CHAPTER 34

Alterations in the Female Reproductive System

Structure and Function of the Female Reproductive System

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The reproductive function of the female is far more complex than the male. Not only must the female produce germ cells, but she must also nourish the developing embryo and prepare to nurse the infant once childbirth has occurred. This chapter includes a review of the structure and function of the female reproductive system and a discussion of disorders of the internal and external female reproductive organs.

STRUCTURE AND FUNCTION OF THE FEMALE REPRODUCTIVE SYSTEM

The female genitourinary system consists of the external and internal genital organs. The external sex organs of the female are referred to as the genitalia or vulva. The internal genital organs include the vagina, uterus, uterine tubes, and ovaries. These organs are largely located within the pelvic cavity (Fig. 34-1).

External Genitalia

The external genitalia are located at the base of the pelvis in the perineal area. The external genitalia, also called the vulva, include the mons pubis, labia majora, labia minora, clitoris, and
perineal body (Fig. 34-2). Because of their location, the urethra and anus usually are considered in a discussion of the external genitalia.

The mons pubis is a rounded skin-covered fat pad located anterior to the symphysis pubis. Running posteriorly from the mons pubis is two elongated hair-covered fatty folds, the labia majora. The labia majora are analogous to the male scrotum. The labia majora enclose the labia minora, which are smaller than the labia majora and are composed of skin, fat, and some erectile tissue. The clitoris is located below the clitoral hood, which is formed by the joining of the two labia minora. The female clitoris is an erectile organ, rich in vascular and nervous supply. Analogous to the male penis, it is a highly sensitive organ that becomes distended during sexual stimulation.

The area between the labia minora is called the vestibule. Located in the vestibule are the urethral and vaginal openings and Bartholin’s lubricating glands. The urethra is located posterior to the clitoris and usually is closer to the vaginal opening than to the clitoris. The urethral opening is the site of Skene’s glands, which have a lubricating function. The vaginal orifice, commonly known as the introitus, is the opening between the external and internal genitalia.

**Internal Genitalia**

**Vagina**
The vagina is a fibromuscular tube that connects the external and internal genitalia. The vagina, which is essentially free of sensory nerve fibers, is located behind the urinary bladder and urethra and anterior to the rectum (Fig. 34-3). The uterine cervix projects into the vagina at its upper end, forming recesses called fornices. The vagina functions as a route for discharge of menses and other secretions. It also serves as an organ of sexual fulfillment and reproduction.

**Cervix, Uterus, and Uterine Tubes**

**Cervix.** The round cervix forms the neck of the uterus. The opening, or os, of the cervix, forms a pathway between the uterus and the vagina. The vaginal opening is called the external os and the uterine opening, the internal os. The space between these two openings is called the endocervical canal. Secretions from the columnar epithelium of the endocervix protect the uterus from infection, alter receptivity to sperm, and form a mucoid “plug” during pregnancy. The endocervical canal provides a route for menstrual discharge and entry of sperm.

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**THE FEMALE GENITOURINARY SYSTEM**

- The female reproductive system, which consists of the external and internal genitalia, has both sexual and reproductive functions.

- The external genitalia (labia majora, labia minora, clitoris, and vestibular glands) surround the openings of the urethra and vagina. Although the female urinary and genital structures are anatomically separate, their close proximity provides a means for cross-contamination and shared symptomatology.

- The internal genitalia of the female reproductive system are specialized to participate in sexual intercourse (the vagina), to produce and maintain the female egg cells (the ovaries), to transport these cells to the site of fertilization (the fallopian tubes), to provide a favorable environment for development of the offspring (the uterus), and to produce the female sex hormones (the ovaries).
Uterus. The uterus is a thick-walled muscular organ. This pear-shaped, hollow structure is located between the bladder and the rectum. The uterus can be divided into three parts: (1) the upper portion above the insertion of the fallopian tubes, called the fundus; (2) the central tapering portion, called the body; and (3) the inferior constricted part, called the cervix (Fig. 34-4).

The wall of the uterus is composed of three layers: the perimetrium, the myometrium, and the endometrium. The perimetrium is the outer serous covering that is derived from the abdominal peritoneum. This outer layer merges with the peritoneum that covers the broad ligaments. Anteriorly, the perimetrium is reflected over the bladder wall, forming the vesicouterine pouch; posteriorly, it extends to form the cul-de-sac, or pouch of Douglas (Fig. 34-3). Because of the proximity of the perimetrium to the urinary bladder, infection of this organ often causes uterine symptoms, particularly during pregnancy.

The middle muscle layer, the myometrium, forms the major portion of the uterine wall. It is continuous with the myometrium of the fallopian tubes and the vagina and extends into all the supporting ligaments with the exception of the broad ligaments. The inner fibers of the myometrium run in various directions, giving it an interwoven appearance. Contractions of these muscle fibers help to expel menstrual flow and the products of conception during miscarriage or childbirth.

The endometrium, or inner layer of the uterus, is continuous with the lining of the fallopian tubes and vagina. It consists of two distinct layers, or zones, that are responsive to hormonal stimulation: a basal layer and a functional layer. The basal layer lies adjacent to the myometrium and is not sloughed during menstruation. The functional layer, which can be subdivided into a thin compact superficial layer and a deeper spongiosa layer, arises from the basal layer and undergoes proliferative changes and menstrual sloughing. The endometrial cycle can be divided into three phases: proliferative, secretory, and menstrual. The proliferative, or preovulatory, phase is the period during which the glands and stroma of the superficial layer grow rapidly under the influence of estrogen. The secretory, or postovulatory, phase is the period during which progesterone produces glandular dilation and active mucus secretion and the endometrium becomes highly vascular and edematous. The menstrual phase is the period during which the superficial layer degenerates and sloughs off.

Uterine Tubes. The fallopian, or uterine, tubes are slender cylindrical structures attached bilaterally to the uterus and supported by the upper folds of the broad ligament. The end of the fallopian tube nearest the ovary forms a funnel-like opening with fringed fingerlike projections, called fimbriae, that pick up the ovum following its release into the peritoneal cavity after ovulation (see Fig. 34-4). The fallopian tubes are formed of smooth muscle and lined with a ciliated, mucus-producing epithelial layer. The beating of the cilia, along with contractile movements of the smooth muscle, propels the nonmobile ovum toward the uterus. Besides providing a passageway for

![Figure 34-3](Image)

Median section of the vagina.

![Figure 34-4](Image)

Schematic drawing of female reproductive organs, showing the path of the oocyte as it moves from the ovary into the fallopian (uterine) tube; the path of sperm is also shown, as is the usual site of fertilization.
ova and sperm, the fallopian tubes provide for drainage of tubal secretions into the uterus.

**Ovaries**

In the adult, the ovaries are flat, almond-shaped structures that are 4 × 2.5 × 1.5 cm in dimension. They are located on either side of the uterus below the ends of the two fallopian tubes. The ovaries are attached to the posterior surface of the broad ligament and to the uterus by the ovarian ligament (see Fig. 34-4). They are covered with a thin layer of surface epithelium that is continuous with the lining of the peritoneum. The integrity of this covering is periodically broken at the time of ovulation.

The tissues of the adult ovary can be conveniently divided into four compartments, or units: (1) the stroma, or supporting tissue; (2) the interstitial cells; (3) the follicles; and (4) the corpus luteum. The stroma is the connective tissue substance of the ovary in which the follicles are distributed. The interstitial cells are estrogen-secreting cells that resemble the Leydig’s cells, or interstitial cells, of the testes. The follicles contain the female germ cells or ovum. The corpus luteum (yellow body) develops after expulsion of the ovum from the follicle.

**Ovarian Hormones**

The ovaries produce estrogens, progesterone, and androgens. Ovarian hormones are secreted in a cyclic pattern as a result of the interaction between the hypothalamic gonadotrophic releasing hormone (GnRH) and the pituitary gonadotropic hormones, follicle stimulating hormone (FSH), and luteinizing hormone (LH). The secretion of LH and FSH is stimulated by GnRH from the hypothalamus (Fig. 34-5). In addition to LH and FSH, the anterior pituitary secretes a third hormone called prolactin. The primary function of prolactin is the stimulation of lactation in the postpartum period. During pregnancy, prolactin and other hormones such as estrogen, progesterone, insulin, and cortisol contribute to breast development in preparation for lactation.

**Estrogens.** Estrogens are a family of structurally related female sex hormones synthesized and secreted by cells in the ovaries and, in small amounts, by cells in the adrenal cortex. Androgens can be converted to estrogens peripherally, especially in fat tissue. Three estrogens occur naturally in humans: estrone, estradiol, and estriol. Of these, estradiol is the most biologically potent and the most abundantly secreted product of the ovary. Estrogens are secreted throughout the menstrual cycle. Two peaks occur: one before ovulation and the other in the middle of the luteal phase. Estrogens are transported in the blood bound to specific plasma globulins, inactivated and conjugated in the liver, and then excreted in the bile.

Estrogens are necessary for the normal female physical maturation. In concert with other hormones, estrogens provide for the reproductive processes of ovulation, implantation of the products of conception, pregnancy, parturition, and lactation by stimulating the development and maintaining the growth of the accessory organs. The estrogens stimulate the intruterine development of the vagina, uterus, and uterine tubes in the embryo. They also stimulate the stromal development and ductal growth of the breasts at puberty, are responsible for the accelerated pubertal skeletal growth phase and for closure of the epiphyses of the long bones, contribute to the growth of axillary and pubic hair, and alter the distribution of body fat to produce the typical female body contours.

