversely affect the fetus and should be avoided during pregnancy if possible.

- **Aldosterone antagonists** (spironolactone and eplerenone) should be avoided because they may cause feminization of a male fetus.

Infectious Disease in Pregnancy

Most common maternal infections (eg, UTIs, skin and respiratory tract infections) are usually not serious problems during pregnancy, although some genital infections (bacterial vaginosis and genital herpes) affect labor or choice of delivery method. Thus, the main issue is usually use and safety of antimicrobial drugs. However, certain maternal infections can damage the fetus (for congenital cytomegalovirus or herpes simplex virus infection, rubella, toxoplasmosis, hepatitis, or syphilis, see Ch. 279; for HIV infection,

see p. 2847).

Listeriosis is more common during pregnancy. Listeriosis increases risk of spontaneous abortion, premature labor, and stillbirth. Neonatal transmission is possible.

Bacterial vaginosis and possibly **genital chlamydial infection** predispose to premature rupture of the membranes and preterm labor. Tests for these infections are done during routine prenatal evaluations or if symptoms develop.

Genital herpes can be transmitted to the neonate during delivery. Risk is high enough that cesarean delivery is preferred in the following situations:

- When women have visible herpetic lesions
- When women who have a known history of infection develop prodromal symptoms before labor
- When herpes infection first occurs during the late 3rd trimester (when the virus is likely to be excreted from the cervix at delivery)

If visible lesions or prodrome is absent, even in women with recurrent infections, risk is low, and vaginal delivery is possible. If women are asymptomatic, serial antepartum cultures do not help identify those at risk of transmission. If women have recurrent herpes infections during pregnancy but no other risk factors for transmission, labor can sometimes be induced so that delivery occurs between recurrences. When delivery is vaginal, cervical and neonatal herpesvirus cultures are done. Acyclovir (oral and topical) appears to be safe during pregnancy.

Antibacterials: Not giving antibacterials to pregnant patients without strong evidence of a bacterial infection is particularly important. Generally, penicillins, cephalosporins, and macrolides are considered safe. Use of any antibacterial during pregnancy should be based on whether benefits outweigh risk, which varies by trimester (see Table 264-2 on p. 2656 for specific adverse effects). Severity of the infection and other options for treatment are also considered.

Aminoglycosides may be used during pregnancy to treat pyelonephritis and chorioamnionitis, but treatment should be carefully monitored to avoid maternal or fetal damage.

Chloramphenicol, even in large doses, does not harm the fetus; however, neonates cannot adequately metabolize chloramphenicol, and the resulting high blood levels may lead to circulatory collapse (gray baby syndrome). Chloramphenicol is rarely used in the US.

Metronidazole use during the 1st trimester is controversial, but the drug is routinely used to treat bacterial vaginosis and trichomoniasis during the 2nd and 3rd trimesters.

Fluoroquinolones are not used during pregnancy; they tend to have a high affinity for bone and cartilage and thus may have adverse musculoskeletal effects.

Sulfonamides are usually safe during pregnancy. However, long-acting sulfonamides cross the placenta and can displace bilirubin from binding sites. These drugs are often avoided after 34 wk gestation because neonatal kernicterus is a risk.

Tetracyclines cross the placenta and are concentrated and deposited in fetal bones and teeth, where they combine with Ca and impair development (see Table 264-2 on p. 2656); they are not used from the middle to the end of pregnancy.

Renal Insufficiency in Pregnancy

Pregnancy often does not worsen renal disorders; it seems to exacerbate noninfectious renal disorders only when uncontrolled hypertension coexists. However, significant renal insufficiency (serum creatinine > 3 mg/dL [> 270 µmol/L] or BUN > 30 mg/dL [> 10.5 mmol urea/L]) before pregnancy usually prevents

women from maintaining a pregnancy to term. Maternal renal insufficiency may cause fetal growth restriction and stillbirth.

After renal transplantation, full-term, un-complicated pregnancy is often possible if women have all of the following:

• A transplanted kidney that has been in place for > 2 yr

• Normal renal function

• No episodes of rejection

• Normal BP

Treatment requires close consultation with a nephrologist. BP and weight are measured every 2 wk; BUN and creatinine levels plus creatinine clearance are measured often, at intervals dictated by severity and progression of disease. Furosemide is given only to control BP or excessive edema; some women require other drugs to control BP. Women with severe renal insufficiency may require hospitalization after 28 wk gestation for bed rest, BP control, and close fetal monitoring. Which antenatal tests are done depends on the stage of pregnancy. Nonstress tests are usually done first, followed by an oxytocin challenge test or a biophysical profile if required. If results remain normal and reassuring, the pregnancy continues.

Delivery is usually required before term because preeclampsia, fetal growth restriction, or uteroplacental insufficiency develop. Sometimes amniocentesis to check fetal lung maturity can help determine when delivery should be done; a lecithin/sphingomyelin ratio of > 2:1 or presence of phosphatidylglycerol indicates maturity. Cesarean delivery is very common, although vaginal delivery may be possible if the cervix is ripe and no impediments to vaginal delivery are evident.

Seizure Disorders in Pregnancy

Seizure disorders may impair fertility. But certain anticonvulsants may make oral contraceptives less effective, resulting in unintentional pregnancy.

The dose of anticonvulsant drugs may have to be increased during pregnancy to maintain therapeutic levels. If women get enough sleep and anticonvulsant levels are kept in the therapeutic range, seizure frequency does not usually increase during pregnancy, and pregnancy outcome is good; however, risks of preeclampsia, fetal growth restriction, and stillbirth are slightly increased. Generally, uncontrolled seizures are more harmful during pregnancy than is use of anticonvulsants; thus, the top priority of treatment during pregnancy is to control seizures. Preconception consultation with a neurologist is recommended to stabilize maternal seizures before pregnancy; the lowest possible dose of anticonvulsant should be used.

Anticonvulsants slightly increase risk of congenital malformations and may tend to slightly decrease intelligence in offspring; risk of intellectual disability may be increased. Risk of hemorrhagic disease of the newborn (erythroblastosis neonatorum) may be increased by in utero exposure to certain anticonvulsants (eg, phenytoin, carbamazepine, pheno-barbital); however, if prenatal vitamins with vitamin D are taken and vitamin K is given to the neonate, hemorrhagic disease is rare.

Taken during pregnancy, phenobarbital may reduce the physiologic jaundice neonates commonly have, perhaps because the drug induces neonatal hepatic conjugating enzymes. Phenytoin is generally preferred.

All anticonvulsants increase the need for supplemental folate; 1 mg po is given once/day. Ideally, it is started before conception.

Vaginal delivery is usually preferred, but if women have repeated seizures during labor, cesarean delivery is indicated. Anticonvulsant levels can rapidly change postpartum and should be closely monitored then.

Disorders Requiring Surgery During Pregnancy

Certain disorders treated with surgery are difficult to diagnose during pregnancy. A high level of suspicion is required; assuming that all abdominal symptoms are pregnancy-related is an error.

Major surgery, particularly intra-abdominal, increases risk of preterm labor and fetal death. However, surgery is tolerated well by pregnant women and the fetus when appropriate supportive care and anesthesia (maintaining BP and oxygenation at normal levels) are provided, so physicians should not be reluctant to operate; delaying treatment of an abdominal emergency is far more dangerous.

Appendicitis: Appendicitis may occur during pregnancy but is more common immediately postpartum. Because the appendix rises in the abdomen as pregnancy progresses, pain and tenderness may not occur in the classic right lower quadrant location, and pain may be mild and cramping, mimicking pregnancy-related symptoms. Also, WBC count is normally somewhat elevated during pregnancy, making WBC count even less useful than usual. Serial clinical assessment and compression-graded ultrasonography are useful. Because diagnosis is often delayed, mortality rate from ruptured appendix is increased during pregnancy and particularly postpartum. Thus, if appendicitis is suspected, surgical evaluation (laparoscopy or laparotomy depending on the stage of pregnancy) should proceed without delay.

Benign ovarian cysts: These cysts are common during pregnancy. Cysts that occur during the first 14 to 16 wk are often corpus luteal cysts, which spontaneously resolve. Adnexal torsion may occur (see p. 2532). If adnexal torsion does not resolve, surgical therapy to unwind the adnexa or removal may be required. After 12 wk, cysts become difficult to palpate because the ovaries, with the uterus, rise out of the pelvis. Ovarian masses are evaluated first by ultrasonography (see p. 2533). Definitive evaluation (eg, excision) is delayed, if possible, until after 14 wk unless any of the following occur:

- The cyst enlarges continuously.
- The cyst is tender.
- The cyst has radiographic characteristics of cancer (eg, a solid component, surface excrescences, size > 6 cm, irregular shape).

Gallbladder disease: This disease occurs occasionally. If possible, treatment is expectant; if women do not improve, immediate surgery is needed.

Intestinal obstruction: During pregnancy, intestinal obstruction may cause intestinal gangrene with peritonitis and maternal or fetal morbidity or mortality. If pregnant women have symptoms and signs of intestinal obstruction and risk factors (eg, previous abdominal surgery, intra-abdominal infection), prompt exploratory laparotomy is indicated.

Thromboembolic Disorders in Pregnancy

In the US, thromboembolic disorders—deep venous thrombosis (DVT—see p. 2224) or pulmonary embolism (PE—see p. 1908)—are a leading cause of maternal mortality. During pregnancy, risk is increased because venous capacitance and venous pressure in the legs are increased, resulting in stasis, and because pregnancy causes a degree of hypercoagulability. However, most thromboemboli develop postpartum and result from vascular trauma during delivery. Cesarean delivery also increases risk.

Symptoms of thrombophlebitis or their absence does not accurately predict the diagnosis, disease severity, or risk of embolization. Thromboembolic disorders can occur without symptoms, with only minimal symptoms, or with significant symptoms. Also, calf edema, cramping, and tenderness, which may occur normally during pregnancy, may simulate Homans' sign.

Diagnosis

- Doppler ultrasonography or sometimes CT with contrast for DVT

• Helical CT for PE

Diagnosis of DVT is usually by Doppler ultrasonography. In the postpartum period, if Doppler ultrasonography and plethysmography are normal but iliac, ovarian, or other pelvic venous thrombosis is suspected, CT with contrast is used.

Diagnosis of PE is increasingly being made by helical CT rather than ventilation-perfusion scanning because CT involves less radiation and is equally sensitive. If the diagnosis of PE is uncertain, pulmonary angiography is required.

Treatment

• Similar to that in nonpregnant patients, except for avoidance of warfarin

If DVT or PE is detected during pregnancy, the anticoagulant of choice is a low molecular weight heparin (LMWH). LMWH, because of its molecular size, does not cross the placenta. It does not cause maternal osteoporosis and may be less likely to cause thrombocytopenia, which can result from prolonged (≥ 6 mo) use of unfractionated heparin. Warfarin crosses the placenta and may cause fetal abnormalities or death (see Table 264-2 on p. 2656). Indications for thrombolysis during pregnancy are the same as for patients who are not pregnant.

If PE recurs despite effective anticoagulation, surgery, usually placement of an inferior vena cava filter just distal to the renal vessels, is indicated.

If women developed DVT or PE during a previous pregnancy or have an underlying thrombophilic disorder, they are treated with prophylactic LMWH 5000 units sc bid beginning at the first diagnosis of pregnancy and continuing until 6 wk postpartum.

Thyroid Disorders in Pregnancy

(See also Ch. 93.)

Thyroid disorders may predate or develop during pregnancy. Pregnancy does not change the symptoms of hypothyroidism and hyperthyroidism or the normal values and ranges of free serum thyroxine (T_4) and thyroid-stimulating hormone (TSH).

Fetal effects vary with the disorder and the drugs used for treatment. But generally, hyperthyroidism causes fetal growth restriction and stillbirth, and hypothyroidism causes intellectual deficits in offspring and miscarriage. The most common causes of maternal hypothyroidism are Hashimoto's thyroiditis and treatment of Graves' disease.

If women have or have had a thyroid disorder, thyroid status should be closely monitored during and after pregnancy in the women and in the offspring.

Graves' disease: Maternal Graves' disease is monitored clinically and with free T_4 and high-sensitivity TSH assays.

Treatment varies. Usually, pregnant women are given the lowest possible dose of oral propylthiouracil (50 to 100 mg q 8 h). Therapeutic response occurs over 3 to 4 wk; then the dose is changed if needed. Propylthiouracil crosses the placenta and may cause goiter and hypothyroidism in the fetus. Simultaneous use of L-thyroxine or L-triiodothyronine is contraindicated because these hormones may mask the effects of excessive propylthiouracil in pregnant women and result in hypothyroidism in the fetus. Methimazole is an alternative to propylthiouracil. Graves' disease commonly abates during the 3rd trimester, often allowing dose reduction or discontinuation of the drug.

In centers with experienced thyroid surgeons, a 2nd-trimester thyroidectomy, although very uncommon, may be considered after drug treatment restores euthyroidism. After thyroidectomy, women are given full

replacement of L-thyroxine (0.15 to 0.2 mg/day), beginning 24 h later.

Radioactive iodine (diagnostic or therapeutic) and iodide solutions are contraindicated during pregnancy because of adverse effects on the fetal thyroid gland. β-Blockers are used only for thyroid storm or severe maternal symptoms.

If pregnant women have or have had Graves' disease, fetal hyperthyroidism may develop. Whether these women are clinically euthyroid, hyperthyroid, or hypothyroid, thyroidstimulating immunoglobulins (Igs) and thyroid-blocking Igs (if present) cross the placenta. Fetal thyroid function reflects the relative fetal levels of these stimulating and blocking Igs. Hyperthyroidism can cause fetal tachycardia (> 160 beats/min), growth restriction, and goiter, which can lead to decreased fetal swallowing, polyhydramnios, and preterm labor. Ultrasonography is used to evaluate fetal growth, thyroid gland, and heart.

Congenital Graves' disease: If pregnant women have taken propylthiouracil, congenital Graves' disease in the fetus may be masked until 7 to 10 days after birth, when the drug's effect subsides.

Maternal hypothyroidism: Women with mild to moderate hypothyroidism frequently have normal menstrual cycles and can become pregnant. During pregnancy, the usual dose of L-thyroxine is continued. As pregnancy progresses, minor dose adjustments may be necessary, ideally based on TSH measurement after several weeks. If hypothyroidism is first diagnosed during pregnancy, L-thyroxine is started at 0.1 mg po once/day.

Hashimoto's thyroiditis: Maternal immune suppression during pregnancy often ameliorates this disorder; however, hypothyroidism or hyperthyroidism that requires treatment sometimes develops.

Acute (subacute) thyroiditis: Common during pregnancy, this disorder usually produces a tender goiter during or after a respiratory infection. Transient, symptomatic hyperthyroidism with elevated T_4 can occur, often resulting in misdiagnosis as Graves' disease. Usually, treatment is unnecessary.

Postpartum maternal thyroid dysfunction: Hypothyroid or hyperthyroid dysfunction occurs in 4 to 7% of women during the first 6 mo after delivery. Incidence seems to be higher among pregnant women with any of the following:

• Goiter

• Hashimoto's thyroiditis

• A strong family history of autoimmune thyroid disorders

• Type 1 (insulin-dependent) diabetes mellitus

In women with any of these risk factors, TSH and free serum T_4 levels should be checked during the 1st trimester and postpartum. Dysfunction is usually transient but may require treatment. After delivery, Graves' disease may recur transiently or persistently.

Painless thyroiditis with transient hyperthyroidism is a recently recognized postpartum, probably autoimmune disorder. It occurs abruptly in the first few weeks postpartum, results in a low radioactive iodine uptake, and is characterized by lymphocytic infiltration. Diagnosis is based on symptoms, thyroid function tests, and exclusion of other conditions. This disorder may persist, recur transiently, or progress.

Urinary Tract Infection in Pregnancy

(See also Ch. 233.)

UTI is common during pregnancy, apparently because of urinary stasis, which results from hormonal ureteral dilation, hormonal ureteral hypoperistalsis, and pressure of the expanding uterus against the ureters. Asymptomatic bacteriuria occurs in about 15% of pregnancies and sometimes progresses to symptomatic cystitis or pyelonephritis. Frank UTI is not always preceded by asymptomatic bacteriuria.

Asymptomatic bacteriuria, UTI, and pyelonephritis increase risk of preterm labor and premature rupture of the membranes.

Diagnosis

Urinalysis and culture are routinely done at initial evaluation to check for asymptomatic bacteriuria. Diagnosis of symptomatic UTI is not changed by pregnancy.

Treatment

• Antibacterial drugs such as cephalexin, nitrofurantoin, or trimethoprim/sulfamethoxazole

• Proof-of-cure cultures and sometimes suppressive therapy

Treatment of symptomatic UTI is not changed by pregnancy, except drugs that may harm the fetus are avoided (see Table 264-2 on p. 2656). Because asymptomatic bacteriuria may lead to pyelonephritis, it should be treated with antibiotics similar to an acute UTI.

Antibacterial drug selection is based on individual and local susceptibility and resistance patterns, but good initial empiric choices include the following:

• Cephalexin

• Nitrofurantoin

• Trimethoprim/sulfamethoxazole

After treatment, proof-of-cure cultures are required. Women who have pyelonephritis or have had > 1 UTI may require suppressive therapy, usually with trimethoprim/sulfamethoxazole (before 34 wk) or nitrofurantoin, for the rest of the pregnancy. In women who have bacteriuria with or without UTI or pyelonephritis, urine should be cultured monthly.

Chapter 264. High-Risk Pregnancy

Introduction

In a high-risk (at-risk) pregnancy, the mother, fetus, or neonate is at increased risk of morbidity or mortality before or after delivery.

In the US, overall maternal mortality rate is 6/100,000 deliveries; incidence is 3 to 4 times higher in nonwhite women. The most common causes of death are hemorrhage, preeclampsia, pulmonary embolism, and infection.