Estrogens have a number of important extragenital metabolic effects. They are responsible for maintaining the normal structure of skin and blood vessels in women. Estrogens decrease the rate of bone resorption by antagonizing the effects of calcitonin on bone; for this reason, osteoporosis is a common problem in estrogen-deficient postmenopausal women (see Chapter 43). In the liver, estrogens increase the synthesis of transport proteins for thyroxine, estrogen, testosterone, and other hormones. Estrogens also affect the composition of the plasma lipoproteins. They produce an increase in high-density lipoproteins (HDLs), a slight reduction in low-density lipoproteins (LDLs), and a reduction in cholesterol levels (see Chapter 15). Estrogens also increase plasma triglyceride levels, and they enhance the coagulability of blood by effecting increased circulating levels of plasminogen and factors II, VII, IX, and X.

The estrogens cause moderate retention of sodium and water. Most women retain sodium and water and gain weight just before menstruation. This occurs because the estrogens facilitate the movement of intravascular fluids into the extracellular spaces, producing edema and increased sodium and water retention by the kidneys because of the decreased plasma volume. The actions of estrogens are summarized in Table 34-1.

**Progesterone.** Although the word progesterone refers to a substance that maintains pregnancy, progesterone is secreted as part of the normal menstrual cycle. The corpus luteum of the ovary secretes large amounts of progesterone after ovulation, and the adrenal cortex secretes small amounts. The hormone circulates in the blood attached to a specific plasma protein. It is metabolized in the liver and conjugated for excretion in the bile.

The local effects of progesterone on reproductive organs include the glandular development of the lobular and alveolar

![FIGURE 34-5] Hypothalamic-pituitary feedback control of estrogen and progesterone levels in the female. The dashed line represents negative feedback.
Ovary, 25% from the adrenal cortex, and 50% from ovarian follicles. Approximately 25% of these androgens are secreted from the ovaries, 25% from the adrenal cortex, and 50% from ovarian or adrenal precursors. In the female, androgens contribute to normal hair growth at puberty and may have other important metabolic effects.

**Ovarian Follicle Development and Ovulation**

Unlike the male gonads, which produce sperm throughout a man’s reproductive life, the female gonads contain a fixed number of ova at birth that diminishes throughout a woman’s life. The process of oogenesis begins during the sixth week of fetal life and proceeds to the development of the primary oocytes with their surrounding granulosa cells, which become surrounded by a single layer of granulosa cells. The primary oocytes with their surrounding granulosa cells are referred to as primordial follicles. These primitive germ cells provide the 1 to 2 million oocytes that are present in the ovaries at birth. Throughout childhood, the granulosa cells provide nourishment for the ovum and secrete an inhibiting factor that keeps the ovum suspended in a primordial state. After puberty, when FSH and LH from the anterior pituitary begin to be secreted in sufficient amounts, the entire ovaries, together with some of the follicles within them, begin to grow.

**Ovarian Cycle.** The monthly series of events associated with the maturation of the ovum is called the ovarian cycle. It consists of two phases: the follicular phase and the luteal phase. The follicular phase, typically days 1 to 14, is the period of follicle growth. The luteal phase, days 14 to 28, is the period of corpus luteum activity. The typical ovarian cycle repeats at intervals of 28 days, with ovulation occurring midcycle. However, cycles as long as 40 days and as short as 21 days are not uncommon.

Follicles at all stages of development can be found in both ovaries, except in menopausal women (Fig. 34-6). Most follicles exist as primary follicles, each of which consists of a round oocyte surrounded by a single layer of flattened, epithelium-derived granulosa cells and a basement membrane. The primary follicles constitute an inactive pool of follicles from which all the ovulating follicles develop.

Under the influence of FSH and LH stimulation, 6 to 12 primary follicles develop into secondary follicles once every ovulatory cycle. During the development of the secondary follicle, the primary oocyte increases in size, and the surrounding granulosa cells proliferate to form a multilayered wall around it. In addition, cells from the surrounding ovarian interstitium align themselves to form a cellular wall called the theca. The cells of the theca become differentiated into two layers: an inner theca interna, which lies adjacent to the follicular cells, and an outer theca externa. The cells in the theca interna take on epithelioid characteristics similar to those of the granulosa cells and develop the ability to secrete additional sex hormones (estrogen and progesterone). The theca externa develops into a highly vascular connective tissue capsule that becomes the capsule for the developing follicle.
As the follicle enlarges, a single large cavity, or antrum, is formed, and a portion of the granulosa cells and the oocytes are displaced to one side of the follicle by the fluid that accumulates. The secondary oocyte remains surrounded by a crown of granulosa cells, the corona radiata. As the granulosa cells continue to divide and the follicle grows, the theca and granulosa cells cooperate to secrete a follicular fluid that contains a high concentration of estrogen. Selection of a dominant follicle occurs with the conversion to an estrogen microenvironment. The dominant follicle accumulates a greater mass of granulosa cells, and the theca becomes richly vascular, giving the follicle a hyperemic appearance. The lesser follicles, although continuing to divide and the follicle grows, the theca layer. A rapid accumulation of blood and fluid forms a hemorrhage that enlarges to form a large cyst, usually retroperitoneal. Leakage of this blood onto the peritoneal surface that surrounds the ovary is thought to contribute to the mittelschmerz (“middle [or intermenstrual] pain”) of ovulation. During the luteal stage, progesterone is secreted from the corpus luteum. If fertilization does not take place, the corpus luteum atrophies and is replaced by white scar tissue called the corpus albicans; the hormonal support of the endometrium is withdrawn, and menstruation occurs. In the event of fertilization, the corpus luteum remains functional for 3 months and provides hormonal support for pregnancy until the placenta is fully functional.

**In summary**, the genitourinary system as a whole serves sexual and reproductive functions throughout a woman’s life. The female reproductive system consists of external and internal genitalia. The internal genitalia consist of the vagina, uterus, uterine tubes, and paired ovaries. The uterus is a thick-walled, muscular organ. The wall of the uterus is composed of three layers: the outer perimetrium; the myometrium or muscular layer, which is continuous with the myometrium of the fallopian tubes and the vagina; and the inner lining or endometrium, which is continuous with the lining of the fallopian tubes and vagina.

The gonads, or ovaries, which are internal in the female (unlike the testes in the male), have the dual function of storing the female germ cells, or ova, and producing the female sex hormones. Through the regulation and release of sex hormones, the ovaries influence the development of secondary sexual characteristics, regulation of menstrual cycles, maintenance of pregnancy, and advent of menopause.

**DISORDERS OF THE FEMALE REPRODUCTIVE ORGANS**

Disorders of the female genitourinary system have widespread effects on physical and psychological function, affecting sexuality and reproductive function. The reproductive organs are located close to other pelvic structures, particularly those of the urinary system, and disorders of the reproductive system may affect urinary function. This section of the chapter focuses on infections and benign and malignant disorders of the external and internal genitalia.

**Disorders of the External Genitalia**

**Bartholin Gland Cyst and Abscess**

A Bartholin gland cyst is a fluid-filled sac that results from the occlusion of the duct system of the gland. When the cyst becomes infected, the contents become purulent; if the infection goes untreated, an abscess can result. Most commonly cyst and abscess formation follows a bacterial, chlamydial, or gonococcal infection. Cysts can attain the size of an orange and frequently recur. Abscesses can be extremely tender and painful. Treatment of symptomatic cysts consists of the administration of appropriate antibiotics, local application of moist heat, and incision and drainage.

**Non-neoplastic Epithelial Disorders**

The term non-neoplastic epithelial disorders refers to nonmalignant atrophic and hyperplastic changes of the vulvar skin and mucosa. The condition, commonly referred to as leukoplakia, presents as white lesions of the vulva. Itching is the most common symptom, and dyspareunia (painful intercourse) is common.4

There are two forms of non-neoplastic epithelial lesions: lichen sclerosus and lichen simplex chronicus. *Lichen sclerosus* patches are hypopigmented, parchment-thin, and atrophic. Such lesions occur in all age groups but are most common in postmenopausal women. They may also occur on other areas of the skin. Although slowly progressive in its development, lichen sclerosus is not premalignant. *Lichen simple chronics*
lesions are thick, gray-white plaques. The thickened epithelium displays a marked increase in superficial keratin, which imparts a white appearance to the vulva. Because squamous carcinoma may also appear as white plaques, biopsy is required to distinguish benign from malignant lesions.

**Vulvodynia**

Vulvodynia is a syndrome of unexplained vulvar pain, also referred to as *vulvar pain syndrome* or *burning vulva syndrome*. It is characterized by burning, stinging, irritation, and rawness. Several forms or subsets of vulvodynia have been identified. It may occur as localized tenderness near the vaginal opening at the onset of intercourse or tampon insertion (*i.e.*, insertional vulvodynia), as a sensitivity to tight-fitting pants, bicycling, or prolonged sitting (*vulvar vestibulitis*), or as episodic flares that occur only before menses or after coitus (*cyclic vulvodynia*). Symptoms that are in general noncyclic and pruritic and develop progressively during the perimenopausal or postmenopausal years are characteristic of *vulvar dermatoses*.

**Vulvar dysesthesia**, also known as *idiopathic* or *essential vulvodynia*, involves severe, constant, widespread burning that interferes with daily activities. Although the cause is unknown, the quality of pain with vulvar dysesthesia resembles reflex sympathetic dystrophy (see Chapter 39). One of the proposed causes is *pubental neuralgia* or pain along the pudendal nerve.

Possible causes for other forms of vulvodynia include candidal hypersensitivity related to chronic recurrent yeast infections; chemical irritation or drug effects, especially prolonged use of topical steroid creams; and dermatoses such as lichen sclerosus. Herpes simplex virus may be related to episodic vulvodynia.