Perinatal mortality rate in offspring is 11.5/1000 deliveries: 6.7/1000 are fetal, and 4.8/1000 are neonatal (age < 28 days). The most common causes of death are congenital malformations and preterm delivery.

Risk assessment is part of routine prenatal care. Risk is also assessed during or shortly after labor and at any time that events may modify risk status. Risk factors (see Table 264-1) are assessed systematically because each risk factor present increases overall risk. High-risk pregnancies require close monitoring and sometimes referral to a perinatal center. When referral is needed, transfer before rather than after delivery results in lower neonatal morbidity and mortality rates. The most common reasons for referral before delivery are

• Preterm labor (often due to premature rupture of the membranes)

• Preeclampsia

• Hemorrhage

Risk Factors

Risk factors include preexisting maternal disorders (see Ch. 263), physical and social characteristics, age, problems in previous pregnancies (eg, spontaneous abortions), and problems that develop during pregnancy (see Ch. 265) or during labor and delivery (see Ch. 266).

Hypertension: Pregnant women are considered to have chronic hypertension (CHTN) if hypertension was present before the pregnancy or if it develops before 20 wk of pregnancy. CHTN is differentiated from gestational hypertension, which develops after 20 wk of pregnancy. In either case, hypertension is defined as systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg on 2 occasions > 24 h apart. Hypertension increases risk of fetal growth restriction by decreasing uteroplacental

[**Table 264-1.** Pregnancy Risk Assessment]

blood flow and risk of adverse fetal and maternal outcomes (see p. 2645).

Before attempting to conceive, women with hypertension should be counseled about the risks of pregnancy. If they become pregnant, prenatal care begins as early as possible and includes measurements of baseline renal function (eg, serum creatinine, BUN), funduscopic examination, and directed cardiovascular evaluation (auscultation and sometimes ECG, echocardiography, or both). Each trimester, 24-h urine protein, serum uric acid, serum creatinine, and Hct are measured. Ultrasonography to monitor fetal growth is done at 28 wk and every 4 wk thereafter. Delayed growth is evaluated with multivessel Doppler testing by a maternal-fetal medicine specialist (for management of hypertension during pregnancy, see p. 2646).

Diabetes: Diabetes mellitus occurs in 3 to 5% of pregnancies, but incidence is increasing as the incidence of obesity increases.

If pregnant women have preexisting insulin-dependent diabetes, risk is increased for pyelonephritis, ketoacidosis, preeclampsia, fetal death, major fetal malformations, fetal macrosomia (fetal weight > 4.5 kg), and, if vasculopathy is present, fetal growth restriction. Insulin requirements usually increase during

pregnancy.

If women have gestational diabetes, risk of hypertensive disorders and fetal macrosomia is increased. Gestational diabetes is routinely screened for at 24 to 28 wk or, if women have risk factors, also during the 1st trimester. Risk factors include previous gestational diabetes, a macrosomic infant in a previous pregnancy, family history of non-insulin-dependent diabetes, unexplained fetal losses, and body mass index (BMI) > 30 kg/m^2. Some clinicians think the diagnosis can be based on a fasting plasma glucose of ≥ 126 mg/dL or a random plasma glucose of ≥ 200 mg/dL. However, most accurate results are obtained with a glucose tolerance test. A 50-g, 1-h glucose tolerance test is used. If the result is 140 to 199 mg/dL, a full glucose tolerance test is done (see Table 99-2 on p. 867); if glucose is ≥ 200 mg/dL, insulin is begun. If ≥ 2 test results are abnormal, women are treated for the rest of the pregnancy with diet and, if necessary, insulin or oral hypoglycemic drugs.

Good control of plasma glucose during pregnancy almost eliminates the risk of adverse outcomes attributable to diabetes (for management of diabetes during pregnancy, see p. 2638).

Sexually transmitted diseases (STDs—see Ch. 156): (Fetal syphilis in utero can cause fetal death, congenital malformations, and severe disability. Risk of transmission of HIV from woman to offspring in utero or perinatally is 30 to 50% within 6 mo (see pp. 1439 and 2847). During pregnancy, bacterial vaginosis, gonorrhea, and genital chlamydial infection increase risk of preterm labor and premature rupture of the membranes. Routine prenatal care includes screening tests for these infections at the first prenatal visit. Syphilis testing is repeated during pregnancy if risk continues and at delivery for all women. Pregnant women who have any of these infections are treated with antimicrobials.

Treatment of bacterial vaginosis, gonorrhea, or chlamydial infection may prolong the interval from rupture of the membranes to delivery and may improve fetal outcome by decreasing fetal inflammation. Treating HIV with zidovudine or nevirapine reduces risk of transmission by two thirds; risk is probably lower (< 2%) with a combination of 2 or 3 antivirals (see p. 2858). These drugs are recommended despite potential toxic effects in the fetus and woman.

Pyelonephritis: Pyelonephritis increases risk of premature rupture of the membranes, preterm labor, and infant respiratory distress syndrome. Pregnant women with pyelonephritis are hospitalized for evaluation and treatment, primarily with urine culture plus sensitivities, IV antibiotics (eg, a 3rd-generation cephalosporin with or without an aminoglycoside), antipyretics, and hydration. Pyelonephritis is the most common nonobstetric cause of hospitalization during pregnancy. Oral antibiotics specific to the causative organism are begun 24 to 48 h after fever resolves and continued to complete the whole course of antibiotic therapy, usually 7 to 10 days. Prophylactic antibiotics (eg, nitrofurantoin, trimethoprim/sulfamethoxazole) with periodic urine cultures are continued for the rest of the pregnancy.

Acute surgical problems: Major surgery, particularly intra-abdominal, increases risk of preterm labor and fetal death. However, surgery is usually tolerated well by pregnant women and the fetus when appropriate supportive care and anesthesia (maintaining BP and oxygenation at normal levels) are provided, so physicians should not be reluctant to operate; delaying treatment of an abdominal emergency is far more dangerous.

After surgery, antibiotics and tocolytic drugs are given for 12 to 24 h. If nonemergency surgery is necessary during pregnancy, it is most safely done during the 2nd trimester.

Genital tract abnormalities: Structural abnormalities of the uterus and cervix (eg, uterine septum, bicornuate uterus) make fetal malpresentation, dysfunctional labor, and the need for cesarean delivery more likely. Although unlikely, uterine fibroids can cause placental abnormalities (eg, placenta previa), preterm labor, and recurrent spontaneous abortion. Fibroids may grow rapidly or degenerate during pregnancy; degeneration often causes severe pain and peritoneal signs. Cervical insufficiency (incompetence—see p. 2661) makes preterm delivery more likely. If women have had a myomectomy before pregnancy in which the uterine cavity was entered, cesarean delivery is required because uterine rupture is a risk during subsequent vaginal delivery. Uterine abnormalities that lead to poor obstetric outcomes often require surgical correction, which is done after delivery.

Maternal age: Adolescents, who account for 13% of all pregnancies, have an increased incidence of preeclampsia, preterm labor, and anemia, which often leads to fetal growth restriction. The cause, at least in part, is that adolescents tend to neglect prenatal care, frequently smoke, and have higher rates of STDs.

In women > 35, the incidence of preeclampsia is increased, as is that of gestational diabetes, dysfunctional labor, abruptio placentae, stillbirth, and placenta previa. These women are also more likely to have preexisting disorders (eg, CHTN, diabetes). Because risk of fetal chromosomal abnormalities increases as maternal age increases, genetic testing should be offered (see p. 2599).

Maternal weight: Pregnant women whose BMI was < 19.8 kg/m^2 before pregnancy are considered underweight, which predisposes to low birth weight (< 2.5 kg) in neonates. Such women are encouraged to gain at least 12.5 kg during pregnancy.

Pregnant women whose BMI was > 29.0 kg/m^2 before pregnancy are considered overweight, making maternal hypertension and diabetes, postterm pregnancy, fetal macrosomia, and the need for cesarean delivery more likely. Such women are encouraged to limit weight gain during pregnancy to < 11.5 kg.

Maternal height: Short (about < 152 cm) women are more likely to have a small pelvis, which can lead to dystocia with fetopelvic disproportion or shoulder dystocia. For short women, preterm labor and intrauterine growth restriction are also more likely.

Exposure to teratogens: Common teratogens (agents that cause fetal malformation) include infections, drugs, and physical agents. Malformations are most likely to result if exposure occurs between the 2nd and 8th wk after conception (the 4th to 10th wk after the last menstrual period), when organs are forming. Other adverse pregnancy outcomes are also more likely. Pregnant women exposed to teratogens are counseled about increased risks and referred for detailed ultrasound evaluation to detect malformations.

Common infections that may be teratogenic include herpes simplex, viral hepatitis, rubella, varicella, syphilis, toxoplasmosis, and cytomegalovirus and coxsackievirus infections.

Commonly used drugs that may be teratogenic include alcohol, tobacco, cocaine, and some prescription drugs (see Table 264-2).

Cigarette smoking is the most common addiction among pregnant women. Also, percentages of women who smoke and of those who smoke heavily appear to be increasing. Only 20% of smokers quit during pregnancy. Carbon monoxide and nicotine in cigarettes cause hypoxia and vasoconstriction, increasing risk of spontaneous abortion (fetal loss or delivery at < 20 wk), fetal growth restriction, abruptio placentae, placenta previa, premature rupture of the membranes, preterm birth, chorioamnionitis, and stillbirth. Neonates whose mothers smoke are also more likely to have anencephaly, congenital heart defects, orofacial clefts, sudden infant death syndrome, deficiencies in physical growth and intelligence, and behavioral problems. Smoking cessation or limitation reduces risks.

Alcohol is the most commonly used teratogen. Drinking alcohol during pregnancy increases risk of spontaneous abortion. Risk is probably related to amount of alcohol consumed, but no amount is known to be risk-free. Regular drinking decreases birth weight by about 1 to 1.3 kg. Binge drinking in particular, possibly as little as 45 mL of pure alcohol (equivalent to about 3 drinks) a day, can cause fetal alcohol syndrome. This syndrome occurs in 2.2/1000 live births; it includes fetal growth restriction, facial and cardiovascular defects, and neurologic dysfunction. It is a leading cause of intellectual disability (mental retardation) and can cause neonatal death due to failure to thrive.

Cocaine use has indirect fetal risks (eg, maternal stroke or death during pregnancy). It also directly causes fetal vasoconstriction and hypoxia. Repeated use increases risk of spontaneous abortion, fetal growth restriction, abruptio placentae, preterm birth, stillbirth, and congenital malformations (eg, CNS, GU, and skeletal malformations; isolated atresias).

Although marijuana's main metabolite can cross the placenta, recreational use of marijuana use does not consistently appear to increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities.

Prior stillbirth: Causes of stillbirth (fetal death at > 20 wk) may be maternal, placental, or fetal (see p. 2675). Having had a stillbirth or late abortion (ie, at 16 to 20 wk) increases risk of fetal death in subsequent pregnancies. Fetal surveillance using antepartum testing (eg, nonstress testing, biophysical profile) is recommended. Treatment of maternal disorders (eg, CHTN, diabetes, infections) may lower risk of stillbirth in a current pregnancy.

Prior preterm delivery: Preterm delivery is delivery before 37 wk (see p. 2683). Previous preterm delivery due to preterm labor increases risk of future preterm deliveries; if the previous preterm neonate weighed < 1.5 kg, risk of preterm delivery in the next pregnancy is 50%. Women with prior preterm delivery due to

[**Table 264-2.** Drugs with Adverse Effects During Pregnancy]

preterm labor should be closely monitored at 2-wk intervals after 20 wk. Monitoring includes

• Ultrasound evaluation, including measurement of cervical length and shape, at 16 to 18 wk

• Uterine contraction monitoring

• Testing for bacterial vaginosis

• Measurement of fetal fibronectin

Women with prior preterm birth due to preterm labor or with shortening (< 25 mm) or funneling of the cervix should be given 17 α-OH-progesterone 250 mg IM once/wk.

Prior neonate with a genetic or congenital disorder: Risk of having a fetus with a chromosomal disorder is increased for most couples who have had a fetus or neonate with a chromosomal disorder (recognized or missed—see p. 2598). Recurrence risk for most genetic disorders is unknown. Most congenital malformations are multifactorial; risk of having a subsequent fetus with malformations is ≤ 1%. If couples have had a neonate with a genetic or chromosomal disorder, genetic screening is recommended. If couples have had a neonate with a congenital malformation, genetic screening, high-resolution ultrasonography, and evaluation by a maternal-fetal medicine specialist is recommended.

Polyhydramnios (hydramnios) and oligohydramnios: Polyhydramnios (excess amniotic fluid) can lead to severe maternal shortness of breath and preterm labor. Risk factors include uncontrolled maternal diabetes, multifetal pregnancy, isoimmunization, and fetal malformations (eg, esophageal atresia, anencephaly, spina bifida).

Oligohydramnios (deficient amniotic fluid) often accompanies congenital malformations of the fetal urinary tract and severe fetal growth restriction (< 3rd percentile). Also, Potter's syndrome with pulmonary hypoplasia or fetal surface compression abnormalities may result, usually in the 2nd trimester, and cause fetal death.

Polyhydramnios and oligohydramnios are suspected if uterine size does not correspond to gestational date or may be discovered incidentally via ultrasonography, which is diagnostic.

Multifetal (multiple) pregnancy: Multifetal pregnancy increases risk of fetal growth restriction, preterm labor, abruptio placentae, congenital malformations, perinatal morbidity and mortality, and, after delivery, uterine atony and hemorrhage (see p. 2680). Multifetal pregnancy is detected during routine ultrasonography at 18 to 20 wk.

Prior birth injury: Most cases of cerebral palsy and developmental delay are caused by factors unrelated to a birth injury.

Injuries such as brachial plexus damage can result from procedures such as forceps or vacuum extractor delivery but often result from intrauterine forces during labor or malposition during the last weeks of pregnancy. Previous shoulder dystocia is a risk factor for future dystocia, and the delivery records should be reviewed for potentially modifiable risk factors (eg, fetal macrosomia, operative vaginal delivery) that may have predisposed to the injury.

Chapter 265. Abnormalities of Pregnancy

Introduction

Abnormalities that develop during pregnancy may be directly related to the pregnancy or not (for nonobstetric disorders, see Ch. 263). Obstetric abnormalities increase the risk of morbidity or mortality for the woman, fetus, or neonate, as do such factors as maternal characteristics, problems in previous pregnancies, and drug use (see Ch. 264).

Abruptio Placentae

Abruptio placentae is premature separation of a normally implanted placenta from the uterus after 20 wk gestation. It is an obstetric emergency. Manifestations may include vaginal bleeding, uterine pain and tenderness, hemorrhagic shock, and disseminated intravascular coagulation. Diagnosis is clinical and sometimes by ultrasonography. Treatment is bed rest for mild symptoms and prompt delivery for severe or persistent symptoms.

Abruptio placentae occurs in 0.4 to 1.5% of all pregnancies; incidence peaks at 24 to 26 wk gestation.

Abruptio placentae may involve any degree of placental separation, from a few millimeters to complete detachment. Separation can be acute or chronic. Separation results in bleeding into the decidua basalis behind the placenta (retroplacentally). Cause is unknown.

Risk factors: Risk factors include the following:

• Older maternal age

• Hypertension (pregnancy-induced or chronic)

• Placental ischemia (ischemic placental disease) manifesting as intrauterine growth restriction

• Polyhydramnios

• Intra-amniotic infection (chorioamnionitis)

• Vasculitis

• Other vascular disorders

• Prior abruptio placentae

• Abdominal trauma

• Maternal thrombotic disorders

• Tobacco use

• Premature rupture of membranes

• Cocaine use (risk of up to 10%)

Complications: Complications include the following:

• Maternal blood loss (possibly with shock, disseminated intravascular coagulation [DIC], or both)

• Fetal ischemia (causing fetal distress or death if ischemia is acute or severe growth restriction if ischemia is chronic and mild)

• Sometimes fetomaternal transfusion and Rh sensitization

Symptoms and Signs

Acute abruptio placentae may result in bright red blood exiting through the cervix (external hemorrhage). Blood may also remain behind the placenta (concealed hemorrhage). Severity of symptoms and signs depends on degree of separation and blood loss. As separation continues, the uterus may be painful, tender, and irritable to palpation. Hemorrhagic shock may occur, as may signs of DIC. Chronic abruptio placentae may cause continued or intermittent dark brown spotting.

Abruptio placentae may cause no or minimal symptoms and signs.

Diagnosis

• Combination of clinical, laboratory, and ultrasonographic findings

Diagnosis is suggested if any of the following occur during late pregnancy:

• Vaginal bleeding

• Uterine pain and tenderness

• Fetal distress or death

• Hemorrhagic shock

• DIC

• Tenderness or shock disproportionate to the degree of vaginal bleeding

The diagnosis should also be considered in women who have had abdominal trauma. If bleeding occurs during late pregnancy, placenta previa, which has similar symptoms, must be ruled out before pelvic examination is done; if placenta previa is present, examination may increase bleeding.

Evaluation includes the following:

• Fetal heart monitoring

• CBC

• Blood and Rh typing

• PT/PTT

• Serum fibrinogen and fibrin-split products (the most sensitive indicator)

• Transabdominal or pelvic ultrasonography

• Kleihauer-Betke test if the patient has Rh-negative blood—to calculate the dose of Rh_0(D) immune globulin needed

Fetal heart monitoring may detect a nonreassuring pattern or fetal death.

Transvaginal ultrasonography may be done if transabdominal ultrasonography rules out placenta previa. However, ultrasonography is insensitive; thus, diagnosis may ultimately be clinical.

Treatment

• Usually prompt delivery and aggressive supportive measures

• Trial of hospitalization and bed rest if the pregnancy is not near term and if mother and fetus are stable

Prompt cesarean delivery is usually indicated if any of the following is present:

• Maternal hemodynamic instability

• Nonreassuring fetal heart rate pattern

• Near-term pregnancy

However, oxytocin may be given to accelerate vaginal delivery, depending on the stage of labor and the rapidity of maternal and fetal deterioration (eg, oxytocin may be given if delivery appears imminent and the mother and fetus are stable). Amniotomy (deliberate rupture of membranes) is done early because it may accelerate delivery, preventing DIC.