Treatment of vulvodynia is aimed at symptom relief and elimination of suspected underlying problems. Careful history taking and physical assessment are essential for differential diagnosis and treatment. Psychosocial support often is needed because this condition can cause strain in sexual, family, and work relationships. Severe forms of the disorder often need to be managed from a multidimensional, chronic pain perspective.

**Premalignant and Malignant Neoplasms**

Carcinoma of the vulva accounts for approximately 3% of all cancers of the female genitaliourinary system, occurring most often in women who are 60 years of age or older. Approximately 90% of vulvar malignancies are squamous cell carcinomas; the remainder are adenocarcinomas, melanomas, and basal cell carcinomas.

Vulvar intraepithelial neoplasia (VIN), which is a precursor lesion of squamous cell carcinoma, represents a spectrum of neoplastic changes that range from minimal cellular atypia to invasive cancer. There has been a significant increase in frequency of one form of VIN among younger women (40 to 60 years of age) during the past several decades. The increase is more common in women who smoke and those with human papillomavirus (HPV) infections, particularly HPV type 16 (see Chapter 35). A second form of VIN, which is seen more often in older women, often is preceded by chronic vulvar irritation or lichen sclerosus. This form of VIN does not appear to be associated with HPV.

The initial lesion of squamous cell vulvar carcinoma may appear as an inconspicuous thickening of the skin, a small raised area or lump, or an ulceration that fails to heal. It may be single or multiple and vary in color from white to velvety red or black. The lesions may resemble eczema or dermatitis and may produce few symptoms, other than pruritus, local discomfort, and exudation. A recurrent, persistent, pruritic vulvitis may be the only complaint. The symptoms frequently are treated with various home remedies before medical treatment is sought. The lesion often becomes secondarily infected, and this causes pain and discomfort. The malignant lesion gradually spreads superficially or as a deep furrow involving all of one labial side. Because there are many lymph channels around the vulva, the cancer metastasizes freely to the regional lymph nodes. The most common extension is to the superficial inguinal, deep femoral, and external iliac lymph nodes.

Early diagnosis is important in the treatment of vulvar carcinoma. Outlook for survival diminishes with increasing tumor size and nodal involvement. Treatment is primarily wide surgical excision of the lesion for noninvasive cancer and vulvectomy with node resection for invasive cancer.

**Disorders of the Vagina**

The normal vaginal ecology depends on the delicate balance of hormones and bacterial flora. The vagina is lined with mucus-secreting stratified squamous epithelial cells. The epithelial cells of the vagina, like other tissues of the reproductive system, respond to changing levels of the ovarian sex hormones. Estrogen stimulates the proliferation and maturation of the vaginal mucosa; this results in a thickening of the vaginal mucosa and an increased glycogen content of the epithelial cells.

Vaginal tissue usually is moist, with a pH maintained within the bacteriostatic range of 3.8 to 4.2. Döderlein’s bacilli, part of the normal vaginal flora, metabolize glycogen, and in the process produce the lactic acid that normally maintains the vaginal pH below 4.5. The vaginal ecology can be disrupted at many levels, rendering it susceptible to infection. Pregnancy and the use of oral contraceptive agents increase the amount of estrogen in the system. Diabetes or a prediabetic state may increase the glycogen content of the cells. The use of systemic antibiotics may decrease the number of lactobacilli in the vagina. Decreased estrogen stimulation after menopause causes the vaginal mucosa to become thin and dry, often resulting in dyspareunia (*i.e.*, painful intercourse), atrophic vaginitis, and occasionally in vaginal bleeding.

**Vaginitis**

Vaginitis is an inflammatory condition of the vagina. It is characterized by vaginal discharge and burning, itching, redness, and swelling of vaginal tissues. Pain often occurs with urination and sexual intercourse. Vaginitis may be caused by chemical irritants, foreign bodies, and infectious agents. The causes of vaginitis differ in various age groups. In premenarchal girls, most vaginal infections have nonspecific causes, such as poor hygiene, intestinal parasites, or the presence of foreign bodies. *C. albicans*, *Trichomonas vaginalis*, and bacterial vaginosis are the most common causes of vaginitis in the childbearing years, and some of these organisms can be transmitted sexually (see Chapter 35). Atrophic vaginitis, which is caused by a decrease in estrogen levels, is the most common form in postmenopausal
Every woman has a normal vaginal discharge during the menstrual cycle, but it should not cause burning or itching or have an unpleasant odor. These symptoms suggest inflammation or infection. Because these symptoms are common to the different types of vaginitis, precise identification of the organism is essential for proper treatment. A careful history should include information about systemic disease conditions, the use of drugs such as antibiotics that foster the growth of yeast, dietary habits, stress, and other factors that alter the resistance of vaginal tissue to infections. A physical examination usually is done to evaluate the nature of the discharge and its effects on the genital structures. Treatment is directed at the cause of the disorder.

Cancer of the Vagina

Primary cancers of the vagina are extremely rare. They account for approximately 3% of all cancers of the female reproductive system. Approximately 85% to 90% of primary vaginal cancers are squamous cell carcinomas. Adenocarcinoma of the vagina is a rare tumor that is seen almost exclusively in women exposed in utero to diethylstilbestrol (DES). DES is a nonsteroidal synthetic estrogen that was commonly prescribed between 1940 and 1971 to prevent miscarriage. Fortunately, less than 0.14% of women exposed to DES actually develop adenocarcinoma. Vaginal cancers may also result from local extension of cervical cancer, from local irritation such as occurs with prolonged use of a pessary, or from exposure to sexually transmitted herpesvirus or HPV.

Disorders of the Uterine Cervix

The cervix is composed of two distinct types of tissue. The exocervix, or visible portion, is covered with stratified epithelium, which also lines the vagina. The endocervical canal is lined with columnar epithelium (see Chapter 1). The junction of these two tissue types (i.e., squamocolumnar junction) appears at various locations on the cervix at different points in a woman’s life (Fig. 34-7). During periods of high estrogen production, particularly fetal existence, menarche, and the first pregnancy, the cervix everts or turns outward, exposing the columnar epithelium to the vaginal environment. The combination of estrogen and low vaginal pH leads to a gradual transformation from columnar to squamous epithelium—a process called metaplasia (see Chapter 2). The dynamic area of change where metaplasia occurs is called the transformation zone. The transformation zone is a critical area for the development of cervical cancer. During metaplasia, the newly developed squamous epithelial cells are vulnerable to the development of dysplastic changes.

The process of transformation is increased by trauma and infections occurring during the reproductive years. As the squamous epithelium expands and obliterates the surface columnar papillae, it covers and obstructs crypt openings, with trapping of mucus in the deeper crypts (glands) to form retention cysts, called nabothian cysts. These are benign cysts that require no treatment unless they become so numerous that they cause cervical enlargement. The nabothian cyst farthest away from the external cervical os indicates the outer aspect of the transformation zone.

Cervicitis and Cervical Polyps

Cervicitis is an acute or chronic inflammation of the cervix. Acute cervicitis may result from the direct infection of the cervix or may be secondary to a vaginial or uterine infection. It
Carcinoma of the cervix is often considered a sexually transmitted disease. A preponderance of evidence suggests a causal link between HPV infection and uterine cancer. Certain strains of HPV have been identified in invasive carcinoma of the cervix, whereas others are associated more often with dysplasia or carcinoma in situ. The strongest link is with HPV types 16, 18, 31, and 33 (see Chapter 35). Because these viruses are spread by sexual contact, their association with cervical cancer provides a tempting hypothesis to explain the relation between sexual practices and cervical cancer. Other factors such as smoking, nutrition, and coexisting sexual partners may play a contributing role in determining whether a woman with HPV infection develops cervical cancer. The recent development of an HPV type 16 vaccine offers hope for the future prevention of cervical cancer.

Precursor Lesions. One of the most important advances in the early diagnosis and treatment of cancer of the cervix was made possible by the observation that this cancer arises from precursor lesions, which begin with the development of atypical (i.e., dysplasia) cervical cells. Atypical cells differ from normal cervical squamous epithelium. There are changes in the nuclear and cytoplasmic parts of the cell and more variation in cell size and shape (i.e., dysplasia). These atypical cells gradually progress to carcinoma in situ, which is localized to the epithelial layer, to invasive cancer of the cervix. Carcinoma in situ is localized to the epithelial layer, whereas invasive cancer of the cervix spreads to deeper layers. A system of grading devised to describe the dysplastic changes of cancer precursors uses the term cervical intraepithelial neoplasia (CIN). The CIN system uses the thickness of the epithelial layer involvement as a means of grading the dysplastic changes (see Table 34-2).

The Pap Smear. There are no specific signs or symptoms of cervical dysplasia or cancer in situ. A presumptive diagnosis is made by Pap smear studies of an asymptomatic population with no visible cervical changes. The purpose of the Pap smear (see Chapter 5) is to detect the presence of abnormal cells on the surface of the cervix or in the endocervix. This test detects precancerous and cancerous lesions. Although the American Cancer Society has suggested that the Pap smear need not be done annually if there have been three negative tests in succes-
sion, many clinicians maintain that performing an annual test is the safest course to follow. If the woman has risk factors, such as previous HPV infection, DES exposure in utero, or a strong family history of cervical cancer, more frequent Pap smears may be recommended.

It has been estimated that approximately 15% to 25% of women with intraepithelial lesions have normal Pap smear results. New techniques of specimen collection, slide preparation and processing, and computer-assisted evaluation of Pap smears are being evaluated and offer the hope of improved accuracy in the diagnosis of precancerous cervical changes.