Hospitalization and bed rest are advised if all of the following are present:

• Bleeding does not threaten the life of the mother or fetus.

• The fetal heart rate pattern is reassuring.

• The pregnancy is not near term.

This approach ensures that mother and fetus can be closely monitored and, if needed, rapidly treated. Corticosteroids should be considered (to accelerate fetal lung maturity) if gestational age is < 34 wk. If bleeding resolves and maternal and fetal status remains stable, ambulation and usually hospital discharge are allowed. If bleeding continues or if status deteriorates, prompt cesarean delivery is indicated.

Complications (eg, shock, DIC) are managed with aggressive replacement of blood and blood products.

Cervical Insufficiency

Cervical insufficiency (formerly called cervical incompetence) is painless cervical dilation resulting in delivery of a live fetus during the 2nd trimester. Transvaginal cervical ultrasonography during the 2nd trimester may help assess risk. Treatment is reinforcement of the cervical ring with suture material (cerclage).

Cervical insufficiency refers to presumed weakness of cervical tissue that contributes to or causes premature delivery not explained by another abnormality. Estimated incidence varies greatly (1/100 to 1/2000).

Etiology

The cause is not well understood but seems to involve some combination of structural abnormalities and biochemical factors (eg, inflammation, infection); these factors may be acquired or genetic.

Risk factors: Most women with cervical insufficiency do not have risk factors; however, the following risk factors have been identified:

• Congenital disorders of collagen synthesis (eg, Ehlers-Danlos syndrome)

• Prior cone biopsies (particularly when ≥ 1.7 to 2.0 cm of the cervix was removed)

• Prior deep cervical lacerations (usually secondary to vaginal or cesarean delivery)

• Prior excessive or rapid dilation with instruments (now uncommon)

• Mullerian duct defects (eg, bicornuate or septate uterus)

• ≥ 3 prior fetal losses during the 2nd trimester

Recurrence: Overall risk of recurrence of fetal loss due to cervical insufficiency is probably ≤ 30%, leading to the question of how large a role fixed structural abnormalities have. Risk is greatest for women with ≥ 3 prior 2nd-trimester fetal losses.

Symptoms and Signs

Cervical insufficiency is often asymptomatic until premature delivery occurs. Some women have earlier symptoms, such as vaginal pressure, vaginal bleeding or spotting, nonspecific abdominal or lower back pain, or vaginal discharge. The cervix may be soft, effaced, or dilated.

Diagnosis

• Transvaginal ultrasonography at > 16 wk for women with symptoms or risk factors

The diagnosis is suspected in women with risk factors or characteristic symptoms or signs. Then, transvaginal ultrasonography is done. Results are most accurate after 16 wk gestation. Suggestive ultrasonographic findings include cervical shortening to < 2.5 cm, cervical dilation, and protrusion of fetal membranes into the cervical canal.

Ultrasonography of women without symptoms or risk factors is not recommended because results do not accurately predict preterm delivery.

Treatment

• Cerclage

Cerclage (reinforcement of the cervical ring with suture material) appears to prevent preterm delivery in patients with ≥ 3 prior 2nd-trimester fetal losses. For other patients, the procedure should probably be done only if they have a history strongly suggesting cervical insufficiency and if cervical shortening is detected by ultrasonography before 22 to 24 wk gestation; restricting cerclage to such patients does not appear to increase risk of preterm delivery and reduces the number of cerclages currently being done by two thirds. Evidence does not support use of cerclage simply for ultrasound-detected cervical shortening.

Treatments such as corticosteroids, progesterone, and bed rest are often used when preterm labor is suspected.

Intra-Amniotic Infection

(Chorioamnionitis)

Intra-amniotic infection (formerly called chorioamnionitis) is infection of the chorion, amnion, amniotic fluid, placenta, or a combination. Infection increases risk of obstetric complications and problems in the fetus. Symptoms include fever, uterine tenderness, foul-smelling vaginal discharge, and maternal and fetal tachycardia. Diagnosis is by specific criteria or, for subclinical infection, analysis of amniotic fluid. Treatment includes broad-spectrum antibiotics and delivery.

Intra-amniotic infection typically results from an infection that ascends through the genital tract.

Risk factors: Risk factors include the following:

• Preterm labor

- Nulliparity
- Meconium-stained amniotic fluid
- Internal fetal or uterine monitoring
- Presence of genital tract pathogens (eg, those that cause sexually transmitted diseases or bacterial vaginosis, group B streptococci)
- Digital examinations during labor in women with ruptured membranes
- Long labor
- Preterm premature rupture of membranes

Complications: Intra-amniotic infection can cause as well as result from preterm premature rupture of membranes or preterm delivery. This infection accounts for 50% of deliveries before 30 wk gestation. It occurs in 33% of women who have preterm labor with intact membranes, 40% who have premature rupture of membranes (PROM) and are having contractions when admitted, and 75% who go into labor after admission for PROM.

Fetal complications include increased risk of the following:

- Preterm delivery
- Apgar score < 3
- Infection (eg, sepsis, pneumonia, meningitis)
- Seizures
- Cerebral palsy
- Death

Maternal complications include increased risk of the following:

- Bacteremia
- Need for cesarean delivery
- Uterine atony
- Postpartum hemorrhage
- Pelvic abscess
- Thromboembolism
- Wound complications

Septic shock, coagulopathy, and adult respiratory distress syndrome are also risks but are uncommon if infection is treated.

Symptoms and Signs

Intra-amniotic infection typically causes fever. Other findings can include maternal tachycardia, fetal tachycardia, uterine tenderness, and foul-smelling amniotic fluid. However, infection may not cause typical

symptoms (ie, subclinical infection).

Diagnosis

• Clinical criteria

• Amniocentesis for suspected subclinical infection

Diagnosis usually requires a maternal temperature of > 38° C (> 100.4° F) plus ≥ 2 of the following:

• Maternal WBC count > 15,000 cells/µL

• Maternal tachycardia (heart rate > 100 beats/min)

• Fetal tachycardia (heart rate > 160 beats/min)

• Uterine tenderness

• Foul-smelling amniotic fluid

Presence of a single symptom or sign, which may have other causes, is less reliable. For example, uterine pain and tenderness may result from abruptio placentae. Maternal tachycardia may be due to pain, epidural anesthesia, or drugs (eg, ephedrine); fetal tachycardia may be due to maternal use of drugs or fetal hypoxemia. Maternal and fetal heart rates also increase during fever. However, if intra-amniotic infection is absent, heart rates return to baseline as these conditions resolve. If fetal or maternal tachycardia is disproportionate to or occurs without such conditions or if it persists despite resolution of these conditions, intra-amniotic infection is suspected.

Subclinical infection: Refractory preterm labor (persisting despite tocolysis) may suggest subclinical infection. If membranes rupture prematurely before term, clinicians should also consider subclinical infection so that they can determine whether induction of labor is indicated.

Amniocentesis with culture of amniotic fluid is the best way to diagnose subclinical infection. The following fluid findings suggest infection:

• Presence of any bacteria or leukocytes using Gram staining

• Glucose level < 15 mg/dL

• WBC count > 30 cells/µL

• Leukocyte esterase level at trace or higher levels

Other diagnostic tests for subclinical infection are under study.

Treatment

• Broad-spectrum antibiotics

Treatment is broad-spectrum IV antibiotics plus delivery. A typical antibiotic regimen is ampicillin 2 g IV q 6 h plus gentamicin 1.5 mg/kg IV q 8 h. The antibiotics reduce risk of morbidity due to infection for mother and neonate.

Risk of intra-amniotic infection is decreased by avoiding or minimizing digital pelvic examinations in patients with preterm PROM (see p. 2682).

Ectopic Pregnancy

In ectopic pregnancy, implantation occurs in a site other than the endometrial lining of the uterine cavity—in the fallopian tube, uterine cornua, cervix, ovary, or abdominal or pelvic cavity. Ectopic pregnancies cannot be carried to term and eventually rupture or involute. Early symptoms and signs include pelvic pain, vaginal bleeding, and cervical motion tenderness. Syncope or hemorrhagic shock can occur with rupture. Diagnosis is by measurement of the β subunit of human chorionic gonadotropin and ultrasonography. Treatment is with laparoscopic or open surgical resection or with IM methotrexate.

Incidence of ectopic pregnancy is about 2/100 diagnosed pregnancies.

Etiology

Tubal lesions increase risk. Factors that particularly increase risk include

• Prior ectopic pregnancy (10 to 25% risk of recurrence)

• History of pelvic inflammatory disease (particularly due to *Chlamydia trachomatis*)

• Prior abdominal or particularly tubal surgery, including tubal ligation

Other specific risk factors include

• Intrauterine device (IUD) use

• Infertility

• Multiple sex partners

• Cigarette smoking

• Exposure to diethylstilbestrol

• Prior induced abortion

Pregnancy is less likely to occur when an IUD is in place; however, about 5% of such pregnancies are ectopic.

Pathophysiology

The most common site of ectopic implantation is a fallopian tube, followed by the uterine cornua. Pregnancies in the cervix, a cesarean delivery scar, an ovary, the abdomen, or fallopian tube interstitium are rare.

Heterotopic pregnancy (simultaneous ectopic and intrauterine pregnancies) occurs in only 1/10,000 to 30,000 pregnancies but may be more common among women who have had ovulation induction or used assisted reproductive techniques such as in vitro fertilization and gamete intrafallopian tube transfer (GIFT); in these women, the overall reported ectopic pregnancy rate is ≤ 1%.

The structure containing the fetus usually ruptures after about 6 to 16 wk. Rupture results in bleeding that can be gradual or rapid enough to cause hemorrhagic shock. Intraperitoneal blood irritates the peritoneum. The later the rupture, the more rapidly blood is lost and the higher the risk of death.

Symptoms and Signs

Symptoms vary and are often absent until rupture occurs. Most patients have pelvic pain (which is sometimes crampy), vaginal bleeding, or both. Menses may or may not be delayed or missed, and patients may not be aware that they are pregnant.

Rupture may be heralded by sudden, severe pain, followed by syncope or by symptoms and signs of hemorrhagic shock or peritonitis. Rapid hemorrhage is more likely in ruptured cornual pregnancies.

Cervical motion tenderness, unilateral or bilateral adnexal tenderness, or an adnexal mass may be present. The uterus may be slightly enlarged (but often less than anticipated based on date of the last menstrual period).

Diagnosis

• Serum β-human chorionic gonadotropin (β-hCG) levels

• Pelvic ultrasonography

• Sometimes laparoscopy

Ectopic pregnancy is suspected in any female of reproductive age with pelvic pain, vaginal bleeding, or unexplained syncope or hemorrhagic shock, regardless of sexual, contraceptive, and menstrual history. Findings of physical (including pelvic) examination are neither sensitive nor specific.

The first step is doing a urine pregnancy test, which is about 99% sensitive for pregnancy (ectopic and otherwise). If urine β-hCG is negative and if clinical findings do not strongly suggest ectopic pregnancy, further evaluation is unnecessary unless symptoms recur or worsen. If urine β-hCG is positive or if clinical findings strongly suggest ectopic pregnancy, quantitative serum β-hCG and pelvic ultrasonography are indicated.

If quantitative serum β-hCG is < 5 mIU/mL, ectopic pregnancy is excluded. If ultrasonography detects an intrauterine gestational sac, ectopic pregnancy is extremely unlikely except in women who have used assisted reproductive techniques (which increase risk of heterotopic pregnancy); however, cornual and intra-abdominal pregnancies may appear to be intrauterine pregnancies. Ultrasonographic findings suggesting ectopic pregnancy (noted in 16 to 32%) include complex (mixed solid and cystic) masses, particularly in the adnexa, and free fluid in the cul-de-sac.

If serum β-hCG is above a certain level (called the discriminatory zone), ultrasonography should detect a gestational sac in patients with an intrauterine pregnancy. This level is usually about 2000 mIU/mL. If the β-hCG level is higher than the discriminatory zone and an intrauterine gestational sac is not detected, an ectopic pregnancy is likely. Use of transvaginal and color Doppler ultrasonography may improve detection rates.

If the β-hCG level is below the discriminatory zone and ultrasonography is unremarkable, patients may have an early intrauterine pregnancy or an ectopic pregnancy. If clinical evaluation suggests ectopic pregnancy (eg, signs of significant hemorrhage or peritoneal irritation), diagnostic laparoscopy may be necessary for confirmation. If ectopic pregnancy appears unlikely and patients are stable, serum levels of β-hCG can be measured serially on an outpatient basis (typically every 2 days). Normally, the level doubles every 1.4 to 2.1 days up to 41 days; in ectopic pregnancy (and in abortions), levels may be lower than expected by dates and usually do not double as rapidly. If β-hCG levels do not increase as expected or if they decrease, the diagnoses of spontaneous abortion and ectopic pregnancy are reconsidered.

Prognosis

Ectopic pregnancy is fatal to the fetus, but if treatment occurs before rupture, maternal death is very rare. In the US, ectopic pregnancy probably accounts for 9% of pregnancy-related maternal deaths.

Treatment

• Surgical resection (usually)

• Methotrexate for some small, unruptured ectopic pregnancies

Surgical resection: Hemodynamically unstable patients require immediate laparotomy and treatment of hemorrhagic shock (see p. 2296). For stable patients, treatment is usually laparoscopic surgery; sometimes laparotomy is required. If possible, salpingotomy, usually using cautery, high-frequency (harmonic) ultrasound devices, or a laser, is done to conserve the tube, and the products of conception are evacuated.

Salpingectomy is indicated in any of the following cases:

• When ectopic pregnancies recur or are > 5 cm

• When the tubes are severely damaged

• When no future childbearing is planned

Only the irreversibly damaged portion of the tube is removed, maximizing the chance that tubal repair can restore fertility. The tube may or may not be repaired. After a cornual pregnancy, the tube and ovary involved can usually be salvaged, but occasionally repair is impossible, making hysterectomy necessary.

Methotrexate: If unruptured tubal pregnancies are < 3.0 cm in diameter, no fetal heart activity is detected, and the β-hCG level is < 5,000 mIU/mL ideally but up to 15,000 mIU/mL, women can be given a single dose of methotrexate 50 mg/m^2 IM. β-hCG measurement and ultrasonography are repeated on about days 4 and 7. If the β-hCG level does not decrease by 15%, a 2nd dose of methotrexate or surgery is needed. Alternatively, the β-hCG level is measured on days 1 and 7, and a 2nd dose of methotrexate is given if the level does not decrease by 25%. About 15 to 20% of women treated with methotrexate eventually require a 2nd dose.

The β-hCG level is measured weekly until it is undetectable. Success rates with methotrexate are about 87%; 7% of women have serious complications (eg, rupture). Surgery is indicated when methotrexate is ineffective.

Erythroblastosis Fetalis

Erythroblastosis fetalis is hemolytic anemia in the fetus or neonate caused by transplacental transmission of maternal antibodies to fetal RBCs. The disorder usually results from incompatibility between maternal and fetal blood groups, often Rh_0(D) antigens. Diagnosis begins with prenatal maternal antigenic and antibody screening and may require paternal screening, serial measurement of maternal antibody titers, and fetal testing. Treatment may involve intrauterine fetal transfusion or neonatal exchange transfusion. Prevention is Rh_0(D) immune globulin injection for women at risk.

Erythroblastosis fetalis classically results from Rh_0(D) incompatibility, which may develop when a woman with Rh-negative blood is impregnated by a man with Rh-positive blood and conceives a fetus with Rh-positive blood (see also p. 2784). Other fetomaternal incompatibilities that can cause erythroblastosis fetalis involve the Kell, Duffy, Kidd, MNSs, Lutheran, Diego, Xg, P, Ee, and Cc antigen systems, as well as other antigens. Incompatibilities of ABO blood types do not cause erythroblastosis fetalis.

Pathophysiology

Fetal RBCs normally move across the placenta to the maternal circulation throughout pregnancy. Movement is greatest at delivery or termination of pregnancy. Movement of large volumes (eg, 10 to 150 mL) is considered significant fetomaternal hemorrhage; it can occur after trauma and sometimes after delivery or termination of pregnancy. In women who have Rh-negative blood and who are carrying a fetus with Rh-positive blood, fetal RBCs stimulate maternal antibody production against the Rh antigens. The larger the fetomaternal hemorrhage, the more antibodies produced. The mechanism is the same when other antigen systems are involved; however, Kell antibody incompatibility also directly suppresses RBC production in bone marrow.

Other causes of maternal anti-Rh antibody production include injection with needles contaminated with Rh-positive blood and inadvertent transfusion of Rh-positive blood.

No complications develop during the initial sensitizing pregnancy; however, in subsequent pregnancies, maternal antibodies cross the placenta and lyse fetal RBCs, causing anemia, hypoalbuminemia, and possibly high-output heart failure or fetal death. Anemia stimulates fetal bone marrow to produce and release immature RBCs (erythroblasts) into fetal peripheral circulation (erythroblastosis fetalis). Hemolysis results in elevated indirect bilirubin levels in neonates, causing kernicterus (see p. 2793). Usually, isoimmunization does not cause symptoms in pregnant women.

Diagnosis

- Maternal blood and Rh typing and reflex antibody screening
- Serial antibody level measurements and sometimes middle cerebral artery blood flow measurements for pregnancies at risk

At the first prenatal visit, all women are screened for blood type, Rh type, and anti-Rh_0(D) and other antibodies that are formed in response to antigens and that can cause erythroblastosis fetalis (reflex antibody screening). If women have Rh-negative blood and test positive for anti-Rh_0(D) or they test positive for another antibody that can cause erythroblastosis fetalis, the father's blood type and zygosity (if paternity is certain) are determined. If he has Rh-negative blood and is negative for the antigen corresponding to the antibody identified in the mother, no further testing is necessary. If he has Rh-positive blood or has the antigen, maternal anti-Rh antibody titers are measured. If titers are positive but less than a laboratory-specific critical value (usually 1:8 to 1:32), they are measured monthly until 24 wk, then every 2 wk. If the critical value is exceeded, fetal middle cerebral artery blood flow is measured at intervals of 1 to 2 wk depending on titers and patient history; the purpose is to detect high-output heart failure, indicating high risk of anemia. Elevated blood flow for gestational age should prompt percutaneous umbilical blood sampling to obtain a sample of fetal blood. If paternity is reasonably certain and the father is likely to be heterozygous for Rh_0(D), the fetus's Rh type is determined. If fetal blood is Rh positive or status is unknown and if middle cerebral artery flow is elevated, fetal anemia is likely.

Treatment

- Fetal blood transfusions
- Delivery at 32 to 34 wk

If fetal blood is Rh negative or if middle cerebral artery blood flow remains normal, pregnancy can continue to term untreated. If fetal anemia is likely, the fetus can be given intravascular intrauterine blood transfusions by a specialist at an institution equipped to care for high-risk pregnancies. Transfusions occur every 1 to 2 wk until fetal lung maturity is confirmed (usually at 32 to 34 wk), when delivery should be done. Corticosteroids should be given before the first transfusion if the pregnancy is > 24 wk, possibly > 23 wk.

Neonates with erythroblastosis are immediately evaluated by a pediatrician to determine need for exchange transfusion (see p. 2786).

Prevention

Prevention involves giving the mother

- Rh_0(D) immune globulin at 28 wk gestation and within 72 h of pregnancy termination

Delivery should be as atraumatic as possible. Manual removal of the placenta should be avoided because it may force fetal cells into maternal circulation.

Maternal sensitization and antibody production due to Rh incompatibility can be prevented by giving the woman Rh_0(D) immune globulin. This preparation contains high titers of anti-Rh antibodies, which neutralize Rh-positive fetal RBCs. Because fetomaternal transfer and likelihood of sensitization is greatest at termination of pregnancy, the preparation is given within 72 h after termination of each pregnancy, whether by delivery, abortion, or treatment of ectopic pregnancy. The standard dose is 300 µg IM. A rosette test can be used to rule out significant fetomaternal hemorrhage, and if results are positive, a Kleihauer-Betke (acid elution) test can measure the amount of fetal blood in the maternal circulation. If test results indicate fetomaternal hemorrhage is massive (> 30 mL whole blood), additional injections (300 µg for every 30 mL of fetal whole blood, up to 5 doses within 24 h) are necessary.

Treatment at termination of pregnancy is occasionally ineffective because sensitization occurred earlier during pregnancy. Therefore, at about 28 wk, all pregnant women with Rh-negative blood and no known prior sensitization are given a dose. Some experts recommend a 2nd dose if delivery has not occurred by 40 wk. Rh_0(D) immune globulin should also be given after any episode of vaginal bleeding and after amniocentesis or chorionic villus sampling. Anti-Rh antibodies persist for > 3 mo after one dose.

Pemphigoid Gestationis

(Herpes Gestationis)

Pemphigoid gestationis is a pruritic papular and vesicobullous eruption that occurs during pregnancy or postpartum. Diagnosis is clinical or by skin biopsy. Treatment is with topical or systemic corticosteroids.

Pemphigoid gestationis appears to be an autoimmune phenomenon, probably caused by an IgG antibody to a 180-kD antigen in the basement membrane zone of the epidermis. Although previously called herpes gestationis, this disorder is not caused by herpesvirus.

Pemphigoid gestationis occurs in 1/2,000 to 50,000 pregnancies; it usually begins during the 2nd or 3rd trimester but may begin during the 1st trimester or immediately postpartum. It usually recurs with subsequent pregnancies and occurs after oral contraceptive use in about 25% of women. Flare-ups can occur during subsequent menses or ovulation.

Most fetuses are unaffected; however, transient lesions occur in < 5% of neonates born to mothers with pemphigoid gestationis. Risks are increased after premature delivery and in infants who are small for gestational age.

Symptoms and Signs

The rash is very pruritic. Lesions often start around the umbilicus, then become widespread. Vesicles and bullae are the most specific lesions; erythematous plaques may develop. The palms, soles, trunk, buttocks, and extremities may be affected but usually not the face or mucous membranes.

The rash worsens during labor or immediately postpartum in up to 75% of women, typically remitting within a few weeks or months.

Neonates may have erythematous plaques or vesicles that resolve spontaneously in a few weeks.

Diagnosis

• Clinical evaluation

• Sometimes biopsy with direct immunofluorescence

Pemphigoid gestationis may be confused clinically with several other pruritic eruptions of pregnancy, particularly pruritic urticarial papules and plaques of pregnancy. Pemphigoid gestationis can often be distinguished because it usually begins in the periumbilical area; pruritic urticarial papules and plaques of pregnancy usually begin in the striae.

Direct immunofluorescence examination of perilesional skin is diagnostic. It detects a linear band of C3 at the basement membrane zone.

Treatment

• Corticosteroids topically or, for severe symptoms, orally

For mild symptoms, topical corticosteroids (eg, 0.1% triamcinolone acetonide cream up to 6 times/day) may be effective. Prednisone (eg, 40 mg po once/day) relieves moderate or severe pruritus and prevents new lesions; dose is tapered until few new lesions erupt, but it may need to be increased if symptoms become more severe (eg, during labor). Systemic corticosteroids given late in pregnancy do not seem to harm the fetus.

Nonsedating oral antihistamines can also be used to relieve pruritus.

Hyperemesis Gravidarum

Hyperemesis gravidarum is uncontrollable vomiting during pregnancy that results in dehydration, weight loss, and ketosis. Diagnosis is clinical and by measurement of urine ketones and renal function. Treatment is with temporary suspension of oral intake and with IV fluids, antiemetics if needed, and vitamin and electrolyte repletion.

Pregnancy frequently causes nausea and vomiting; the cause appears to be rapidly increasing levels of estrogens or the β subunit of human chorionic gonadotropin (β-hCG). Vomiting usually develops at about 5 wk gestation, peaks at about 9 wk, and disappears by about 16 or 18 wk. It usually occurs in the morning (as so-called morning sickness), although it can occur any time of day. Women with morning sickness continue to gain weight and do not become dehydrated. Hyperemesis gravidarum is probably an extreme form of normal nausea and vomiting during pregnancy. It is distinguished because it causes the following:

• Weight loss (> 5% of weight)

• Dehydration

• Ketosis

• Electrolyte abnormalities (in many women)

Psychologic factors (eg, ambivalence, anxiety) may trigger hyperemesis gravidarum. Hyperemesis gravidarum may cause mild, transient hyperthyroidism. Hyperemesis gravidarum that persists past 16 to 18 wk is uncommon but may seriously damage the liver, causing severe centrilobular necrosis or widespread fatty degeneration, and may cause Wernicke's encephalopathy or esophageal rupture.

Diagnosis

• Clinical evaluation (including serial weights)

• Urine ketones

• Exclusion of other causes (eg, acute abdomen)

If hyperemesis gravidarum is suspected, urine ketones, thyroid-stimulating hormone, serum electrolytes, BUN, creatinine, AST, ALT, Mg, P, and sometimes body weight are measured. Obstetric ultrasonography should be done to rule out hydatidiform mole and multifetal pregnancy.

Other disorders that can cause vomiting must be excluded; they include gastroenteritis, hepatitis, appendicitis, cholecystitis, other biliary tract disorders, peptic ulcer disease, intestinal obstruction,

hyperthyroidism not caused by hyperemesis gravidarum (eg, caused by Graves' disease), gestational trophoblastic disease, nephrolithiasis, pyelonephritis, diabetic ketoacidosis or gastroparesis, benign intracranial hypertension, and migraine headaches. Prominent symptoms in addition to nausea and vomiting often suggest another cause. Tests for alternative diagnoses are done based on laboratory, clinical, or ultrasound findings.

Treatment

• Temporary suspension of oral intake, followed by gradual resumption

• Fluids, thiamin, multivitamins, and electrolytes as needed

• Antiemetics if needed

At first, patients are given nothing by mouth. Initial treatment is IV fluid resuscitation, beginning with 2 L of Ringer's lactate infused over 3 h to maintain a urine output of > 100 mL/h. If dextrose is given, thiamin 100 mg should be given IV first, to prevent Wernicke's encephalopathy. This dose of thiamin should be given daily for 3 days.

Subsequent fluid requirements vary with patient response but may be as much as 1 L q 4 h or so for up to 3 days. Electrolyte deficiencies are treated; K, Mg, and P are replaced as needed. Care must be taken not to correct low plasma Na levels too quickly because too rapid correction can cause osmotic demyelination syndrome.

Vomiting that persists after initial fluid and electrolyte replacement is treated with an antiemetic taken as needed; antiemetics include

• Vitamin B_6 10 to 25 mg po q 8 h or q 6 h

• Doxylamine 12.5 mg po q 8 h or q 6 h (can be taken in addition to vitamin B_6)

• Promethazine 12.5 to 25 mg po, IM, or rectally q 4 to 8 h

• Metoclopramide 5 to 10 mg IV or po q 8 h

• Ondansetron 8 mg po or IM q 12 h

• Prochlorperazine 5 to 10 mg po or IM q 3 to 4 h

After dehydration and acute vomiting resolve, small amounts of oral liquids are given. Patients who cannot tolerate any oral fluids after IV rehydration and antiemetics may need to be hospitalized or given IV therapy at home and take nothing by mouth for a longer period (sometimes several days or more). Once patients tolerate fluids, they can eat small, bland meals, and diet is expanded as tolerated. IV vitamin therapy is required initially and until vitamins can be taken by mouth.

If treatment is ineffective, TPN may be necessary, and corticosteroids, although controversial, can be tried; eg, methylprednisolone 16 mg q 8 h po or IV may be given for 3 days, then tapered over 2 wk to the lowest effective dose. Corticosteroids should be used for < 6 wk and with extreme caution. They should not be used during fetal organogenesis (between 20 and 56 days after fertilization); use of these drugs during the 1st trimester is weakly associated with facial clefting. The mechanism for corticosteroids' effect on nausea is unclear.

If progressive weight loss, jaundice, or persistent tachycardia occurs despite treatment, termination of the pregnancy should be considered.

Placenta Previa

Placenta previa is implantation of the placenta over or near the internal os of the cervix.

Typically, painless vaginal bleeding with bright red blood occurs after 20 wk gestation. Diagnosis is by transvaginal or abdominal ultrasonography. Treatment is bed rest for minor vaginal bleeding before 36 wk gestation, with cesarean delivery at 36 wk if fetal lung maturity is documented. If bleeding is severe or refractory or if fetal status is nonreassuring, immediate delivery, usually cesarean, is indicated.

Placenta previa may be total (covering the internal os completely), partial (covering part of the os), or marginal (at the edge of the os), or the placenta may be low-lying (near the os without reaching it). Incidence of placenta previa is 1/200 deliveries. If placenta previa occurs during early pregnancy, it usually resolves by 20 wk as the uterus enlarges.

Risk factors: Risk factors include the following:

• Multiparity

• Prior cesarean delivery

• Uterine abnormalities that inhibit normal implantation (eg, fibroids, prior curettage)

• Smoking

• Multifetal pregnancy

• Older maternal age

Complications: For patients with placenta previa or a low-lying placenta, risks include fetal malpresentation, preterm premature rupture of the membranes, fetal growth restriction, vasa previa, and velamentous insertion of the umbilical cord.

Symptoms and Signs

Symptoms usually begin during late pregnancy. Then, sudden, painless vaginal bleeding often begins; the blood may be bright red, and bleeding may be heavy, sometimes resulting in hemorrhagic shock. In some patients, uterine contractions accompany bleeding.

Diagnosis

• Transvaginal ultrasonography

Placenta previa is considered in all women with vaginal bleeding after 20 wk. If placenta previa is present, digital pelvic examination may increase bleeding, sometimes causing sudden, massive bleeding; thus, if vaginal bleeding occurs after 20 wk, digital pelvic examination is contraindicated unless placenta previa is first ruled out by ultrasonography. Placenta previa frequently cannot be distinguished from abruptio placentae except by ultrasonography. Transvaginal ultrasonography is an accurate, safe way to diagnose placenta previa.

In all women with suspected symptomatic placenta previa, fetal heart rate monitoring is indicated. Unless the case is an emergency (requiring immediate delivery), amniotic fluid is tested at 36 wk to assess fetal lung maturity and thus document whether delivery at this time is safe.

Treatment

• Hospitalization and bed rest for a first episode of bleeding before 36 wk

• Delivery if mother or fetus is unstable or if fetal lungs are mature

For a first (sentinel) episode of vaginal bleeding before 36 wk, management consists of hospitalization, bed rest, and avoidance of sexual intercourse, which can cause bleeding by initiating contractions or

causing direct trauma. If bleeding stops, ambulation and usually hospital discharge are allowed.

Some experts recommend giving corticosteroids to accelerate fetal lung maturity when early delivery may become necessary and gestational age is < 34 wk. Typically for a 2nd bleeding episode, patients are readmitted and kept for observation until delivery.

Delivery is indicated for any of the following:

• Heavy or uncontrolled bleeding

• Nonreassuring results of fetal heart monitoring

• Maternal hemodynamic instability

• Fetal lung maturity (usually at 36 wk)

Delivery is almost always cesarean, but vaginal delivery may be possible for women with a low-lying placenta if the fetal head effectively compresses the placenta and labor is already advanced or if the pregnancy is < 23 wk and rapid delivery is expected.

Hemorrhagic shock is treated (see p. 2296). Prophylactic Rh_0(D) immune globulin should be given if the mother has Rh-negative blood.

Placenta Accreta

Placenta accreta is an abnormally adherent placenta, resulting in delayed delivery of the placenta. Placental function is normal, but trophoblastic invasion extends beyond the normal boundary (called Nitabuch's layer). In such cases, manual removal of the placenta, unless scrupulously done, results in massive postpartum hemorrhage. Prenatal diagnosis is by ultrasonography. Treatment is usually with scheduled cesarean hysterectomy.

In placenta accreta, the placental villi are not contained by uterine decidual cells, as occurs normally, but extend to the myometrium. Related abnormalities include placenta increta (invasion of chorionic villi into the myometrium) and placenta percreta (penetration of chorionic villi into or through the uterine serosa). All 3 abnormalities cause similar problems.

Etiology

The main risk factor for placenta accreta is

• Prior uterine surgery

In the US, placenta accreta most commonly occurs in women who have had placenta previa after cesarean delivery in a previous pregnancy. Incidence of placenta accreta has increased from about 1/30,000 in the 1950s to about 1/500 to 2000 in the 1980s and 1990s. Risk in women who have had placenta previa increases from about 10 to 25% if they have had one cesarean delivery to about 50 to 67% if they have had > 4 cesarean deliveries.

Other risk factors include the following:

• Maternal age > 35

• Increasing parity

• Submucosal fibroids

• Smoking

• Endometrial lesions such as Asherman's syndrome

Symptoms and Signs

Usually, women present with profuse vaginal bleeding during manual separation of the placenta after delivery of the fetus.

Diagnosis

• Ultrasonography for women at risk

Thorough evaluation of the uteroplacental interface by ultrasonography (transvaginal or transabdominal) is warranted in women at risk; it can be done periodically, beginning at 20 to 24 wk gestation. If ultrasonography is inconclusive, MRI or Doppler flow studies may help.

During delivery, the disorder is suspected if the placenta has not been delivered within 30 min of the infant's delivery, if no plane of separation can be created with attempts at manual removal, or if placental traction causes large-volume hemorrhage. When placenta accreta is suspected, laparotomy with preparation for large-volume hemorrhage is required.

Treatment

• Scheduled cesarean hysterectomy

Preparation for delivery is best. Unless the patient objects, scheduled cesarean hysterectomy is done as soon as fetal lung maturity is confirmed (usually at about 35 to 36 wk).

If cesarean hysterectomy is done (preferably by an experienced pelvic surgeon), a fundal incision followed by immediate clamping of the cord after delivery can help minimize blood loss. The placenta is left in situ while hysterectomy is done. Balloon occlusion of the aorta or internal iliac vessels may be done preoperatively but requires a skilled angiographer and may cause serious thromboembolic complications.

Preeclampsia and Eclampsia

Preeclampsia is new-onset hypertension and proteinuria after 20 wk gestation. Eclampsia is unexplained generalized seizures in patients with preeclampsia. Diagnosis is clinical and by urine protein measurement. Treatment is usually with IV Mg sulfate and delivery at term.

Preeclampsia affects 3 to 7% of pregnant women. Preeclampsia and eclampsia develop after 20 wk gestation; up to 25% of cases develop postpartum, most often within the first 4 days but sometimes up to 6 wk postpartum.

Untreated preeclampsia usually smolders for a variable time, then suddenly progresses to eclampsia, which occurs in 1/200 patients with preeclampsia. Untreated eclampsia is usually fatal.

Etiology

Etiology is unknown; however, risk factors include the following:

• Nulliparity

• Preexisting chronic hypertension

• Vascular disorders (eg, renal disorders, diabetic vasculopathy)

• Pregestational or gestational diabetes

• Older (> 35) or very young (eg, < 17) maternal age

- Family history of preeclampsia
- Preeclampsia or poor outcome in previous pregnancies
- Multifetal pregnancy
- Obesity
- Thrombotic disorders (eg, antiphospholipid antibody syndrome—see p. 975)

Pathophysiology

Pathophysiology of preeclampsia and eclampsia is poorly understood. Factors may include poorly developed uterine placental spiral arterioles (which decrease uteroplacental blood flow during late pregnancy), a genetic abnormality on chromosome 13, immunologic abnormalities, and placental ischemia or infarction. Lipid peroxidation of cell membranes induced by free radicals may contribute to preeclampsia.