**Squamous Cell Cervical Carcinoma.** The majority of cervical cancers are squamous cell carcinomas. Cancers of the cervix have a long latent period; untreated dysplasia or CIN gradually progresses to carcinoma in situ, which may remain static for 7 to 10 years before it becomes invasive. After the preinvasive period, growth may be rapid, and survival rates decline significantly, depending on the extent of disease at the time of diagnosis.

Diagnosis of cervical cancer requires pathologic confirmation. Although the Pap smear has been shown to be a cost-effective cancer prevention method, it remains a screening method, not a diagnostic method. Pap smear results demonstrating squamous intraepithelial lesions often require further evaluation by colposcopy. This is a vaginal examination that is done using a colposcope, an instrument that affords a well-lit and magnified stereoscopic view of the cervix. A biopsy sample may be obtained from suspect areas and examined microscopically. A diagnostic cone biopsy, which involves the removal of a cone-shaped wedge of cervix, may be indicated when a lesion is partly or completely beyond colposcopic view.

**Disorders of the Uterus**

**Infectious Disorders of the Uterus and Pelvic Structures**

The uterus and pelvic structures are subject to infections by a number of agents, including *N. gonorrhoeae* and *C. trachomatis*, as well as endogenous microorganisms such as anaerobes, *Haemophilus influenzae*, enteric gram-negative rods, and *Streptococci*. Tuberculosis salpingitis is rare in the United States but more common in developing countries.

**Endometritis.** Inflammation or infection of the endometrium is an ill-defined entity that produces variable symptoms. Endometritis can occur as a postpartum or postabortal infection, with gonococcal or chlamydial salpingitis, or after instrumentation or surgery, or can be associated with an intrauterine device. Abnormal vaginal bleeding, mild to severe uterine tenderness, fever, malaise, and foul-smelling discharge have been associated with endometritis, but the clinical picture is variable. Treatment involves oral or intravenous antibiotic therapy, depending on the severity of the condition.

**Pelvic Inflammatory Disease.** Pelvic inflammatory disease (PID) is an inflammation of the upper reproductive tract that involves the uterus (endometritis), fallopian tubes (salpingitis), or ovaries (oophoritis). Most women with acute salpingitis have *N. gonorrhoeae* or *C. trachomatis* identified in the reproductive tract. PID is a polymicrobial infection, and the cause varies by geographic location and population.

The organisms ascend through the endocervical canal to the endometrial cavity and then to the tubes and ovaries. The endocervical canal is slightly dilated during menstruation, allowing bacteria to gain entrance to the uterus and other pelvic structures. After entering the upper reproductive tract, the organisms multiply rapidly in the favorable environment of the sloughing endometrium and ascend to the fallopian tube. Factors that predispose women to the development of PID include an age of 16 to 24 years, unmarried status, nulliparity, history of multiple sexual partners, and previous history of PID.

The symptoms of PID include lower abdominal pain, which may start just after a menstrual period; purulent cervical discharge; pelvic tenderness; and an excessively painful cervix. Fever (>101°F), increased erythrocyte sedimentation rate, and an elevated white blood cell count (>10,000 cells/mL)
Diagnosis is based on the presence of lower abdominal pain and pelvic or cervical tenderness. A newer test involves measurement of C-reactive protein in the blood. Elevated C-reactive protein levels equate with inflammation. Endocervical cultures may be done to document the presence of *N. gonorrhoeae* or *C. trachomatis*. Transvaginal ultrasonography or imaging techniques may be used. Laparoscopy is often used to confirm a diagnosis of PID.

Treatment is aimed at preventing complications, which can include pelvic adhesions, infertility, ectopic pregnancy, chronic abdominal pain, and tubo-ovarian abscesses. It may involve hospitalization with intravenous administration of antibiotics. If the condition is diagnosed early, outpatient antibiotic therapy may be sufficient.

**Endometriosis**

Endometriosis is the condition in which functional endometrial tissue is found in ectopic sites outside the uterus. The site may be the ovaries, broad ligaments, pouch of Douglas (cul-de-sac), pelvis, vagina, vulva, perineum, or intestines. Rarely, endometrial implants have been found in the nostrils, umbilicus, lungs, and limbs.

The cause of endometriosis is unknown. There appears to have been an increase in its incidence in the developed Western countries during the past four to five decades. Approximately 10% to 15% of premenopausal women have some degree of endometriosis. The incidence may be higher in women with infertility (25% to 40%) or women younger than 20 years of age with chronic pelvic pain (45% to 70%). It is more common in women who have postponed childbearing. Risk factors for endometriosis may include early menarche; regular periods with shorter cycles (<27 days), longer duration (>7 days), or heavier flow; increased menstrual pain; and other first-degree relatives with the condition.

Several theories attempt to account for endometriosis. One theory suggests that menstrual blood containing fragments of endometrium is forced upward through the fallopian tubes into the peritoneal cavity. Retrograde menstruation is not an uncommon phenomenon, and it is unknown why endometrial cells implant and grow in some women but not in others. Another proposal is that dormant, immature cellular elements from embryonic development persist into adult life and develop into ectopic endometrial tissue. Another theory suggests that the endometrial tissue may metastasize through the lymphatics or vascular system. Altered cellular immunity and genetic components also have been studied as contributing factors to the development of endometriosis.

The gross pathologic changes that occur in endometriosis differ with location and duration. In the ovary, the endometrial tissue may form cysts (i.e., endometriomas filled with old blood that resembles chocolate syrup [chocolate cysts]). Rupture of these cysts can cause peritonitis and adhesions. Elsewhere in the pelvis, the tissue may take the form of small hemorrhagic lesions, some of which may be surrounded by scar tissue. These ectopic implants respond to hormonal stimulation in the same way normal endometrium does, becoming proliferative, then secretory, and finally undergoing menstrual breakdown. Bleeding into the surrounding structures can cause pain and the development of significant pelvic adhesions. Extensive fibrotic tissue can develop and cause bowel obstruction.

Endometriosis may be difficult to diagnose because its symptoms mimic those of other pelvic disorders, and the severity of the symptoms does not always reflect the extent of the disease. The classic triad of dysmenorrhea, dyspareunia, and infertility strongly suggests endometriosis. Accurate diagnosis can be accomplished only through laparoscopy. This minimally invasive surgery allows direct visualization of pelvic organs to determine the presence and extent of endometrial lesions.

Treatment goals for endometriosis are pain management or restoration of fertility. Treatment modalities fall into three cat-
categories: pain relief, endometrial suppression, and surgery. In young women, who have no fertility concerns, simple observation and antiprostaglandin analogs (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]) may be sufficient treatment. The use of hormones to induce physiologic amenorrhea is based on the observation that pregnancy affords temporary relief by inducing atrophy of the endometrial tissue.

Surgery is the most definitive therapy for many women with endometriosis. With the advent of lasers, in-depth treatment of endometriosis or pelvic adhesions can be accomplished by means of laparoscopy.16 Radical treatment involves total hysterectomy and bilateral salpingo-oophorectomy (i.e., removal of the fallopian tubes and ovaries) when the symptoms are unbearable or the woman’s childbearing is completed.

Treatment offers relief but not cure. Recurrence of endometriosis is not uncommon, regardless of the treatment (except for radical surgery). Pregnancy may delay, but does not preclude, recurrence.

**Adenomyosis**

Adenomyosis is the condition in which endometrial glands and stroma are found within the myometrium, interspersed between the smooth muscle fibers. It is thought that events associated with repeated pregnancies, deliveries, and uterine involution may cause the endometrium to be displaced throughout the myometrium. In contrast to endometriosis, which usually is a problem of young, infertile women, adenomyosis typically is found in multiparous women in their late fourth or fifth decade. Up to 70% of these women have a retrospective history of painful, heavy periods.17

The diagnosis of adenomyosis often occurs as an incidental finding in a uterus removed for symptoms indicative of myoma or hyperplasia. Adenomyosis resolves with menopause. Conservative therapy using oral contraceptives or gonadotropin-releasing hormone (GnRH) agonists is the first choice for treatment. Hysterectomy (with preservation of the ovaries in premenopausal women) is considered when this approach fails.17

**Endometrial Cancer**

Endometrial cancer is the most common invasive cancer of the female reproductive tract. It accounts for 7% of all invasive cancers in women, excluding skin cancers.2 There is now an estimated 34,000 new diagnoses of endometrial cancer a year, compared with 13,000 new invasive cervical cancers.2

Endometrial cancer occurs more frequently in older women (peak ages of 55 to 65 years) and is uncommon in women younger than 40 years of age. A major risk factor for endometrial cancer is prolonged estrogenic stimulation with excessive growth (i.e., hyperplasia) of the endometrium. Obesity, anovulatory cycles, conditions that alter estrogen metabolism, estrogen-secreting neoplasms, and unopposed estrogen therapy all increase the risk of endometrial cancer.21 Estrogens are synthesized in body fats from adrenal and ovarian androgen precursors; endometrial hyperplasia and endometrial cancer appear to be related to obesity. The degree of risk correlates with body weight, with the risk increasing 10-fold for women who are more than 50 pounds overweight.2 Ovulatory dysfunction that causes infertility at any age or occurs with declining ovarian function in perimenopausal women also can result in unopposed estrogen and increase the risk of endometrial cancer. Diabetes mellitus, hypertension, and polycystic ovary syndrome are conditions that alter estrogen metabolism and elevate estrogen levels.