Complications: Fetal growth restriction may result. Diffuse or multifocal vasospasm can result in ischemia, eventually damaging multiple organs, particularly the brain, kidneys, and liver. Factors that may contribute to vasospasm include decreased prostacyclin (an endothelium-derived vasodilator), increased endothelin (an endothelium-derived vasoconstrictor), and increased soluble Flt-1 (a circulating receptor for vascular endothelial growth factor).

The coagulation system is activated, possibly secondary to endothelial cell dysfunction, leading to platelet activation. The HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count) develops in 10 to 20% of women with severe preeclampsia or eclampsia; this incidence is about 100 times that for all pregnancies (1 to 2/1000).

Symptoms and Signs

Preeclampsia may be asymptomatic or may cause edema or excessive weight gain. Non-dependent edema, such as facial or hand swelling (the patient's ring may no longer fit her finger), is more specific than dependent edema. Reflex reactivity may be increased, indicating neuromuscular irritability, which can progress to seizures (eclampsia). Petechiae may develop, as may other signs of bleeding.

Severe preeclampsia may cause organ damage; manifestations may include headache, visual disturbances, confusion, epigastric or right upper quadrant abdominal pain (reflecting hepatic ischemia or capsular distention), nausea, vomiting, dyspnea (reflecting pulmonary edema or acute respiratory distress syndrome [ARDS]), stroke (rarely), and oliguria (reflecting decreased plasma volume or ischemic acute tubular necrosis).

Diagnosis

- New-onset hypertension (BP > 140/90 mm Hg) plus new unexplained proteinuria > 300 mg/24 h after 20 wk

Diagnosis is suggested by symptoms or presence of hypertension, defined as systolic BP > 140 mm Hg, diastolic BP > 90 mm Hg, or both. Except in emergencies, hypertension should be documented in > 2 measurements taken > 6 h apart. Urine protein excretion is measured in a 24-h collection.

The following points help differentiate among hypertensive disorders in pregnant women:

- **Chronic hypertension** is identified if hypertension precedes pregnancy, is present at < 20 wk gestation, or persists for > 6 wk (usually > 12 wk) postpartum (even if hypertension is first documented at > 20 wk gestation). Chronic hypertension may be masked during early pregnancy by the physiologic decrease in BP.

- **Gestational hypertension** is hypertension without proteinuria or other findings of preeclampsia; it first occurs at > 20 wk gestation in women known not to have hypertension before pregnancy and resolves by 12 wk (usually by 6 wk) postpartum.

- **Preeclampsia superimposed on chronic hypertension** is diagnosed when a woman with hypertension develops new-onset proteinuria after 20 wk gestation.

- **Preeclampsia** is diagnosed in women who have known hypertension and proteinuria if BP increases to ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic in the last half of pregnancy even if they do not have proteinuria, particularly if the increase is accompanied by symptoms, increased liver enzymes (aminotransferases), or thrombocytopenia.

Further evaluation: If preeclampsia is diagnosed, tests include urinalysis, CBC, platelet count, uric acid, liver function tests, and measurement of serum electrolytes, BUN, creatinine, and creatine clearance. The fetus is assessed with a nonstress test or biophysical profile.

HELLP syndrome is suggested by micro-angiopathic findings (eg, schistocytes, helmet cells) on peripheral blood smears, elevated liver enzymes, and a low platelet count.

Severe preeclampsia is differentiated from mild by one or more of the following:

- CNS dysfunction (eg, blurred vision, scotomata, altered mental status, severe headache unrelieved by acetaminophen)

- Symptoms of liver capsule distention (eg, right upper quadrant or epigastric pain)

- Nausea and vomiting

- Serum AST or ALT > 2 times normal

- Systolic BP > 160 mm Hg or diastolic BP > 110 mm Hg on 2 occasions ≥ 6 h apart

- Platelet count < 100,000/μL

- Urine protein > 5 g/24 h

- Urine output < 500 mL/24 h

- Severe fetal growth restriction

- Pulmonary edema or cyanosis

- Stroke

Treatment

- Usually hospitalization and sometimes anti-hypertensive treatment

- Delivery, depending on factors such as fetal maturity and severity of preeclampsia

- Mg sulfate for prevention or treatment of seizures

General approach: Definitive treatment is delivery. However, risk of early delivery is balanced against severity of preeclampsia and response to other treatments. Usually, immediate delivery after maternal stabilization (eg, controlling seizures, beginning to control BP) is indicated for the following:

- Pregnancy of ≥ 37 wk

• Eclampsia

• Severe preeclampsia if pregnancy is > 34 wk or if fetal lung maturity is documented

• Deteriorating renal or hepatic function

• Nonreassuring results of fetal monitoring

Other treatments aim to optimize maternal health, which usually optimizes fetal health. If delivery can be delayed in pregnancies of about 32 to 34 wk, corticosteroids are given for 48 h to accelerate fetal lung maturity.

Most patients are hospitalized. Patients with eclampsia or severe preeclampsia are often admitted to an ICU.

Mild preeclampsia: If preeclampsia is mild, outpatient treatment is possible; it includes strict bed rest, lying on the left side whenever possible, BP evaluation and physician visits 2 to 3 times/wk, a normal salt intake, and increased fluid intake.

However, most patients with mild eclampsia require hospitalization; some also need drug treatment for a few hours to stabilize them and to lower systolic BP to 140 to 155 mm Hg and diastolic BP to 90 to 105 mm Hg. Delivery follows unless preeclampsia does not progress and the fetus is very premature.

Monitoring: Outpatients are usually evaluated once every 2 or 3 days for seizures, symptoms of severe preeclampsia, and vaginal bleeding. BP, reflexes, and fetal heart status (with nonstress testing or a biophysical profile) are also checked. Platelet count, serum creatinine, and serum liver enzymes are measured at least weekly. All hospitalized patients are followed by an obstetrician and evaluated as described above but more frequently, particularly patients that are in an ICU.

Mg sulfate: As soon as eclampsia or severe preeclampsia is diagnosed, Mg sulfate must be given to stop or prevent seizures and reduce reflex reactivity. Whether patients with mild preeclampsia always require Mg sulfate before delivery is controversial.

Mg sulfate 4 g IV over 20 min is given, followed by a constant IV infusion of about 1 to 3 g/h, with supplemental doses as necessary. Dose is adjusted based on the patient's reflexes, BP, and serum Mg levels (therapeutic range, 4 to 7 mEq/L). Patients with excess Mg levels (eg, with Mg levels > 10 mEq/L or a sudden decrease in reflex reactivity) or hypoventilation are treated with Ca gluconate 1 g IV.

IV Mg sulfate may cause lethargy, hypotonia, and transient respiratory depression in neonates. However, serious neonatal complications are uncommon.

Supportive treatments: Hospitalized patients are given IV Ringer's lactate or 0.9% normal saline solution, beginning at about 125 mL/h (to increase urine output). Persistent oliguria is treated with a fluid challenge, followed by furosemide 10 to 20 mg IV; diuretics are not used otherwise. If fluids plus furosemide are ineffective, determining intravascular volume and cardiac output with a pulmonary artery catheter may be considered. Anuric patients with normovolemia may require renal vasodilators or dialysis.

If seizures occur despite Mg therapy, diazepam or lorazepam can be given IV to stop seizures, and IV hydralazine or labetalol is given in a dose titrated to lower systolic BP to 140 to 155 mm Hg and diastolic BP to 90 to 105 mm Hg.

Delivery method: The most efficient method of delivery should be used. If the cervix is favorable and rapid vaginal delivery seems feasible, a dilute IV infusion of oxytocin is given to accelerate labor; if labor is active, the membranes are ruptured. If the cervix is unfavorable and prompt vaginal delivery is unlikely, cesarean delivery is indicated. Preeclampsia and eclampsia, if not resolved before delivery, usually resolve rapidly afterward, beginning within 6 to 12 h.

All patients are typically given Mg sulfate for 24 h postpartum.

Follow-up: Patients should be evaluated every 1 to 2 wk postpartum with periodic BP measurement. If BP remains high after 6 wk postpartum, patients may have chronic hypertension.

Pruritic Urticarial Papules and Plaques of Pregnancy

Pruritic urticarial papules and plaques of pregnancy are pruritic eruptions of unknown cause that develop during pregnancy.

Most cases occur during a first pregnancy. Overall incidence is 1/160 to 300 pregnancies; however, with multiple gestation, risk is 8 to 12 times higher.

Symptoms and Signs

Lesions are intensely itchy, erythematous, solid, superficial, and elevated; some are surrounded by blanching, and some have minute vesicles in the center. Itching keeps most patients awake, but excoriation is uncommon. Lesions begin on the abdomen, frequently on striae atrophicae (stretch marks), and spread to the thighs, buttocks, and occasionally the arms. The palms, soles, and face are usually spared. Most patients have hundreds of lesions.

Lesions develop during the 3rd trimester, most often in the last 2 to 3 wk and occasionally in the last few days or postpartum. They usually resolve within 15 days after delivery. They may recur in up to 5% of subsequent pregnancies.

Diagnosis

Diagnosis is clinical. Differentiation from other pruritic eruptions may be difficult.

Treatment

• Corticosteroids

Mild symptoms are treated with topical corticosteroids (eg, 0.1% triamcinolone acetonide cream up to 6 times/day). Rarely, more severe symptoms require systemic corticosteroids (eg, prednisone 40 mg po once/day, tapered as tolerated). Systemic corticosteroids given late in pregnancy do not seem to harm the fetus.

Spontaneous Abortion

(Miscarriage)

Spontaneous abortion is noninduced embryonic or fetal death or passage of products of conception before 20 wk gestation. Threatened abortion is vaginal bleeding occurring during this time frame, indicating that spontaneous abortion may occur. Diagnosis is by clinical criteria and ultrasonography. Treatment is usually observation for threatened abortion and, if spontaneous abortion has occurred or appears unavoidable, uterine evacuation.

Fetal death and early delivery are classified as follows:

• Abortion: Death of the fetus or passage of products of conception (fetus and placenta) before 20 wk gestation

• Late fetal death: Fetal death after 20 wk

• Stillbirth: Delivery after late fetal death

• Preterm delivery: Passage of a live fetus between 20 and 37 wk (see p. 2683)

Abortions may be classified as early or late, spontaneous or induced for therapeutic or elective reasons (see p. 2591), threatened or inevitable, incomplete or complete, recurrent (also called recurrent pregnancy loss), missed, or septic (see Table 265-1).

About 20 to 30% of women with confirmed pregnancies bleed during the first 20 wk of pregnancy; half of these women spontaneously

[**Table 265-1.** Classification of Abortion]

abort. Thus, incidence of spontaneous abortion is about 10 to 15% in confirmed pregnancies. Incidence in all pregnancies is probably higher because some very early abortions are mistaken for a late menstrual period.

Etiology

Isolated spontaneous abortions may result from certain viruses—most notably cytomegalovirus, herpesvirus, parvovirus, and rubella virus—or from disorders that can cause sporadic abortions or recurrent pregnancy loss (eg, chromosomal or mendelian abnormalities, luteal phase defects). Acquired and hereditary thrombophilias appear to cause abortions after ≥ 10 wk. Immunologic abnormalities and major trauma may be causes. Cause is often unknown.

Risk factors include

• Age > 35

• History of spontaneous abortion

• Cigarette smoking

• Use of certain drugs (eg, cocaine, alcohol, high doses of caffeine)

• Uterine abnormalities (eg, leiomyoma, adhesions)

Subclinical thyroid disorders, well-controlled or subclinical diabetes mellitus, retroverted uterus, and minor trauma have not been shown to cause spontaneous abortions.

Symptoms and Signs

Symptoms include crampy pelvic pain, bleeding, and eventually expulsion of tissue. Late spontaneous abortion may begin with a gush of fluid when the membranes rupture. Hemorrhage is rarely massive. A dilated cervix indicates that abortion is inevitable.

If products of conception remain in the uterus after spontaneous abortion, vaginal bleeding may occur, usually after a delay of hours to days. Infection may also develop, causing fever, pain, and sometimes sepsis.

Diagnosis

• Clinical criteria

• Usually ultrasonography and quantitative β subunit of human chorionic gonadotropin (β-hCG)

Diagnosis of threatened, inevitable, incomplete, or complete abortion is often possible based on clinical criteria (Table 265-2) and a positive urine pregnancy test. However, ultrasonography and quantitative measurement of serum β-hCG are usually done to exclude ectopic pregnancy and to determine whether

products of conception remain in the uterus (suggesting that abortion is incomplete rather than complete). However, results may be inconclusive, particularly during early pregnancy.

Missed abortion is suspected if the uterus does not progressively enlarge or if quantitative β-hCG is low for gestational age or does not double within 48 to 72 h. Missed abortion is confirmed if ultrasonography shows any of the following:

- Disappearance of previously detected embryonic cardiac activity
- Absence of such activity when the fetal crown-rump length is > 5 mm (determined by transvaginal ultrasonography)

[Table 265-2. Characteristic Symptoms and Signs in Spontaneous Abortions]

- Absence of a fetal pole (determined by transvaginal ultrasonography) when the mean sac diameter (average of diameters measured in 3 orthogonal planes) is > 18 mm

For **recurrent pregnancy loss**, testing to determine the cause of abortion is necessary (see below).

Treatment

- Observation for threatened abortion
- Uterine evacuation for inevitable, incomplete, or missed abortions
- Emotional support

For **threatened abortion**, treatment is observation. No evidence suggests that bed rest decreases risk of subsequent completed abortion. If the cervix is dilated, avoidance of intercourse is often recommended to prevent infection; however, intercourse has not been shown to cause loss.

For **inevitable, incomplete, or missed abortions,** treatment is uterine evacuation or waiting for spontaneous passage of the products of conception. Evacuation usually involves suction curettage at < 12 wk, dilation and evacuation at 12 to 23 wk, or medical induction (for women without prior uterine surgery) at > 16 to 23 wk (for treatment of late fetal death, see Stillbirth on p. 2675). The later the uterus is evacuated, the greater the likelihood of placental bleeding, uterine perforation by long bones of the fetus, and difficulty dilating the cervix. These complications are reduced by preoperative use of osmotic cervical dilators (eg, laminaria), misoprostol, or mifepristone (RU 486).

If **complete abortion** is suspected, uterine evacuation is done when bleeding occurs or other signs indicate that products of conception may be retained. Uterine evacuation need not be done routinely.

After an **induced or spontaneous abortion,** parents commonly feel grief and guilt. They are given emotional support and, in the case of spontaneous abortions, reassured that their actions were not the cause. Formal counseling is rarely indicated but should be made available.

Recurrent Pregnancy Loss

(Recurrent or Habitual Abortion)

Recurrent pregnancy loss is ≥ 3 consecutive spontaneous abortions. Determining the cause may require extensive evaluation of both parents. Some causes can be treated.

Etiology

Recurrent pregnancy loss usually results from disorders that cause intrauterine fetal damage, such as maternal or paternal chromosomal abnormalities (eg, balanced translocations). Chromosomal abnormalities may cause 50% of recurrent pregnancy losses, which are more common during early

pregnancy; aneuploidy is involved in up to 80% of all spontaneous abortions occurring at < 10 wk gestation but in < 15% of those occurring at 20 wk.

Other common causes may include maternal luteal phase defects (particularly at < 6 wk), overt endocrine disorders (eg, polycystic ovary syndrome, hypothyroidism, hyperthyroidism, poorly controlled diabetes mellitus), severe chronic renal disorders, immunologic abnormalities (eg, lupus anticoagulant, anticardiolipin antibodies, anti-β_2 glycoprotein I), and, particularly after 10 wk, inherited maternal thrombotic disorders (eg, activated protein C resistance; factor V Leiden mutation; prothrombin G20210A gene mutation; hyperhomocysteinemia; deficiencies of antithrombin or protein Z, C, or S). Cervical incompetence and structural abnormalities of the uterine cavity (eg, polyps, fibroids, congenital malformations) may predispose to delivery at < 20 wk but do not necessarily cause intrauterine fetal damage.

For women who have a history of recurrent pregnancy loss and who become pregnant, risk of fetal growth restriction and premature delivery may be higher.

Diagnosis

Evaluation should include the following to determine the cause:

- Genetic evaluation (karyotyping) as clinically indicated to exclude possible genetic causes (see p. 2599)
- Anticardiolipin antibodies, anti-β_2 glycoprotein I, and lupus anticoagulant
- Thyroid-stimulating hormone
- Evaluation of ovarian reserve including measuring follicle-stimulating hormone level on day 3 of the menstrual cycle
- Hysterosalpingography or sonohysterography to check for structural uterine abnormalities
- Screening for activated protein C resistance, factor V Leiden mutation, prothrombin G20210A mutation, antithrombin activity, protein Z and C deficiencies, and protein S deficiency (if fetal losses occurred at > 9 wk gestation)

Cause cannot be determined in up to 50% of women.

Treatment

Some causes can be treated. If the cause cannot be identified, the chance of a live birth in the next pregnancy is 35 to 85%.

Septic Abortion

Septic abortion is serious uterine infection during or shortly before or after an abortion.

Septic abortions usually result from induced abortions done by untrained practitioners using nonsterile techniques; they are much more common when induced abortion is illegal. Typical causative organisms include *Escherichia coli, Enterobacter aerogenes, Proteus vulgaris*, hemolytic streptococci, staphylococci, and some anaerobic organisms (eg, *Clostridium perfringens*).

Symptoms and Signs

Symptoms and signs are similar to those of pelvic inflammatory disease (eg, chills, fever, vaginal discharge, often peritonitis) and often those of threatened or incomplete abortion (eg, vaginal bleeding, cervical dilation, passage of products of conception). Septic shock may result, causing hypothermia, hypotension, oliguria, and respiratory distress. Sepsis due to *C. perfringens* may result in

thrombocytopenia, ecchymoses, and findings of intravascular hemolysis (eg, anuria, anemia, jaundice, hemoglobinuria, hemosiderinuria).

Diagnosis

Septic abortion is usually obvious clinically but must be confirmed by pregnancy testing and usually ultrasonography.

Treatment

Treatment is intensive antibiotic therapy plus uterine evacuation as soon as possible. A typical antibiotic regimen includes clindamycin 900 mg IV q 8 h plus gentamicin 5 mg/kg IV once/day, with or without ampicillin 2 g IV q 4 h. Alternatively, a combination of ampicillin, gentamicin, and metronidazole 500 mg IV q 8 h can be used.

Stillbirth

Stillbirth is delivery of a dead fetus at > 20 wk gestation. Maternal and fetal testing is done to determine the cause. Management is as for routine care after live delivery.

Etiology

Fetal death during late pregnancy may have maternal, placental, or fetal anatomic or genetic causes (see Table 265-3). Overall, the most common cause is

• Abruptio placentae

Complications: If a fetus dies during late pregnancy or near term but remains in the uterus for weeks, disseminated intravascular coagulation (DIC) may occur.

Diagnosis

Tests to determine cause include the following:

• Fetal karyotype and autopsy

• Maternal CBC (for evidence of anemia or leukocytosis)

• Kleihauer-Betke test

• Thrombotic screening (including factor V Leiden mutation; prothrombin G20210A mutation; protein C, S, and Z levels; activated protein C resistance; antithrombin activity; fasting homocysteine level; anti-phospholipid antibody)

• TORCH test (toxoplasmosis [with IgG and IgM], other pathogens [eg, human parvovirus B19, varicella-zoster viruses], rubella, cytomegalovirus, herpes simplex)

[**Table 265-3.** Common Causes of Stillbirth]

• Rapid plasma reagin (RPR)

• Examination of the placenta

Often, cause cannot be determined.

Treatment

• Routine postdelivery care

• Emotional support

Postdelivery management is similar to that for live birth. If DIC occurs, labor is induced (eg, with IV oxytocin infusion, sometimes preceded by a prostaglandin to make the cervix favorable—ie, open and effaced). Any coagulopathy that develops should be promptly and aggressively managed by replacing blood or blood products as needed while preparations for delivery are being made.

After the products of conception are expelled, curettage may be needed to remove placental fragments.

Alternatively, dilation and extraction (D&E) may be done. In all cases, preabortion osmotic dilator cervical ripening should be used with or without misoprostol.

Parents typically feel significant grief and require emotional support and sometimes formal counseling. Risks with future pregnancy should be discussed with patients; risks are based on the stillbirth's cause.

Chapter 266. Abnormalities and Complications of Labor and Delivery

Introduction

Abnormalities and complications of labor and delivery should be diagnosed and managed as early as possible. Most (eg, multifetal pregnancy, postterm pregnancy, premature rupture of membranes, abnormal fetal presentation) are usually evident before onset of labor. Some (eg, amniotic fluid embolism, shoulder dystocia, fetopelvic disproportion, preterm labor, protracted labor, umbilical cord prolapse) develop or become evident during labor or the delivery period. Alternatives to spontaneous labor and vaginal delivery may be needed. Some complications (eg, postpartum hemorrhage, inverted uterus) occur immediately after delivery of the fetus and around the time the placenta is delivered. Placenta accreta (see p. 2669) may be discovered during pregnancy or only after delivery.

For neonatal resuscitation and disorders of the birth process, see Ch. 274; for meconium aspiration syndrome, see p. 2872.

Alternatives to Spontaneous Labor and Delivery

Abnormalities or difficulties in pregnancy or during labor and delivery can necessitate alternative delivery methods.

Operative vaginal delivery

Operative vaginal delivery involves application of forceps or a vacuum extractor to the fetal head to assist during the 2nd stage of labor and facilitate delivery.

Forceps delivery and vacuum extraction have essentially the same indications:

- Prolonged 2nd stage of labor (from full cervical dilation until delivery of the fetus)
- Suspicion of fetal compromise (eg, abnormal heart rate pattern)
- Need to shorten the 2nd stage for maternal benefit—eg, if maternal cardiac dysfunction (eg, left-to-right shunting) or neurologic disorders (eg, spinal cord trauma) contraindicate pushing or maternal exhaustion prevents it

A prolonged 2nd stage is defined in nulliparous women as lack of continuing progress for 3 h with a regional anesthetic or 2 h without a regional anesthetic or in multiparous women as lack of continuing progress for 2 h with a regional anesthetic or 1 h without a regional anesthetic.

Choice of device depends largely on user preference and operator experience and varies greatly. These procedures are used when the station of the fetal head is low (≥ +2 cm); then, minimal traction or rotation is required to deliver the head.

Before starting an operative vaginal delivery, the clinician should do the following:

- Confirm complete cervical dilation
- Confirm an engaged fetal vertex
- Confirm rupture of membranes
- Confirm that fetal position is compatible with operative vaginal delivery
- Drain the maternal bladder
- Clinically assess pelvic dimensions (clinical pelvimetry) to ensure that the pelvis is adequate

Also required are informed consent, adequate support and personnel, and adequate analgesia or anesthesia.

Contraindications include unengaged fetal head, unknown fetal position, and certain fetal disorders such as hemophilia. Vacuum extraction is typically considered contraindicated in preterm pregnancies of < 34 wk because risk of intraventricular hemorrhage is increased.

Major complications are maternal and fetal injuries and hemorrhage, particularly if the operator is inexperienced or if candidates are not appropriately chosen. Significant perineal trauma and neonatal bruising are more common with forceps delivery; shoulder dystocia, cephalohematoma, and retinal bleeding are more common with vacuum-assisted delivery.

Induction of Labor

Induction of labor is stimulation of uterine contractions before spontaneous labor to achieve vaginal delivery.

Indications: Induction of labor can be medically indicated (eg, for preeclampsia or fetal compromise) or elective (to control when delivery occurs). Before elective induction, gestational age and fetal lung maturity must be assessed; if gestational age is < 39 wk by best obstetric estimates, amniocentesis is done to determine lecithin/sphingomyelin ratio or other indexes of fetal lung maturity.

Contraindications to induction include the following:

- Fundal uterine surgery
- Prior classic or vertical cesarean incision in the thickened, muscular portion of the uterus
- Active genital herpes
- Placenta or vasa previa
- Abnormal fetal presentation (eg, transverse lie, umbilical cord presentation, certain types of fetopelvic disproportion)

Multiple prior uterine scars and breech presentation are relative contraindications.

Technique: If the cervix is closed, long, and firm (unfavorable), the goal is to cause the cervix to open and become effaced (favorable). Various pharmacologic or mechanical methods can be used. Misoprostol 25 µg vaginally q 3 to 6 h is effective. Alternatives include prostaglandin E_2 given intracervically (0.5 mg) or as an intravaginal pessary (10 mg). Prostaglandins are contraindicated in women with prior cesarean delivery or uterine surgery because these drugs increase the risk of uterine rupture. Oxytocin in low or high doses can also be given. Effective mechanical methods include use of laminaria and transcervical balloon catheters, which may be useful when other methods are ineffective or contraindications exist.

Once the cervix is favorable, labor is induced. Constant IV infusion of oxytocin is the most commonly used method; it is safe and cost-effective. Low-dose oxytocin is given at 0.5 to 2 milliunits/min, increased by 1 to 2 milliunits/min, usually q 15 to 60 min. High-dose oxytocin is given at 6 milliunits/min, increased by 1 to 6 milliunits/min q 15 to 40 min to a maximum of 40 milliunits/min. With doses > 40 milliunits/min, excessive water retention may lead to water intoxication. Use of oxytocin must be supervised to prevent hypertonic uterine contractions, which may compromise the fetus. External fetal monitoring (see p. 2630) is routine; after amniotomy (deliberate rupture of the membranes), internal monitoring may be indicated if fetal status cannot be assessed externally. Amniotomy can be done to augment labor when the fetal head is well applied to a favorable cervix.

Cesarean Delivery

Cesarean delivery is surgical delivery by incision into the uterus.

Up to 30% of deliveries in the US are cesarean. The rate of cesarean delivery fluctuates. It has recently increased, partly because of concern about increased risk of uterine rupture in women attempting vaginal birth after cesarean delivery (VBAC).

Indications: Although morbidity and mortality rates of cesarean delivery are low, they are still several times higher than those of vaginal delivery; thus, cesarean delivery should be done only when it is safer for the woman or fetus than vaginal delivery. The most common specific indications are

• Previous cesarean delivery

• Protracted labor

• Fetal dystocia (particularly breech presentation)

• A nonreassuring fetal heart rate, which requires rapid delivery

Many women are interested in elective cesarean delivery on demand. The rationale includes avoiding damage to the pelvic floor (and subsequent incontinence) and serious intrapartum fetal complications. However, such use is controversial, has limited supporting data, and requires discussion between the woman and her physician; the discussion should include immediate risks and long-term reproductive planning (eg, how many children the woman intends to have).

Many cesarean deliveries are done in women with previous cesarean deliveries because for them, vaginal delivery increases risk of uterine rupture; however, risk of rupture with vaginal delivery is only about 1% overall (risk is higher for women who have had multiple cesarean deliveries or a vertical incision, particularly if it extends through the thickened, muscular portion of the uterus). Vaginal birth is successful in about 75% of women who have had a single prior cesarean delivery and should be offered to those who have had a single prior cesarean delivery by lower uterine transverse incision. Success of VBAC depends on the indication for the initial cesarean delivery. VBAC should be done in a facility where an obstetrician, anesthesiologist, and surgical team are immediately available, which makes VBAC impractical in some situations.

Technique: During cesarean delivery, practitioners skilled in neonatal resuscitation should be readily available. The uterine incision can be classic or lower segment.

• **Classic:** The incision is made vertically in the anterior wall of the uterus, ascending to the upper uterine segment or fundus. This incision typically results in more blood loss than a lower-segment incision and is usually done only when placenta previa is present, fetal position is transverse with the back down, presentation is breech, the fetus is preterm, or the lower uterine segment is poorly developed.

• **Lower segment:** Lower-segment incisions are done most often. A low transverse incision is made in the thinned, elongated lower portion of the uterine body under the bladder reflection. A vertical lower-segment incision is used only for certain abnormal presentations and for excessively large fetuses. In such cases, a transverse incision is not used because it can extend laterally into the uterine arteries, sometimes causing excessive blood loss. Women who have had deliveries by a low transverse uterine incision are advised about the safety of a trial of labor in subsequent pregnancies.

Amniotic Fluid Embolism

Amniotic fluid embolism is entrance of amniotic fluid and fetal cells into the maternal circulation initiating an abnormal response.

Amniotic fluid embolism is a rare obstetric emergency. It usually occurs during late pregnancy; risk is increased with cesarean delivery, advanced maternal age, abruptio placentae, abdominal trauma, placenta previa, and forceps delivery. Amniotic fluid embolizes to the maternal circulation, causing tachycardia, hypotension, respiratory failure, disseminated intravascular coagulation, and often rapid maternal death. Autopsy may show fetal squamous cells and hair in the pulmonary circulation.

About 20% of affected women die, although mortality estimates often vary widely. Survival depends on early recognition and immediate institution of treatment.

Diagnosis is clinical.

Treatment is supportive. It includes transfusion of RBCs (as needed to replace lost blood), fresh frozen plasma and clotting factors (as needed to reverse the coagulopathy), and ventilatory and circulatory support, with inotropic drugs as needed.

Fetal Dystocia

Fetal dystocia is abnormal fetal size or position resulting in difficult delivery. Diagnosis is by examination, ultrasonography, or response to augmentation of labor. Treatment is with physical maneuvers to reposition the fetus, operative vaginal delivery, or cesarean delivery.

Fetal dystocia may occur when the fetus is too large for the pelvic opening (fetopelvic disproportion) or is abnormally positioned (eg, breech presentation). Normal fetal presentation is vertex, with the occiput anterior.

Fetopelvic disproportion: Diagnosis is suggested by prenatal clinical estimates of pelvic dimensions (see p. 2607), ultrasonography, and protracted labor. If augmentation of labor restores normal progress and fetal weight is < 5000 g in women without diabetes or < 4500 g in women with diabetes, labor can safely continue. If progress is slower than expected in the 2nd stage of labor, women are evaluated to determine whether operative vaginal delivery (by forceps or vacuum extractor) is safe and appropriate.

Occiput posterior presentation: The most common abnormal presentation is occiput posterior. The fetal neck is usually somewhat deflexed; thus, a larger diameter of the head must pass through the pelvis. Many occiput posterior presentations require operative vaginal delivery or cesarean delivery.

Face or brow presentation: In face presentation, the head is hyperextended, and position is designated by the position of the chin (mentum). When the chin is posterior, the head is less likely to rotate and less likely to deliver vaginally, necessitating cesarean delivery. Brow presentation usually converts spontaneously to occiput or face presentation.

Breech presentation: The 2nd most common abnormal presentation is breech (buttocks before the head). There are several types:

- Frank breech: The fetal hips are flexed, and the knees extended (pike position).
- Complete breech: The fetus seems to be sitting with hips and knees flexed.
- Single or double footling presentation: One or both legs are completely extended and present before the buttocks.

Breech presentation is a problem primarily because the presenting part is a poor dilating wedge, which can cause the head, which follows, to be trapped during delivery, often compressing the umbilical cord.

Umbilical cord compression may cause fetal hypoxemia. The fetal head is probably compressing the umbilical cord if the fetal umbilicus is visible at the introitus, particularly in primiparas whose pelvic tissues have not been dilated by previous deliveries.

Predisposing factors for breech presentation include premature labor, uterine abnormalities, and fetal anomalies. If delivery is vaginal, breech presentation may increase risk of birth trauma, dystocia, and perinatal death. Preventing complications is more effective and easier than treating them, so abnormal presentation must be identified before delivery. Cesarean delivery is usually done at 39 wk or when the patient presents in labor, although external cephalic version can sometimes move the fetus to vertex

presentation before labor, usually at 37 or 38 wk. This technique involves gently pressing on the maternal abdomen to reposition the fetus. A dose of a short-acting tocolytic (terbutaline 0.25 mg sc) may help. The success rate is about 50 to 75%.

Transverse lie: Fetal position is transverse, with the fetal long axis oblique or perpendicular rather than parallel to the maternal long axis. Shoulder-first presentation requires cesarean delivery unless the fetus is a 2nd twin.

Shoulder dystocia: In this infrequent condition, presentation is vertex, but the anterior fetal shoulder is lodged behind the symphysis pubis, preventing vaginal delivery. Shoulder dystocia is recognized when the fetal head is delivered onto the perineum but appears to be pulled back tightly against the perineum (turtle sign). Risk factors include a large fetus, maternal obesity, diabetes mellitus, prior shoulder dystocia, operative vaginal delivery, and prolonged labor. Risk of neonatal morbidity (eg, brachial plexus injury, bone fractures) and mortality is increased.

Once shoulder dystocia is recognized, extra personnel are summoned to the room, and various maneuvers are tried sequentially to disengage the anterior shoulder:

- The woman's thighs are hyperflexed to widen the pelvic outlet (McRobert's maneuver), and suprapubic pressure is applied to rotate and dislodge the anterior shoulder. Fundal pressure is avoided because it may worsen the condition or cause uterine rupture.

- The obstetrician inserts a hand into the posterior vagina and presses the posterior shoulder to rotate the fetus in whichever direction is easier (Wood's screw maneuver).

- The obstetrician inserts a hand, flexes the posterior elbow, and sweeps the arm and hand across the fetal chest to deliver the infant's entire posterior arm.

These maneuvers increase risk of fracture of the humerus or clavicle. Sometimes the clavicle is intentionally fractured in a direction away from fetal lung to disengage the shoulder. An episiotomy can be done at any time to facilitate the maneuvers.

If all maneuvers are ineffective, the obstetrician flexes the infant's head and reverses the cardinal movements of labor, replacing the fetal head back into the vagina or uterus; the infant is then delivered by cesarean (Zavanelli maneuver).

Inverted Uterus

Inverted uterus is a rare medical emergency in which the corpus turns inside out and protrudes into the vagina or beyond the introitus.

The uterus is most commonly inverted when too much traction is applied to the umbilical cord in an attempt to deliver the placenta. Excessive pressure on the fundus during delivery of the placenta, a flaccid uterus, or placenta accreta (abnormally adherent placenta) can contribute.

Treatment

- Manual reduction

Treatment is immediate manual reduction by pushing up on the fundus until the uterus is returned to its normal position. If the placenta is still attached, the uterus should be replaced before the placenta is removed. Because of discomfort, IV analgesics and sedatives or a general anesthetic are sometimes needed. Terbutaline 0.25 mg IV or nitroglycerin 50 µg IV may also be needed.

If attempts to return the uterus are unsuccessful, a laparotomy may be necessary; the fundus is manipulated vaginally and abdominally to return it to its normal position. Once the uterus is in place, an oxytocin infusion should be started.

Multifetal Pregnancy

Multifetal pregnancy is presence of > 1 fetus in the uterus.

Multifetal (multiple) pregnancy occurs in 1 of 70 to 80 deliveries. Risk factors include

- Ovarian stimulation (usually with clomiphene or gonadotropins)
- Assisted reproduction (eg, in vitro fertilization)
- Prior multifetal pregnancy
- Advanced maternal age

The overdistended uterus tends to stimulate early labor, causing preterm delivery (average gestation is 35 to 36 wk with twins, 32 wk with triplets, and 30 wk with quadruplets). Fetal presentation may be abnormal. The uterus may contract after delivery of the first child, shearing away the placenta and increasing risk for the remaining fetuses. Sometimes uterine distention impairs postpartum uterine contraction, leading to atony and maternal hemorrhage. Multifetal pregnancy increases the risk of preeclampsia, gestational diabetes, postpartum hemorrhage, cesarean delivery, preterm delivery, and growth restriction.