Endometrial cancer risk also is increased in women with estrogen-secreting granulosa cell tumors and in those receiving unopposed estrogen therapy. It is the presence of progesterone in the second half of the normal menstrual cycle that matures the endometrium and the withdrawal of progesterone that ultimately results in endometrial sloughing. Long-term unopposed estrogen exposure without periodic addition of progesterone allows for continued endometrial growth and the development of hyperplasia, with or without the presence of atypical cells. A sharp increase in endometrial cancer was seen during the 1970s among middle-aged women who had received unopposed estrogen therapy (i.e., estrogen therapy without progestrone) for menopausal symptoms. It was later determined that it was not the estrogen exposure that increased the risk of cancer, but administration of estrogen without administration of progestrone. Tamoxifen, a drug that blocks estrogen receptor sites and is used in the treatment of breast cancer, exerts a weak estrogenic effect on the endometrium and represents another exogenous risk factor for endometrial cancer.

A small subset of women in whom endometrial cancer develops do not exhibit increased estrogen levels or pre-existing hyperplasia. These women usually acquire the disease at an older age. These tumors arise from clones of cancer-initiated mutant cells and are more poorly differentiated. This type of endometrial cancer usually is associated with a poorer prognosis than is the endometrial cancer that is associated with prolonged estrogen stimulation and endometrial hyperplasia.21

The major symptom of endometrial hyperplasia or overt endometrial cancer is abnormal, painless bleeding. In menstruating women, this takes the form of bleeding between periods or excessive, prolonged menstrual flow. In postmenopausal women, any bleeding is abnormal and warrants investigation. Abnormal bleeding is an early warning sign of the disease, and because endometrial cancer tends to be slow growing in its early stages, the chances of cure are good if prompt medical care is sought. Later signs of uterine cancer may include cramping, pelvic discomfort, postcoital bleeding, lower abdominal pressure, and enlarged lymph nodes.

Although the Pap smear can identify a small percentage of endometrial cancers, it is not a good screening test for the tumor. Endometrial biopsy is far more accurate. Dilatation and curettage (D & C), which consists of dilating the cervix and scraping the uterine cavity, is the definitive procedure for diagnosis because it provides a more thorough evaluation. Transvaginal ultrasonography may be used to determine the endometrial thickness as an indicator of hypertrophy and possible neoplastic change.

The prognosis for endometrial cancer depends on the clinical stage of the disease when it is discovered and its histologic grade and type. Surgery and radiation therapy are the most successful methods of treatment for endometrial cancer. With early diagnosis and treatment, the 5-year survival rate is approximately 90%. This decreases to 20% for more advanced stages of the disease.

**Leiomyomas**

Leiomyomas are benign neoplasms of smooth muscle origin. They also are known as myomas and sometimes are called fibroids. These are the most common form of pelvic tumor and
are believed to occur in one of every four or five women older than 35 years of age. They are seen more often and their rate of growth is more rapid in black women than in white women. Leiomyomas usually develop in the corpus of the uterus; they may be submucosal, subserosal, or intramural (Fig. 34-9). Intramural fibroids are embedded in the myometrium. They are the most common type of fibroid and present as a symmetric enlargement of the nonpregnant uterus. Subserosal tumors are located beneath the perimetrium of the uterus. These tumors are recognized as irregular projections on the uterine surface; they may become pedunculated, displacing or impinging on other genitourinary structures and causing hydroureter or bladder problems. Submucosal fibroids displace endometrial tissue and are more likely to cause bleeding, necrosis, and infection than either of the other types.

Leiomyomas are asymptomatic approximately half of the time and may be discovered during a routine pelvic examination, or they may cause menorrhagia (excessive menstrual bleeding), anemia, urinary frequency, rectal pressure/constipation, abdominal distention, and infrequently pain. Their rate of growth is variable, but they may increase in size during pregnancy or with exogenous estrogen stimulation (i.e., oral contraceptives or menopausal estrogen replacement therapy). Interference with pregnancy is rare unless the tumor is submucosal and interferes with implantation or obstructs the cervical outlet. These tumors may outgrow their blood supply, become infarcted, and undergo degenerative changes.

Most leiomyomas regress with menopause, but if bleeding, pressure on the bladder, pain, or other problems persist, hysterectomy may be required. Myomectomy (removal of just the tumors) can be done to preserve the uterus for future childbearing. Cesarean section may be recommended if the uterine cavity is entered during myomectomy. Hypothalamic GnRH may be used to suppress leiomyoma growth before surgery. Uterine artery embolization is a nonsurgical therapy for management of heavy bleeding.

Disorders of Pelvic Support and Uterine Position

The muscular floor of the pelvis is a strong, slinglike structure that supports the uterus, vagina, urinary bladder, and rectum (Fig. 34-10). In the female anatomy, nature is faced with the problems of supporting the pelvic viscera against the force of gravity and increases in intra-abdominal pressure associated with coughing, sneezing, defecation, and laughing while at the same time allowing for urination, defecation, and normal reproductive tract function, especially the delivery of an infant.

Disorders of Pelvic Support

The uterus and the pelvic structures are maintained in proper position by the uterosacral ligaments, round ligaments, broad ligament, and cardinal ligaments. The two cardinal ligaments maintain the cervix in its normal position. The uterosacral ligaments normally hold the uterus in a forward position.
Variations in Uterine Position

Variations in the position of the uterus are common. Some variations are innocuous; others, which may be the result of weakness and relaxation of the perineum, give rise to various
ticity and muscle tone occurs. Even in a woman who has not borne children, the combination of aging and postmenopausal changes may give rise to problems related to relaxation of the pelvic support structures. It also may result from pelvic tumors and neurologic conditions, such as spina bifida and diabetic neuropathy, that interrupt the innervation of pelvic muscles. The three most common conditions associated with this relaxation are cystocele, rectocele, and uterine prolapse. These may occur separately or together.

Cystocele is a herniation of the bladder into the vagina (Fig. 34-11 B). It occurs when the normal muscle support for the bladder is weakened, and the bladder sags below the uterus. The vaginal wall stretches and bulges downward because of the force of gravity and the pressure from coughing, lifting, or straining at stool. The bladder herniates through the anterior vaginal wall, and a cystocele forms. The symptoms include an annoying bearing-down sensation, difficulty in emptying the bladder, frequency and urgency of urination, and cystitis. Stress incontinence may occur at times of increased abdominal pressure, such as during squatting, straining, coughing, sneezing, laughing, or lifting.

Rectocele is the herniation of the rectum into the vagina (Fig 34-11 A). It occurs when the posterior vaginal wall and underlying rectum bulge forward, ultimately protruding through the introitus as the pelvic floor and perineal muscles are weakened. The symptoms include discomfort because of the protrusion of the rectum and difficulty in defecation. Digital pressure (i.e., splinting) on the bulging posterior wall of the vagina may become necessary for defecation.

Uterine prolapse is the bulging of the uterus into the vagina that occurs when the primary supportive ligaments (i.e., cardinal ligaments) are stretched. Prolapse is ranked as first, second, or third degree, depending on how far the uterus protrudes through the introitus. First-degree prolapse shows some descent, but the cervix has not reached the introitus. In second-degree prolapse, the cervix or part of the uterus has passed through the introitus. The entire uterus protrudes through the vaginal opening in third-degree prolapse (i.e., procidentia). Prolapse often is accompanied by perineal relaxation, cystocele, or rectocele. The symptoms associated with uterine prolapse result from irritation of the exposed mucous membranes of the cervix and vagina and the discomfort of the protruding mass.

Most of the disorders of pelvic relaxation require surgical correction. These are elective surgeries and usually are deferred until after the childbearing years. The symptoms associated with the disorders often are not severe enough to warrant surgical correction. In other cases, the stress of surgery is contraindicated because of other physical disorders; this is particularly true of older women, in whom many of these disorders occur. Kegel exercises, which strengthen the pubococcygeus muscle, may be helpful in cases of mild cystocele or rectocele or after surgical repair to help maintain the improved function (see Chapter 25). In women with uterine prolapse, a pessary may be inserted to hold the uterus in place and may stave off surgical intervention in women who want to have children or in older women for whom the surgery may pose a significant health risk.
problems that compromise the structural integrity of the pelvic floor, particularly after childbirth.

The uterus usually is flexed approximately 45 degrees anteriorly, with the cervix positioned posteriorly and downward in the anteverted position. When the woman is standing, the angle of the uterus is such that it lies practically horizontal, resting lightly on the bladder. Asymptomatic, normal variations in the axis of the uterus in relation to the cervix (i.e., flexion) and physiologic displacements that arise after pregnancy or with pathology of the cul-de-sac include anteflexion, retroflexion, and retroversion (Fig. 34-12). An anteflexed uterus is flexed forward on itself. Retroflexion is flexion backward at the isthmus. Retroversion describes the condition in which the uterus inclines posteriorly while the cervix remains tilted forward. Simple retroversion is the most common variation. It usually is a congenital condition caused by a short anterior vaginal wall and relaxed uterosacral ligaments. Retroversion also can follow certain diseases, such as endometriosis and PID, which produce fibrous tissue adherence with retraction of the fundus posteriorly. Large leiomyomas can also cause the uterus to move into a posterior position. Symptoms of retroversion include dyspareunia with deep penetration and low back pain with menses.

**Disorders of the Ovaries**

Disorders of the ovaries frequently cause menstrual and fertility problems. Benign conditions of the ovaries can present as primary lesions of the ovarian structures or as secondary disorders related to hypothalamic, pituitary, or adrenal dysfunction.