Multifetal pregnancy is suspected if the uterus is large for dates; it is evident on prenatal ultrasonography. Cesarean delivery is done when indicated. Cesarean delivery is recommended for twins unless the presenting twin is in vertex presentation. Higher-order multiples are typically delivered by cesarean regardless of presentation. (see p. 2678).

Postpartum Hemorrhage

Postpartum hemorrhage is blood loss of > 500 mL during or immediately after the 3rd stage of labor in a vaginal delivery or > 1000 mL in a cesarean delivery. Diagnosis is clinical. Treatment depends on etiology of the hemorrhage.

Causes of postpartum hemorrhage include

- Uterine atony (the most common)
- Lacerations of the genital tract
- Extension of an episiotomy
- Uterine rupture
- Bleeding disorders
- Retained placental tissues
- Hematoma
- Uterine inversion
- Subinvolution (incomplete involution) of the placental site (which usually occurs early but may occur as late as 1 mo after delivery)

Risk factors for uterine atony include uterine overdistention (caused by multifetal pregnancy, polyhydramnios, or an abnormally large fetus), prolonged or dysfunctional labor, grand multi-parity (delivery of ≥ 5 viable fetuses), relaxant anesthetics, rapid labor, and chorioamnionitis.

Uterine fibroids may contribute to postpartum hemorrhage. A history of prior postpartum hemorrhage may indicate increased risk.

Treatment

• Removal of retained placental tissues and repair of genital lacerations

• Uterotonics (eg, oxytocin, prostaglandins)

• Sometimes surgical procedures

Intravascular volume is replenished with 0.9% saline up to 2 L IV; blood transfusion is used if this volume of saline is inadequate. Hemostasis is attempted by bimanual uterine massage and IV oxytocin infusion, and the uterus is explored for lacerations and retained placental tissues. The cervix and vagina are also examined; lacerations are repaired. Bladder drainage via catheter can sometimes reduce uterine atony.

15-Methyl prostaglandin $F_{2\alpha}$ 250 µg IM q 15 to 90 min up to 8 doses or methylergonovine 0.2 mg IM q 2 to 4 h (which may be followed by 0.2 mg po tid to qid for 1 wk) should be tried if excessive bleeding continues during oxytocin infusion; during cesarean delivery, these drugs may be injected directly into the myometrium. Prostaglandins should be avoided in women with asthma; methylergonovine should be avoided in women with hypertension. Sometimes misoprostol 800 to 1000 µg rectally can be used to increase uterine tone.

Uterine packing or placement of a Bakri balloon can sometimes provide tamponade. This silicone balloon can hold up to 500 mL and withstand internal and external pressures of up to 300 mm Hg. If hemostasis cannot be achieved, surgical placement of a B-Lynch suture (a suture used to compress the lower uterine segment via multiple insertions), hypogastric artery ligation, or hysterectomy may be required. Uterine rupture requires surgical repair.

Blood products are transfused as necessary, depending on the degree of blood loss and clinical evidence of shock. Infusion of factor VIIa (50 to 100 µg/kg, as a slow IV bolus over 2 to 5 min) can produce hemostasis in women with severe life-threatening hemorrhage. The dose is given q 2 to 3 h until hemostasis occurs.

Prevention

Predisposing conditions (eg, uterine fibroids, polyhydramnios, multifetal pregnancy, a maternal bleeding disorder, history of puerperal hemorrhage) are identified antepartum and, when possible, corrected. If women have an unusual blood type, that blood type is made available. Careful, unhurried delivery with a minimum of intervention is always wise.

After placental separation, oxytocin 10 units IM or dilute oxytocin infusion (10 or 20 units in 1000 mL of an IV solution at 125 to 200 mL/h for 1 to 2 h) usually ensures uterine contraction and reduces blood loss. After the placenta is delivered, it is thoroughly examined for completeness; if it is incomplete, the uterus is manually explored and retained fragments are removed. Rarely, curettage is required. Uterine contraction and amount of vaginal bleeding must be observed for 1 h after completion of the 3rd stage of labor.

Postterm Pregnancy

Postterm pregnancy refers to gestation that lasts ≥ 42 wk. Nonstress testing, a full or modified biophysical profile, and often routine delivery are recommended at 41 wk.

Accurate gestational age estimation is essential in making a diagnosis of postterm pregnancy. In women with regular, normal menstrual cycles, gestational age can be estimated based on the first day of the last normal menstrual period. If dating is uncertain or inconsistent with menstrual dating, ultrasonography early in gestation (up to 20 wk) is the most accurate with accepted variation of +/- 7 days. Later in gestation, the variation increases to +/- 14 days at 20 to 30 wk gestation and +/- 21 days after 30 wk.

Postterm pregnancy increases risks for the woman and fetus. Risks include

- Abnormal fetal growth (macrosomia and dysmaturity syndrome)
- Oligohydramnios
- Meconium-stained amniotic fluid
- Nonreassuring fetal test results
- Fetal and neonatal death
- Dystocia (abnormal or difficult labor)
- Cesarean delivery

Most experts recommend that antenatal surveillance be initiated at 41 wk; it involves a modified biophysical profile (nonstress testing and assessment of amniotic fluid volume) or a full biophysical profile (assessment of amniotic fluid volume and fetal movement, tone, breathing, and heart rate). If there is evidence of fetal compromise or oligohydramnios, delivery is required. For many obstetricians, the trend is to induce labor (see p. 2677) in all pregnancies > 41 wk, particularly in patients with a favorable cervix.

Premature Rupture of Membranes

Rupture of membranes before onset of labor is considered premature. Diagnosis is clinical. Delivery is sometimes indicated when gestational age is ≥ 34 wk or fetal lungs are mature and is generally indicated for infection or fetal compromise.

Premature rupture of membranes (PROM) may occur at term (≥ 37 wk) or earlier (called preterm PROM if < 37 wk). Preterm PROM predisposes to preterm delivery. PROM at any time increases risk of infection in the woman (chorioamnionitis), neonate (sepsis), or both, as well as risk of abnormal fetal presentation and abruptio placentae. Group B streptococci and *Escherichia coli* are common causes of infection. Other organisms in the vagina may also cause infection. Prolonged preterm PROM before viability (at < 24 wk) increases risk of abnormal joint positioning and pulmonary hypoplasia.

The interval between PROM and onset of spontaneous labor (latent period) and delivery varies inversely with gestational age. At term, > 90% of women with PROM begin labor within 24 h; at 32 to 34 wk, mean latency period is about 4 days.

Symptoms and Signs

Typically, unless complications occur, the only symptom is leakage or a sudden gush of fluid from the vagina. Fever, heavy vaginal discharge, abdominal pain, and fetal tachycardia, particularly if out of proportion to maternal temperature, strongly suggest chorioamnionitis.

Diagnosis

- Visible amniotic fluid or meconium
- Evaluation of vaginal fluid showing ferning or alkalinity (blue color) on Nitrazine paper
- Sometimes ultrasonography showing oligohydramnios

Sterile speculum examination is done to verify PROM, estimate cervical dilation, collect amniotic fluid for fetal maturity tests, and obtain samples for cervical cultures. Digital pelvic examination, particularly multiple examinations, increases risk of infection and is best avoided unless imminent delivery is anticipated. Fetal position should be assessed. If subclinical intra-amniotic infection is a concern, amniocentesis (obtaining amniotic fluid using sterile technique) can confirm this infection.

Diagnosis is assumed if amniotic fluid appears to be escaping from the cervix or if the vernix or meconium is visible. Other less accurate indicators include vaginal fluid that ferns when dried on a glass slide or turns Nitrazine paper blue (indicating alkalinity and hence amniotic fluid; normal vaginal fluid is acidic). Ultrasonography showing oligohydramnios suggests the diagnosis.

If the diagnosis is questionable, indigo carmine dye can be instilled using ultrasound-guided amniocentesis. Appearance of the blue dye on a vaginal tampon or peripad confirms the diagnosis.

If the fetus is viable, women are typically admitted to the hospital for daily fetal assessment.

Treatment

• Delivery if there is fetal compromise, infection, or possibly gestational age > 34 wk or fetal lung maturity

• Otherwise, pelvic rest, close monitoring, antibiotics, and sometimes corticosteroids

Management requires balancing risk of infection when delivery is delayed with risks due to fetal immaturity when delivery is immediate. No one strategy is correct, but generally, signs of fetal compromise or infection (eg, persistently nonreassuring fetal testing results, uterine tenderness plus fever) should prompt delivery. Otherwise, delivery can be delayed for a variable period if fetal lungs are still immature or if labor could start spontaneously (ie, later in the pregnancy). Induction of labor is recommended when gestational age is > 34 wk. When appropriate management is unclear, amniotic fluid tests can be done to assess fetal lung maturity and thus guide management; the sample may be obtained from the vagina or by amniocentesis.

When expectant management is used, the woman's activity is limited to modified bed rest and complete pelvic rest. BP and temperature must be measured ≥ 3 times/day. Antibiotics (usually 48 h of IV ampicillin and erythromycin, followed by 5 days of oral amoxicillin and erythromycin) are given; they lengthen the latency period and reduce risk of neonatal morbidity. In pregnancies of < 32 wk, corticosteroids should be given to accelerate fetal lung maturity (see p. 2683). Their use between 32 and 34 wk is controversial. Use of tocolytics (drugs that stop uterine contractions) to manage preterm PROM is controversial; their use must be determined case by case.

Preterm Labor

Labor (contractions resulting in cervical change) that begins before 37 wk gestation is considered preterm. Risk factors include premature rupture of membranes, infection, cervical incompetence, prior preterm birth, multifetal pregnancy, and placental abnormalities. Diagnosis is clinical. Causes are identified and treated if possible. Management typically includes bed rest, tocolytics (if labor persists), and corticosteroids (if gestational age is < 34 wk). Antistreptococcal antibiotics are given pending negative anovaginal culture results.

Preterm labor may be triggered by premature rupture of membranes, chorioamnionitis (see p. 2662), or another ascending uterine infection; group B streptococci are a common cause of such infections. Preterm labor may also be due to multifetal pregnancy, fetal or placental abnormalities, uterine abnormalities, pyelonephritis, or some sexually transmitted diseases; a cause may not be evident. Prior preterm delivery and cervical incompetence increase the risk.

Cervical cultures are done to check for causes suggested by clinical findings. Anovaginal cultures for group B streptococci are done, and prophylaxis is appropriately initiated. Most women with a presumptive diagnosis of preterm labor do not progress to delivery.

Treatment

• Antibiotics for group B streptococci, pending anovaginal culture results

• Tocolytics

• Corticosteroids if < 34 wk

Bed rest and hydration are commonly used initially.

Antibiotics effective against group B streptococci are given pending negative anovaginal cultures. Choices include the following:

• For women without penicillin allergy: Penicillin G 5 million units IV followed by 2.5 million units q 4 h or ampicillin 2 g IV followed by 1 g q 4 h

• For women with penicillin allergy but a low risk of anaphylaxis (eg, maculopapular rash with prior use): Cefazolin 2 g IV followed by 1 g q 8 h

• For women with penicillin allergy and an increased risk of anaphylaxis (eg, bronchospasm, angioneurotic edema, or hypotension with prior use, particularly within 30 min of exposure): Clindamycin 900 mg IV q 8 h or erythromycin 500 mg IV q 6 h if anovaginal cultures show susceptibility; if cultures document resistance or results are unavailable, vancomycin 1 g IV q 12 h

If the cervix dilates, tocolytics (drugs that stop uterine contractions) can usually delay labor for at least 48 h so that corticosteroids can be given to reduce risks to the fetus. Tocolytics include Mg sulfate, β-adrenergic agonists (eg, terbutaline), Ca channel blockers, and prostaglandin inhibitors. No tocolytic is clearly the first-line choice; choice should be individualized to minimize adverse effects. Mg sulfate is commonly used and is typically well tolerated (see p. 2671). Prostaglandin inhibitors may cause transient oligohydramnios. They are contraindicated after 32 wk gestation because they may cause premature narrowing or closure of the ductus arteriosus.

If the fetus is < 34 wk, women are given corticosteroids: betamethasone 12 mg IM q 24 h for 2 doses or dexamethasone 6 mg IM q 12 h for 4 doses unless delivery is imminent. These corticosteroids accelerate maturation of fetal lungs and decrease risk of neonatal respiratory distress syndrome, intracranial bleeding, and mortality.

A progestin may be recommended in future pregnancies for women who have a preterm delivery to reduce the risk of recurrence.

Protracted Labor

Protracted labor is abnormally slow cervical dilation or fetal descent during active labor. Diagnosis is clinical. Treatment is with oxytocin, operative vaginal delivery, or cesarean delivery.

Active labor usually occurs after the cervix dilates to ≥ 4 cm. Normally, cervical dilation and descent of the head into the pelvis proceed at a rate of at least 1 cm/h and more quickly in multiparous women.

Etiology

Protracted labor may result from fetopelvic disproportion (the fetus cannot fit through the maternal pelvis), which can occur because the maternal pelvis is abnormally small or because the fetus is abnormally large or abnormally positioned (fetal dystocia).

Another cause is uterine contractions that are too weak or infrequent (hypotonic uterine dysfunction) or, occasionally, too strong or close together (hypertonic uterine dysfunction).

Diagnosis

• Assessment of pelvic dimensions, fetal size and position, and uterine contractions

• Response to treatment

Diagnosis is clinical. The cause must be identified because it determines treatment. Assessing fetal and pelvic dimensions and fetal position (see p. 2607) can sometimes determine whether the cause is fetopelvic disproportion. For example, fetal weight > 5000 g (> 4500 g in diabetic women) suggests fetopelvic disproportion. Uterine dysfunction is diagnosed by evaluating the strength and frequency of contractions via palpation of the uterus or an intrauterine pressure catheter.

Diagnosis is often based on response to treatment.

Treatment

• Oxytocin

• Cesarean delivery for fetopelvic disproportion or intractable hypotonic dysfunction

• Sometimes operative delivery during the 2nd stage of labor

If the 1st or 2nd stage of labor proceeds too slowly and fetal weight is < 5000 g (< 4500 g in diabetic women), labor can be augmented with oxytocin, which is the treatment for hypotonic dysfunction. If normal progress is restored, labor can then proceed. If not, fetopelvic disproportion or intractable hypotonic dysfunction may be present, and cesarean delivery may be required. In the 2nd stage of labor, forceps or vacuum extraction may be appropriate after evaluation of fetal size, presentation, and station (≥ +2 cm) and evaluation of the maternal pelvis. Hypertonic uterine dysfunction is difficult to treat, but repositioning, short-acting tocolytics (eg, terbutaline 0.25 mg IV once), discontinuation of oxytocin if it is being used, and analgesics may help.

Umbilical Cord Prolapse

Umbilical cord prolapse is abnormal position of the cord in front of the fetal presenting part, so that the fetus compresses the cord during labor, causing fetal hypoxemia.

The prolapsed umbilical cord may be contained within the uterus (occult) or may protrude into the vagina (overt). Both are uncommon.

In **occult prolapse,** the cord is often compressed by a shoulder or the head. A fetal heart rate pattern that suggests cord compression and progression to hypoxemia (eg, severe bradycardia, severe variable accelerations) may be the only clue. Changing the woman's position may relieve pressure on the cord; however, if the abnormal fetal heart rate pattern persists, immediate cesarean delivery is necessary.

Overt prolapse occurs with ruptured membranes and is more common with breech presentation or a transverse lie. Overt prolapse can also occur with vertex presentation, particularly if membranes rupture (spontaneously or iatrogenically) before the head is engaged. Treatment begins with gently lifting the presenting part and continuously holding it off the prolapsed cord to restore fetal blood flow while immediate cesarean delivery is done. Placing the woman in the knee-to-chest position and giving her terbutaline 0.25 mg IV once may help by reducing contractions.

Uterine Rupture

Uterine rupture is rare. It occurs most often along healed scar lines in women who have had prior cesarean deliveries. Other predisposing factors include congenital uterine abnormalities, trauma, and other uterine surgical procedures such as myomectomies. Uterine rupture can occur before or during labor.

Causes of uterine rupture include uterine overdistention (multiple gestation, polyhydramnios, fetal anomalies), external or internal fetal version, iatrogenic perforation, excessive use of uterotonics, and failure to recognize labor dystocia with excessive uterine contractions against a lower uterine restriction ring. Use of prostaglandins in women who attempt a trial of labor after cesarean delivery increases the risk of uterine rupture and is not recommended.

Symptoms and signs include fetal bradycardia, evidence of hypovolemia, loss of fetal station (detected during cervical examination), and severe or constant abdominal pain.

Diagnosis is confirmed by laparotomy. If the fetus has been expelled from the uterus and is located within the peritoneal cavity, morbidity and mortality increase significantly.

Treatment is immediate laparotomy with cesarean delivery and, if necessary, hysterectomy.

Chapter 267. Postpartum Care

Introduction

Clinical manifestations during the puerperium (6-wk period after delivery) generally reflect reversal of the physiologic changes that occurred during pregnancy (see Table 267-1). These changes are mild and temporary and should not be confused with pathologic conditions.

Clinical parameters: Within the first 24 h, the woman's pulse rate begins to drop, and her temperature may be slightly elevated. Vaginal discharge is grossly bloody (lochia rubra) for 3 to 4 days, then becomes pale brown (lochia serosa), and after the next 10 to 12 days, it changes to yellowish white (lochia alba). About 1 to 2 wk after delivery, eschar from the placental site sloughs off and bleeding occurs; bleeding is usually self-limited. Total blood loss is about 250 mL; comfortably fitting intravaginal tampons (changed frequently) or external pads may be used to absorb it. Tampons should not be used if they might inhibit healing of perineal or vaginal lacerations. Prolonged bleeding (see p. 2680) may be a sign of infection or retained placenta

[**Table 267-1.** Normal Postpartum Changes]

and should be investigated. The uterus involutes progressively; after 5 to 7 days, it is firm and no longer tender, extending midway between the symphysis and umbilicus. By 2 wk, it is no longer palpable abdominally and typically by 4 to 6 wk returns to a prepregancy size. Contractions of the involuting uterus, if painful (afterpains), may require analgesics.