**Ovarian Cysts**

Cysts are the most common form of ovarian tumor. Many are benign. A follicular cyst is one that results from occlusion of the duct of the follicle. Each month, several follicles begin to develop and are blighted at various stages of development. These follicles form cavities that fill with fluid, producing a cyst. The dominant follicle normally ruptures to release the egg (i.e., ovulation) but occasionally persists and continues growing. Likewise, a luteal cyst is a persistent cystic enlargement of the corpus luteum that is formed after ovulation and does not regress in the absence of pregnancy. Functional cysts are asymptomatic unless there is substantial enlargement or bleeding into the cyst. This can cause considerable discomfort or a dull, aching sensation on the affected side. The cyst may become twisted or may rupture into the intra-abdominal cavity (Fig. 34-13). However, usually these regress spontaneously.

**Polycystic Ovary Syndrome.** Ovarian dysfunction associated with infrequent or absent menses in obese, infertile women was first reported in the 1930s by Stein and Leventhal, for whom the syndrome was originally named. Polycystic ovary syndrome (PCOS) is characterized by numerous cystic follicles or follicular cysts. Once thought to be relatively rare, it appears that this clinical entity is one of the most common endocrine disorders among women during the reproductive years. PCOS is characterized by varying degrees of hirsutism, acne, obesity, and anovulation and infertility, and often is associated with hyperinsulinemia or insulin resistance (see Chapter 31).

Chronic anovulation can increase a woman’s risk of endometrial cancer, cardiovascular disease, and hyperinsulinemia leading to diabetes mellitus. This syndrome has been the subject of considerable research. Chronic anovulation, causing amenorrhea or irregular menses, is now thought to be the underlying cause of the bilaterally enlarged “polycystic” ovaries (Fig. 34-14). Thus, the appearance of the ovary is a sign of the disorder, not the disease itself. The precise etiology of this condition is still being de-

![FIGURE 34-12](image1) Variations in uterine position.

![FIGURE 34-13](image2) Follicle cyst of the ovary. The rupture of this thin-walled follicular cyst led to intra-abdominal hemorrhage. The cyst has been opened and rupture site indicated by the dowel stick. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1002]. Philadelphia: Lippincott Williams & Wilkins)
ovulation when obesity is present. When medication is ineffective, laser surgery to puncture the multiple follicles may restore normal ovulatory function, although adhesions formation is a potential problem. If fertility is not desired, oral contraceptives or cyclic progesterone can induce regular menses and prevent the development of endometrial hyperplasia caused by unopposed estrogen.

Benign and Functioning Ovarian Tumors

Benign ovarian tumors can be composed of epithelial tissue, endometriosis tissue, fibrocytes and collagen fibers, or primordial germ cells. Benign epithelial tumors are almost always serous or mucinous. They generally occur in women between the ages of 20 and 60 years and are often large, growing 15 to 30 cm in diameter. They are often cystic, thus the term cystadenomas. However, some of the cystadenomas are considered to have low malignant potential. Endometriomas are the “chocolate cysts” that develop secondary to ovarian endometriosis (see the endometriosis section earlier in this chapter). Ovarian fibromas are connective tissue tumors composed of fibrocytes and collagen. They range in size from 6 to 20 cm. Cystic teratomas, or dermoid cysts, are derived from primordial germ cells and are composed of various combinations of well-differentiated ectodermal, mesodermal, and endodermal elements. Not uncommonly, they contain sebaceous material, hair, or teeth.

Benign ovarian tumors are usually asymptomatic unless their size is sufficient to cause abdominal enlargement. Treatment for all ovarian tumors is surgical excision. Ovarian tissue that is not affected by the tumor can be left intact if frozen-section analysis does not reveal malignancy. When ovarian tumors are very large, as is frequently the case with serous or mucinous cystadenomas, the entire ovary must be removed.

The three types of functioning ovarian tumors are estrogen secreting, androgen secreting, and mixed estrogen-androgen secreting. These tumors may be benign or cancerous. One such tumor, the granulosa cell tumor, is associated with excess estrogen production. When it develops during the reproductive period, the persistent and uncontrolled production of estrogen interferes with the normal menstrual cycle, causing irregular bleeding, endometrial hyperplasia, or amenorrhea and fertility problems. When it develops after menopause, it causes postmenopausal bleeding, stimulation of the glandular tissues of the breast, and other signs of renewed estrogen production. Androgen-secreting tumors inhibit ovulation and estrogen production. They tend to cause hirsutism and development of masculine characteristics, such as baldness, acne, oily skin, breast atrophy, and deepening of the voice. The treatment of functioning ovarian tumors is surgical removal.

Ovarian Cancer

Ovarian cancer is the second most common female genitourinary cancer and the most lethal. In 2000, 23,100 new cases of ovarian cancer were reported in the United States, two thirds of which were in advanced stages of the disease. Of these women, it is estimated that 14,000 will die of the disease, accounting for 53% of all deaths caused by gynecological cancers. The incidence of ovarian cancer increases with age, being greatest between 65 and 84 years of age. Ovarian cancer is difficult to diagnose, and as many as 75% of women have metastatic disease before the time of discovery.
The most significant risk factor for ovarian cancer appears to be ovulatory age—the length of time during a woman's life when her ovarian cycle is not suppressed by pregnancy, lactation, or oral contraceptive use. The incidence of ovarian cancer is much lower in countries where women bear numerous children than in the United States. Family history also is a significant risk factor for ovarian cancer. Women with two or more first- or second-degree relatives who have had site-specific ovarian cancer have as much as a 50% risk for development of the disease. A high-fat Western diet and use of powders containing talc in the genital area are other factors that have been linked to the development of ovarian cancer.

Cancer of the ovary is complex because of the diversity of tissue types that originate in the ovary. As a result of this diversity, there are several types of ovarian cancers. Malignant neoplasms of the ovary can be divided into three categories: epithelial tumors, germ cell tumors, and gonadal stromal tumors. Epithelial tumors account for approximately 90% of cases. These different cancers display various degrees of virulence, depending on the type of tumor and degree of differentiation involved. A well-differentiated cancer of the ovary may have produced symptoms for many months and still be found operable at the time of surgery. A poorly differentiated tumor may have been clinically evident for only a few days but found to be widespread and inoperable. Often no correlation exists between the duration of symptoms and the extent of the disease.

Most cancers of the ovary produce no symptoms or the symptoms are so vague that the woman seldom seeks medical care until the disease is far advanced. These vague discomforts include abdominal distress, flatulence, and bloating, especially after ingesting food. These gastrointestinal manifestations may precede other symptoms by months. It is not fully understood why the initial symptoms of ovarian cancer are manifested as gastrointestinal disturbances. It is thought that biochemical changes in the peritoneal fluids may irritate the bowel or that pain originating in the ovary may be referred to the abdomen and be interpreted as a gastrointestinal disturbance. Clinically evident ascites (i.e., fluid in the peritoneal cavity) is seen in approximately one fourth of women with malignant ovarian tumors and is associated with a worse prognosis.

At present, there are no good screening tests or other early methods of detection for ovarian cancer. The serum tumor marker CA-125 is a cell surface antigen that can be used in monitoring therapy and recurrences when preoperative levels have been elevated. Because it lacks sensitivity and specificity, CA-125 has limited value as a single screening test. Transvaginal ultrasonography (TVS) can be used to evaluate ovarian masses for malignant potential. However, cost has prohibited its use as a universal screening tool. The National Institutes of Health Consensus Panel convened in 1995 recommended against widespread screening of women for ovarian cancer, especially after ingesting food. These gastrointestinal manifestations may precede other symptoms by months. It is not fully understood why the initial symptoms of ovarian cancer are manifested as gastrointestinal disturbances. It is thought that biochemical changes in the peritoneal fluids may irritate the bowel or that pain originating in the ovary may be referred to the abdomen and be interpreted as a gastrointestinal disturbance. Clinically evident ascites (i.e., fluid in the peritoneal cavity) is seen in approximately one fourth of women with malignant ovarian tumors and is associated with a worse prognosis.

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When ovarian cancer is suspected, surgical evaluation is required for diagnosis, complete and accurate staging, and cytoreduction and debulking procedures to reduce the size of the tumor. Recommendations regarding treatment beyond surgery and prognosis depend on the stage of the disease.

In summary, the external genitalia are affected by disorders that affect skin on other parts of the body. Bartholin’s cysts are the result of occluded ducts in Bartholin’s glands. They often are painful and can become infected. Vaginal dyschromies are characterized by thinning and hyperplastic thickening of vulvar tissues. Vulvodynia is a chronic vulvar pain syndrome with several classifications and variable treatment results. Cancer of the vulva, which accounts for 4% of all female genitourinary cancers, is associated with HPV infections.

The normal vaginal ecology depends on the delicate balance of hormones and bacterial flora. Vaginitis or inflammation of the vagina is characterized by vaginal discharge and burning, itching, redness, and swelling of vaginal tissues. It may be caused by chemical irritants, foreign bodies, and infectious agents. Primary cancers of the vagina are uncommon, accounting for 3% of all cancers of the female reproductive system. Daughters of women treated with DES to prevent miscarriage are at increased risk for the development of adenocarcinoma of the vagina.

Disorders of the cervix and uterus include inflammatory conditions (i.e., cervicitis and endometritis), cancer (i.e., cervical and endometrial cancer), endometriosis, and leiomyomas. Acute cervicitis, which may be caused by a number of agents, may result from the direct infection of the cervix or may be secondary to a vaginal or uterine infection. Chronic cervicitis represents a low-grade inflammatory process resulting from trauma or nonspecific infectious agents. Cervical cancer arises from precursor lesions that can be detected on a Papsmear, and if detected early, is the most easily cured of all the cancers of the female reproductive system.

PID is an inflammation of the upper reproductive tract that involves the uterus (endometritis), fallopian tubes (salpingitis), or ovaries (oophoritis). It is most commonly caused by N. gonorrhoeae or C. trachomatis. Endometriosis is the condition in which functional endometrial tissue is found in ectopic sites outside the uterus. It causes dysmenorrhea, dyspareunia, and infertility.

Adenomyosis is the condition in which endometrial glands and stroma are found in the myometrium interspersed between the smooth muscle fibers. Leiomyomas are benign uterine wall neoplasms of smooth muscle origin. They can develop in the corpus of the uterus and can be submucosal, subserosal, or intramural. Submucosal fibroids displace endometrial tissue and are more likely to cause bleeding, necrosis, and infection than either of the other types. Endometrial cancer is the most common cancer found in the female pelvis; it occurs more than twice as often as cervical cancer. Prolonged estrogen stimulation with hyperplasia of the endometrium has been identified as a major risk factor for endometrial cancer.

Alterations in pelvic support frequently occur because of weaknesses and relaxation of the pelvic floor and perineum. Cystocele and rectocele involve herniation of the bladder or rectum into the vagina. Uterine prolapse occurs when the uterus bulges into the vagina. Pelvic relaxation disorders typically result from overstretching of the perineal supporting muscles during pregnancy and childbirth. The loss of elasticity in these structures is a normal accompaniment of aging contributes to these problems. Variations in uterine position are common; they include anteflexion, in which the uterus is...
Disorders of the ovaries include benign cysts, functioning ovarian tumors, and cancer of the ovary; they usually are asymptomatic unless there is substantial enlargement or bleeding into the cyst, or the cyst becomes twisted or ruptures. Polycystic ovary syndrome is characterized by numerous cystic follicles or follicular cysts; it causes various degrees of hirsutism, obesity, and infertility. Benign ovarian tumors consist of endometriomas, which are chocolate cysts that develop secondarily to ovarian endometriosis; ovarian fibromas, which are connective tissue tumors composed of fibrocytes and collagen; and cystic teratomas or dermoid cysts, which are derived from primordial germ cells and are composed of various combinations of well-differentiated ectodermal, mesodermal, and endodermal elements. Functioning ovarian tumors are of three types: estrogen secreting, androgen secreting, and mixed estrogen-androgen secreting, and may be benign or cancerous. Cancer of the ovary is the second most common female genitourinary cancer and the most lethal. It can be divided into three categories: epithelial tumors, germ cell tumors, and gonadal stromal tumors. There are no effective screening methods for ovarian cancer, and often the disease is well advanced at the time of diagnosis.

Menstrual Disorders

Between menarche (i.e., first menstrual bleeding) and menopause (i.e., last menstrual bleeding), the female reproductive system undergoes cyclic changes called the menstrual cycle. This includes the maturation and release of oocytes from the ovary during ovulation and periodic vaginal bleeding resulting from the shedding of the endometrial lining. It is not necessary for a woman to ovulate to menstruate; anovulatory cycles do occur. The menstrual cycle produces changes in the breasts, uterus, skin, ovaries, and perhaps other unidentified tissues. Although each part of the system is essential to normal function, the ovaries are primarily responsible for controlling the cyclic changes and the length of the menstrual cycle. In most women in the middle reproductive years, menstrual bleeding occurs every 25 to 35 days, with a median length of 28 days.

Dysfunctional Menstrual Cycles

Normal menstrual function results from interactions among the central nervous system, hypothalamus, anterior pituitary, ovaries, and associated target tissues. Although each part of the system is essential to normal function, the ovaries are primarily responsible for controlling the cyclic changes and the length of the menstrual cycle. In most women in the middle reproductive years, menstrual bleeding occurs every 25 to 35 days, with a median length of 28 days.

KEY CONCEPTS

DYSFUNCTIONAL MENSTRUAL CYCLES

- The pattern of menstrual bleeding tends to be fairly consistent in most healthy women with regard to frequency, duration, and amount of flow.
- Dysfunctional bleeding in postpubertal women can take the form of absent or scanty periods, infrequent periods, excessive and irregular periods, excessive bleeding during periods, and bleeding between periods.
- When the basic pattern of bleeding is changed, it is most often due to a lack of ovulation and disturbances in the pattern of hormone secretion.
- When the basic pattern is undisturbed and there are superimposed episodes of bleeding or spotting, the etiology is more likely to be related to organic lesions or hematologic disorders.
in amount and duration, with the flow varying with the time and degree of estrogen stimulation and with the degree of estrogen withdrawal. A lack of progesterone can cause abnormal menstrual bleeding; in its absence, estrogen induces development of a much thicker endometrial layer with a richer blood supply. The absence of progesterone results from the failure of any of the developing ovarian follicles to mature to the point of ovulation, with the subsequent formation of the corpus luteum and production and secretion of progesterone.

Periodic bleeding episodes alternating with amenorrhea are caused by variations in the number of functioning ovarian follicles. If sufficient follicles are present and active and if new follicles assume functional capacity, high levels of estrogen develop, causing the endometrium to proliferate for weeks or even months. In time, estrogen withdrawal and bleeding develop. This can occur for two reasons: an absolute estrogen deficiency may develop when several follicles simultaneously degenerate, or a relative deficiency may develop as needs of the enlarged endometrial tissue mass exceed the capabilities of the existing follicles, even though estrogen levels remain constant. Estrogen and progesterone deficiency are associated with the absence of ovulation, thus the term anovulatory bleeding. Because the vasoconstriction and myometrial contractions that normally accompany menstruation are caused by progesterone, anovulatory bleeding seldom is accompanied by cramps, and the flow frequently is heavy. Anovulatory cycles are common among adolescents during the first several years after menarche, when ovarian function is becoming established, and among perimenopausal women, whose ovarian function is beginning to decline.

Dysfunctional menstrual cycles can originate as a primary disorder of the ovaries or as a secondary defect in ovarian function related to hypothalamic-pituitary stimulation. The latter can be initiated by emotional stress, marked variation in weight (i.e., sudden gain or loss), or nonspecific endocrine or metabolic disturbances. Organic causes of irregular menstrual bleeding include endometrial polyps, submucosal myoma (i.e., fibroid), blood dyscrasia, infection, endometrial cancer, polycystic ovarian disease, and pregnancy.

The treatment of dysfunctional bleeding depends on what is identified as the probable cause. The minimum evaluation should include a detailed history with emphasis on bleeding pattern and a physical examination. Endocrine studies (FSH: LH ratio, prolactin, testosterone, DHAS), β-hCG pregnancy test, endometrial biopsy, D & C with or without hysteroscopy, and progesterone withdrawal tests may be needed for diagnosis. If organic problems are excluded and alterations in hormone levels are the primary cause, treatment may include the use of oral contraceptives, cyclic progesterone therapy, or long-acting progesterone injections.

Amenorrhea

There are two types of amenorrhea: primary and secondary. Primary amenorrhea is the failure to menstruate by 16 years of age, or by 14 years of age if failure to menstruate is accompanied by absence of secondary sex characteristics. Secondary amenorrhea is the cessation of menses for at least 6 months in a woman who has established normal menstrual cycles. Primary amenorrhea usually is caused by gonadal dysgenesis, congenital Müllerian agenesis, testicular feminization, or a hypothalamic-pituitary-ovarian axis disorder. Causes of secondary amenorrhea include ovarian, pituitary, or hypothalamic dysfunction and destruction of the endometrial cavity by chronic infections such as tuberculosis or destruction of the endometrium by curettage (surgical scraping). Another cause is anorexia nervosa or participation in athletic activities to the extent that there is an alteration in the critical body fat-muscle ratio needed for menses to occur.

Diagnostic evaluation of amenorrhea resembles that for dysfunctional uterine bleeding, with the possible addition of a computed tomographic scan to exclude a pituitary tumor. Treatment is based on correcting the underlying cause and inducing menstruation with cyclic progesterone or combined estrogen-progesterone regimens.

Dysmenorrhea

Dysmenorrhea is pain or discomfort with menstruation. Although not usually a serious medical problem, it causes some degree of monthly disability for a significant number of women. There are two forms of dysmenorrhea: primary and secondary. Primary dysmenorrhea is menstrual pain that is not associated with a physical abnormality or pathology. It usually occurs with ovulatory menstruation beginning 6 months to 2 years after menarche. Symptoms may begin 1 to 2 days before menses, peak on the first day of flow, and subside within several hours to several days. Severe dysmenorrhea may be associated with systemic symptoms such as headache, nausea, vomiting, diarrhea, fatigue, irritability, dizziness, and syncope. The pain typically is described as dull, lower abdominal aching or cramping, spasmodic or colicky in nature, often radiating to the lower back, labia majora, or upper thighs.

Secondary dysmenorrhea is menstrual pain caused by specific organic conditions, such as endometriosis, uterine fibroids, adenomyosis, pelvic adhesions, or PID. Laparoscopy often is required for diagnosis of secondary dysmenorrhea if medication for primary dysmenorrhea is ineffective.

Treatment for primary dysmenorrhea is directed at symptom control. Although analgesic agents such as aspirin and acetaminophen may relieve minor uterine cramping or low back pain, prostaglandin synthetase inhibitors, such as ibuprofen, naproxen, mefenamic acid, and indomethacin, are more specific for dysmenorrhea. Ovulation suppression and symptomatic relief of dysmenorrhea can be instituted simultaneously with the use of oral contraceptives. Relief of secondary dysmenorrhea depends on identifying the cause of the problem. Medical or surgical intervention may be needed to eliminate the problem.