Laboratory parameters: During the first week, urine temporarily increases in volume; care must be taken when interpreting urinalysis results as lochia can interfere. Because blood volume is redistributed, Hct may fluctuate, although it tends to remain in the prepregnancy range if women do not hemorrhage. Because WBC count increases during labor, marked leukocytosis (up to 20,000 to 30,000/µL) occurs in the first 24 h postpartum; WBC count returns to normal within 1 wk. Plasma fibrinogen and ESR remain elevated during the first week postpartum.

Initial Management

Risk of infection, hemorrhage, and pain must be minimized. Women are typically observed for at least 1 h after the 3rd stage of labor and for several hours longer if general anesthesia was used during delivery (eg, by forceps, vacuum extractor, or cesarean).

Hemorrhage: Minimizing bleeding is the first priority; measures include

• Uterine massage

• Sometimes parenteral oxytocin

During the first hour after the 3rd stage of labor, the uterus is massaged periodically to ensure that it contracts, preventing excessive bleeding. If the uterus does not remain contracted after massage alone, oxytocin 10 units IM or a dilute oxytocin IV infusion (10 or 20 (up to 80) units/1000 mL of IV fluid) at 125 to 200 mL/h is given immediately after delivery of the placenta. The drug is continued until the uterus is firm; then it is decreased or stopped. Oxytocin should not be given as an IV bolus because severe hypotension may occur.

For all women, O_2, type O-negative blood or blood tested for compatibility, and IV fluids must be available during the recovery period. If blood loss was excessive, a CBC to verify that women are not anemic is required before discharge. If blood loss was not excessive, CBC is not required.

Diet and activity: After the first 24 h, recovery is rapid. A regular diet should be offered as soon as women desire food. Full ambulation is encouraged as soon as possible.

Exercise recommendations are individualized depending on presence of other maternal disorders or complications. Usually, exercises to strengthen abdominal muscles can be started once the discomfort of delivery has subsided, typically within 1 day for women who deliver vaginally and later for those who deliver by cesarean. Curl-ups, done in bed with the hips and knees flexed, tighten only abdominal muscles, usually without causing backache. Whether pelvic floor (eg, Kegel) exercises are helpful is unclear, but these exercises can begin as soon as the patient is ready.

Perineal care: If delivery was uncomplicated, showering and bathing are allowed, but vaginal douching is prohibited in the early puerperium. The vulva should be cleaned from front to back. Immediately after delivery, ice packs may help reduce pain and edema at the site of an episiotomy or repaired laceration; later, warm sitz baths can be used several times a day.

Analgesics: NSAIDs, such as ibuprofen 400 mg po q 4 to 6 h, work effectively on both perineal discomfort and uterine cramping. Acetaminophen 500 to 1000 mg po q 4 to 6 h can also be used. Acetaminophen and ibuprofen appear to be relatively safe during breast-feeding. Many other analgesics are secreted in breast milk. After surgery or repair of significant laceration, women may require opioids to relieve discomfort.

Bladder and bowel function: Urine retention, bladder overdistention, and catheterization should be avoided if possible. Rapid diuresis may occur, especially when oxytocin is stopped. Voiding must be encouraged and monitored to prevent asymptomatic bladder overfilling. A midline mass palpable in the suprapubic region or elevation of the uterine fundus above the umbilicus suggests bladder overdistention. If overdistention occurs, catheterization is necessary to promptly relieve discomfort and to prevent long-term urinary dysfunction.

Women are encouraged to defecate before leaving the hospital, although with early discharge, this recommendation is often impractical. If defecation has not occurred within 3 days, a mild cathartic (eg, psyllium, docusate, bisacodyl) can be given. Avoiding constipation can prevent or help relieve existing hemorrhoids, which can also be treated with warm sitz baths. Women with an extensive perineal laceration repair involving the rectum or anal sphincter can be given stool softeners (eg, docusate). Regional (spinal or epidural) anesthesia may delay defecation and spontaneous urination, in part by delaying ambulation.

Vaccination and Rh desensitization: Women who are seronegative for rubella should be vaccinated against rubella on the day of discharge. If women have not yet received tetanus-diphtheria-acellular pertussis (Tdap) vaccination and have not had a tetanus and diphtheria toxoids (Td) booster in ≥ 2 yr, they should be given Tdap before discharge from the hospital or birthing center, regardless of their breast-feeding status.

If women with Rh-negative blood have an infant with Rh-positive blood but are not sensitized, they should be given Rh_0(D) immune globulin 300 µg IM within 72 h of delivery to prevent sensitization (see p. 2666).

Breast engorgement: Milk accumulation may cause painful breast engorgement during early lactation. Breastfeeding helps reduce engorgement. Expressing milk by hand in a warm shower or using a breast pump between feedings can relieve pressure temporarily. However, doing so tends to encourage lactation, so it should be done only when necessary.

For women who are not going to breastfeed, firm support of the breasts is recommended to suppress lactation; gravity stimulates the let-down reflex and encourages milk flow. For many women, tight binding of the breasts, cold packs, and analgesics as needed, followed by firm support, effectively control temporary symptoms while lactation is being suppressed. Suppression of lactation with drugs is not recommended.

Mental disorders: Transient depression (baby blues) is very common during the first week after delivery. Symptoms are typically mild and usually subside by 7 to 10 days. Physicians should ask women about symptoms of depression before and after delivery and be alert to recognizing symptoms of depression, which may resemble the normal effects of new motherhood (eg, fatigue, difficulty concentrating). They

should also advise women to contact them if depressive symptoms continue for > 2 wk or interfere with daily activities or if women have suicidal or homicidal thoughts. In such cases, postpartum depression (see p. 2689) or another mental disorder may be present. A preexisting mental disorder is likely to recur or worsen during the puerperium, so affected women should be monitored closely.

Management at Home

The woman and infant can be discharged within 24 to 48 h postpartum; many family-centered obstetric units discharge them as early as 6 h postpartum if major anesthesia was not used and no complications occurred. Serious problems are rare, but a home visit, office visit, or phone call within 24 to 48 h is necessary. A routine postpartum visit is usually scheduled at 6 wk for women with an un-complicated vaginal delivery. If delivery was cesarean or other complications occurred, follow-up may be scheduled sooner.

Normal activities may be resumed as soon as the woman feels ready.

Intercourse may be resumed as soon as desired and comfortable; however, a laceration or episiotomy repair must be allowed to heal first.

Family planning: Pregnancy must be delayed for 1 mo if women were vaccinated against rubella at hospital discharge; also, subsequent obstetric outcomes are improved by delaying conception for at least 6 mo but preferably 18 mo after delivery. To minimize the chance of pregnancy, women should start using contraception as soon as they are discharged. If women are not breastfeeding, ovulation usually occurs about 4 to 6 wk postpartum, 2 wk before the first menses. However, ovulation can occur earlier; women have conceived as early as 2 wk postpartum. Women who are breastfeeding tend to ovulate and menstruate later, usually closer to 6 mo postpartum, although a few ovulate and menstruate (and become pregnant) as quickly as those who are not breastfeeding.

Women should choose a method of contraception based on the specific risks and benefits of various options. Breastfeeding status affects choice of contraceptive. For breast-feeding women, nonhormonal methods are usually preferred; among hormonal methods, progestin-only oral contraceptives, depot medroxyprogesterone acetate injections, and progestin implants are preferred because they do not affect milk production. Estrogenprogesterone contraceptives can interfere with milk production and should not be initiated until milk production is well established. Combined estrogen-progestin vaginal rings can be used after 4 wk postpartum if women are not breastfeeding.

A diaphragm should be fitted only after complete involution of the uterus, at 6 to 8 wk; meanwhile, foams, jellies, and condoms should be used. Intrauterine devices are typically best placed after 4 to 6 wk postpartum to minimize risk of expulsion.

Mastitis

Mastitis is painful inflammation of the breast, usually accompanied by infection.

Fever later in the puerperium is frequently due to mastitis. Staphylococcal species are the most common causes. Symptoms may include high fever, erythema, induration, tenderness, pain, swelling, and warmth to the touch. Mastitis is different from the pain and cracking of nipples that frequently accompanies the start of breastfeeding. Breast abscesses are very rare and occasionally caused by methicillin-resistant *Staphylococcus aureus*.

Diagnosis is clinical.

Treatment

• Antistaphylococcal antibiotics

Treatment includes encouragement of fluid intake and antibiotics aimed at *Staphylococcus aureus*, the most common causative pathogen. Examples are dicloxacillin 500 mg po q 6 h for 7 to 10 days and, for

women allergic to penicillin, erythromycin 250 mg po q 6 h. If women do not improve and do not have an abscess, vancomycin 1 g IV q 12 h or cefotetan 1 to 2 g IV q 12 h to cover resistant organisms should be considered. Breastfeeding should be continued during treatment because treatment includes emptying the affected breast.

Breast abscesses are treated mainly with incision and drainage. Antibiotics aimed at *S. aureus* are often used.

It is not clear whether antibiotics aimed at methicillin-resistant *S. aureus* are necessary for treatment of mastitis or breast abscess.

Puerperal Endometritis

Puerperal endometritis is uterine infection, typically caused by bacteria ascending from the lower genital or GI tract. Symptoms are uterine tenderness, abdominal or pelvic pain, fever, malaise, and sometimes discharge. Diagnosis is clinical, rarely aided by culture. Treatment is with broad-spectrum antibiotics (eg, clindamycin plus gentamicin).

Incidence of postpartum endometritis is affected mainly by the mode of delivery:

• Vaginal deliveries: 1 to 3%

• Scheduled caesarean deliveries (done before labor starts): 5 to 15%

• Unscheduled caesarean deliveries (done after labor starts): 15 to 20%

Patient characteristics also affect incidence.

Etiology

Endometritis may develop after chorioamnionitis during labor or postpartum. Predisposing conditions include

• Prolonged rupture of the membranes

• Internal fetal monitoring

• Prolonged labor

• Cesarean delivery

• Repeated digital examination

• Retention of placental fragments in the uterus

• Postpartum hemorrhage

• Colonization of the lower genital tract

• Anemia

• Bacterial vaginosis

• Young maternal age

• Low socioeconomic status

Infection tends to be polymicrobial; the most common pathogens include

- Gram-positive cocci (predominantly group *B streptococci, Staphylococcus epidermidis*, and *Enterococcus* sp)

- Anaerobes (predominantly peptostreptococci, *Bacteroides* sp, and *Prevotella* sp)

- Gram-negative bacteria (predominantly *Gardnerella vaginalis, Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*).

Uncommonly, peritonitis, pelvic abscess, pelvic thrombophlebitis (with risk of pulmonary embolism), or a combination develop. Rarely, septic shock and its sequelae, including death, occur.

Symptoms and Signs

Typically, the first symptoms are lower abdominal pain and uterine tenderness, followed by fever—most commonly within the first 24 to 72 h postpartum. Chills, headache, malaise, and anorexia are common. Sometimes the only symptom is a low-grade fever.

Pallor, tachycardia, and leukocytosis usually occur, and the uterus is soft, large, and tender. Discharge may be decreased or profuse and malodorous, with or without blood. When parametria are affected, pain and fever are severe; the large, tender uterus is indurated at the base of the broad ligaments, extending to the pelvic walls or posterior cul-de-sac. Pelvic abscess may manifest as a palpable mass separate from and adjacent to the uterus.

Diagnosis

- Clinical evaluation

- Usually tests to exclude other causes (eg, urinalysis and urine culture)

Diagnosis within 24 h of delivery is based on clinical findings of pain, tenderness, and temperature > 38° C after delivery. After the first 24 h, puerperal endometritis is presumed present if no other cause is apparent in patients with temperature ≥ 38° C on 2 successive days. Other causes of fever and lower abdominal symptoms include UTI, wound infection, septic pelvic thrombophlebitis, and perineal infection. Uterine tenderness is often difficult to distinguish from incisional tenderness in patients who have had a cesarean delivery.

Patients with low-grade fever and no abdominal pain are evaluated for other occult causes, such as atelectasis, breast engorgement or infection, UTI, and leg thrombophlebitis. Fever due to breast engorgement tends to remain ≤ 39° C. If temperature abruptly rises after 2 or 3 days of low-grade fever, the cause is probably an infection rather than breast engorgement.

Urinalysis and urine culture are usually done.

Endometrial cultures are rarely indicated because specimens collected through the cervix are almost always contaminated by vaginal and cervical flora. Endometrial cultures should be done only when endometritis is refractory to routine antibiotic regimens and no other cause of infection is obvious; sterile technique with a speculum is used to avoid vaginal contamination, and the sample is sent for aerobic and anaerobic cultures.

Blood cultures are rarely indicated and should be done only when endometritis is refractory to routine antibiotic regimens or clinical findings suggest septicemia. If fever persists for > 48 h (some clinicians use a 72-h cutoff) after endometritis is adequately treated, other causes such as pelvic abscess and pelvic thrombophlebitis should be considered. Abdominal and pelvic imaging, usually by CT, is sensitive for abscess but detects pelvic thrombophlebitis only if the clots are large. If imaging shows neither abnormality, a trial of heparin is typically begun to treat presumed pelvic thrombophlebitis, usually a diagnosis of exclusion. A therapeutic response confirms the diagnosis.

Treatment

• Clindamycin plus gentamicin, with or without ampicillin

Treatment is a broad-spectrum antibiotic regimen given IV until women are afebrile for 48 h. The first-line choice is clindamycin 900 mg q 8 h plus gentamicin 1.5 mg/kg q 8 h or 5 mg/kg once/day; ampicillin 1 g q 6 h is added if enterococcal infection is suspected or if no improvement occurs by 48 h. Continuing treatment with oral antibiotics is not necessary.

Prevention

Preventing or minimizing predisposing factors is essential. Appropriate hand washing should be encouraged. Vaginal delivery cannot be sterile, but aseptic techniques are used. Prophylactic antibiotics given when delivery is cesarean can reduce risk of endometritis by up to three fourths.

Postpartum Pyelonephritis

Pyelonephritis is bacterial infection of the renal parenchyma.

Pyelonephritis may occur postpartum if bacteria ascend from the bladder. The infection may begin as asymptomatic bacteriuria during pregnancy and is sometimes associated with bladder catheterization to relieve urinary distention during or after labor. The causative organism is usually a type of coliform bacteria (eg, *Escherichia coli*).

Symptoms include fever, flank pain, general malaise, and, occasionally, painful urination.

Diagnosis is by urinalysis and urine culture (see p. 2375).

Treatment

• Antibiotics

Initial treatment is ceftriaxone 1 to 2 g IV q 12 to 24 h alone or ampicillin 1 g IV q 6 h plus gentamicin 1.5 mg/kg IV q 8 h until women are afebrile for 48 h. Sensitivities with culture should be checked. Treatment is adjusted accordingly and continued for a total of 7 to 14 days; oral antibiotics are used after the initial IV antibiotics. Women should be encouraged to consume large amounts of liquids.

A urine culture should be repeated 6 to 8 wk after delivery to verify cure. If episodes of pyelonephritis recur, imaging should be considered to look for calculi or congenital malformations. Imaging during pregnancy is usually with ultrasonography; imaging after pregnancy is usually with contrast CT.

Postpartum Depression

Postpartum depression is depressive symptoms that last > 2 wk after delivery and that interfere with activities of daily living.

Postpartum depression occurs in 10 to 15% of women after delivery. Although every woman is at risk, women with the following are at higher risk:

• Baby blues

• Prior episode of postpartum depression

• Prior diagnosis of depression

• Family history of depression

• Significant life stressors

• Lack of support (eg, from partner or family members)

• Perimenstrual mood disorders

• Poor obstetric outcomes

The exact etiology is unknown; however, prior depression is the major risk, and hormonal changes during the puerperium, sleep deprivation, and genetic susceptibility may contribute.

Unlike the baby blues, which typically lasts 2 to 3 days (up to 2 wk) and is relatively mild, postpartum depression lasts > 2 wk and is disabling, interfering with activities of daily living.

Symptoms and Signs

Symptoms may include

• Extreme sadness

• Uncontrollable crying

• Insomnia or increased sleep

• Loss of appetite or overeating

• Irritability

• Headaches and body aches and pains

• Extreme fatigue

• Unrealistic worries about or disinterest in the baby

• Fear of harming the baby

• Suicidal ideation

• Anxiety

Typically, symptoms develop insidiously over 3 mo, but onset can be more sudden. Postpartum depression interferes with women's ability to care for themselves and the baby.

Psychosis rarely develops, but postpartum depression increases the risk of suicide and infanticide, which are the most severe complications.

Women may not bond with their infant, resulting in emotional, social, and cognitive problems in the child later.

Fathers are at increased risk of depression, and marital stress is increased.

Without treatment, postpartum depression can resolve spontaneously or become chronic depression. Risk of recurrence is about 1 in 3 to 4.

Diagnosis

• Clinical evaluation

• Sometimes formal depression scales

Early diagnosis and treatment substantially improve outcomes for women and their infant. Because of cultural and social factors, women may not volunteer symptoms of depression, so they should be asked about such symptoms before and after delivery. They also should be taught to recognize symptoms of depression, which they may mistake for the normal effects of new motherhood (eg, fatigue, difficulty concentrating). Women can be screened at the postpartum visit for postpartum depression using various depression scales (eg, Edinburgh Postnatal Depression Scale, Postpartum Depression Prediction Inventory, Postpartum Depression Screening Scale).

Postpartum depression (or other serious mental disorders) should be suspected if women have the following:

• Symptoms for > 2 wk

• Symptoms that interfere with daily activities

• Suicidal or homicidal thoughts (women should be asked specifically about such thoughts)

• Hallucinations, delusions, or psychotic behavior

Treatment

Treatment includes antidepressants and psychotherapy. Exercise therapy, light therapy, massage therapy, acupuncture, and ω-3 fatty acid supplementation have shown some benefit in small studies.