Premenstrual Syndrome

The premenstrual syndrome (PMS) is a distinct clinical entity characterized by a cluster of physical and psychological symptoms limited to 3 to 14 days preceding menstruation and relieved by onset of the menses. The incidence of PMS seems to increase with age. It is less common in women in their teens and 20s, and most of the women seeking help for the problem are in their mid-30s.

Although the causes of PMS are poorly documented, they probably are multifactorial. Like dysmenorrhea, it is only recently that PMS has been recognized as a bona fide disorder, rather than merely a psychosomatic illness.
The physical symptoms of PMS include painful and swollen breasts, bloating, abdominal pain, headache, and backache. Psychologically, there may be depression, anxiety, irritability, and behavioral changes. In some cases, there are puzzling alterations in motor function, such as clumsiness and altered handwriting. Women with PMS may report one or several symptoms, with symptoms varying from woman to woman and from month to month in the same patient. Signs and symptoms associated with this disorder are summarized in Table 34-3. PMS can significantly affect a woman’s ability to perform at normal levels. She may lose time from or function ineffectively at work. Family responsibilities and relationships may suffer. More crimes are committed by females during the premenstrual phase of the cycle, and more lives are lost to suicide during this period. The term *premenstrual dysphoric disorder* is a psychiatric diagnosis that has been developed to distinguish women whose symptoms are severe enough to interfere significantly with activities of daily living or in whom the symptoms are not relieved with the onset of menstruation, as is usually the case with PMS.31,32

Diagnosis focuses on identification of the symptom clusters by means of prospective charting for at least 3 months. A complete history and physical examination are necessary to exclude other physical causes of the symptoms. Depending on the symptom pattern, blood studies, including thyroid hormones and glucose tests, may be done. Psychosocial evaluation is helpful to exclude emotional illness that is merely exacerbated premenstrually.

Treatment of PMS is directed toward an integrated program of regular exercise, avoidance of caffeine, and a diet emphasizing complex carbohydrates. Foods high in simple sugars and alcohol should be avoided. Drug therapy should be used cautiously until well-controlled studies establish criteria for use and effective treatment results.

### Menopause and Aging Changes

Menopause is the cessation of menstrual cycles. Like menarche, it is more of a process than a single event. Most women stop menstruating between 48 and 55 years of age. Perimenopause (the years immediately surrounding menopause) precedes menopause by approximately 4 years and is characterized by menstrual irregularity and other menopausal symptoms. Climacteric is a more encompassing term that refers to the entire transition to the nonreproductive period of life. Premature ovarian failure describes the approximately 1% of women who experience menopause before the age of 40 years. A woman who has not menstruated for a full year or has an FSH level greater than 30 mIU/mL is considered menopausal.33

Menopause results from the gradual cessation of ovarian function and the resultant diminished levels of estrogen. Although estrogens derived from the adrenal cortex continue to circulate in a woman’s body, they are insufficient to maintain the secondary sexual characteristics in the same manner as ovarian estrogens. As a result, breast tissue, body hair, skin elasticity, and subcutaneous fat decrease; the ovaries and uterus diminish in size; and the cervix and vagina become pale and friable. Problems that can arise as a result of this urogenital atrophy include vaginal dryness, urinary stress incontinence, urgency, nocturia, vaginitis, and urinary tract infection. The woman may find intercourse painful and traumatic, although some type of vaginal lubrication may be helpful.

Systemically a woman may experience significant vasomotor instability secondary to the decrease in estrogens and the relative increase in other hormones, including FSH, LH, GnRH, dehydroepiandrosterone, androstenedione, epinephrine, corticotropin, β-endorphin, growth hormone, and calcitonin gene-related peptide. This instability may give rise to “hot flashes,” palpitations, dizziness, and headaches as the blood vessels dilate. Despite the association with these biochemical changes, the underlying cause of hot flashes is unknown.34 Tremendous variation exists in the onset, frequency, severity, and length of time that women experience hot flashes. When they occur at night and are accompanied by significant perspiration, they are referred to as *night sweats*. Insomnia as well as frequent awakening because of vasomotor symptoms can lead to sleep deprivation. A woman may experience irritability, anxiety, and depression as a result of these uncontrollable and unpredictable events.

Consequences of long-term estrogen deprivation include osteoporosis, due to an imbalance in bone remodeling (*i.e.*, bone resorption occurs at a faster rate than bone formation), and an increased risk for cardiovascular disease (atherosclerosis is accelerated), which is the leading cause of death for women after menopause.

Hormone replacement therapy (HRT) has recently come under scrutiny. Topical hormone preparations are available to treat symptoms related to vaginal atrophy. Selective estrogen receptor modulators (SERMs) may be used in place of estrogen to prevent osteoporosis.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>Irritability, anxiety, nervousness, fatigue, and exhaustion; increased physical and mental activity; lability; crying spells; depressions; inability to concentrate</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Craving for sweets or salts, lower abdominal pain, bloating, nausea, vomiting, diarrhea, constipation</td>
</tr>
<tr>
<td>Vascular</td>
<td>Headache, edema, weakness, or fainting</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Swelling and tenderness of the breasts, pelvic congestion, ovarian pain, altered libido</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Trembling of the extremities, changes in coordination, clumsiness, backache, leg aches</td>
</tr>
<tr>
<td>General</td>
<td>Weight gain, insomnia, dizziness, acne</td>
</tr>
</tbody>
</table>
In summary, between the menarche and menopause, the female reproductive system undergoes cyclic changes called the menstrual cycle. The normal menstrual function results from complex interactions among the hypothalamus, which produces GnRH, the anterior pituitary gland, which synthesizes and releases FSH, LH, and prolactin; the ovaries, which synthesize and release estrogens, progesterone, and androgens; and associated target tissues, such as the endometrium and the vaginal mucosa. Although each component of the system is essential for normal functioning, the ovarian hormones are largely responsible for controlling the cyclic changes and length of the menstrual cycle.

Menstrual disorders include dysfunctional menstrual cycles, dysmenorrhea, and PMS. Dysfunctional menstrual cycles produce amenorrhea, oligomenorrhea, metrorrhagia, or menorrhagia. Dysmenorrhea is characterized by pain or discomfort during menses. It can occur as a primary or secondary disorder. Primary dysmenorrhea is not associated with other disorders and begins soon after menarche. Secondary dysmenorrhea is caused by a specific organic condition, such as endometriosis or pelvic adhesions. It occurs in women with previously painless menses. PMS represents a cluster of physical and psychological symptoms that precede menstruation by 1 to 2 weeks.

Menopause is the cessation of ovarian function and menstrual cycles. It is accompanied by a decline in secondary sexual characteristics, vasomotor instability, and long-term consequences, including osteoporosis and increased rate of heart disease.

**DISORDERS OF THE BREAST**

Although anatomically separate, the breasts are functionally related to the female genitourinary system in that they respond to the cyclic changes in sex hormones and produce milk for infant nourishment. Most breast diseases may be described as benign or cancerous. Benign breast conditions are nonprogressive; however, some forms of benign disease increase the risk of malignant disease.

**Breast Structures**

The breasts, or mammary tissues, are located between the third and seventh ribs of the anterior chest wall and are supported by the pectoral muscles and superficial fascia. They are specialized glandular structures that have an abundant shared nervous, vascular, and lymphatic supply (Fig. 34-15). Structurally the breast consists of fat, fibrous connective tissue, and glandular tissue. The superficial fibrous connective tissue is attached to the skin, a fact that is important in the visual observation of skin movement over the breast during breast self-examination. The breast mass is supported by the fascia of the pectoralis major and minor muscles and by the fibrous connective tissue of the breast. Fibrous tissue ligaments, called Cooper’s ligaments, extend from the outer boundaries of the breast to the nipple area in a radial manner, like the spokes on a wheel. These ligaments further support the breast and form septa that divide the breast into 15 to 25 lobes. Each lobe consists of grapelike clusters, alveoli or glands, which are interconnected by ducts. Estrogen stimulates the growth of the ductile system, while progesterone stimulates the growth and development of the ductile and alveolar secretory epithelium.

The alveoli are lined with secretory cells capable of producing milk or fluid under the proper hormonal conditions (Fig. 34-16). The route of descent of milk and other breast secretions is from alveoli to duct, to intralobar duct, to lactiferous duct and reservoir, to nipple. Breast milk is produced secondary to complex hormonal changes associated with pregnancy. The breasts respond to the cyclic changes in the menstrual cycle with fullness and discomfort.

The nipple is made up of epithelial, glandular, erectile, and nervous tissue. Areolar tissue surrounds the nipple and is recognized as the darker, smooth skin between the nipple and the breast. The small bumps or projections on the areolar surface known as Montgomery’s tubercles are sebaceous glands that keep the nipple area soft and elastic. At the time of puberty and during pregnancy, increased levels of estrogen and progesterone
cause the areola and nipple to become darker and more prominent and Montgomery’s glands to become more active. The erectile tissue of the nipple is responsive to psychological and tactile stimuli, which contributes to the sexual function of the breasts.

**Mastitis**

Mastitis is inflammation of the breast. It most frequently occurs during lactation but may also result from other conditions. In the lactating woman, inflammation results from an ascending infection that travels from the nipple to the ductile structures. The most common organisms isolated are *Staphylococcus* and *Streptococcus*. The offending organisms originate from the suckling infant’s nasopharynx or the mother’s hands. During the early weeks of nursing, the breast is particularly vulnerable to bacterial invasion because of minor cracks and fissures that occur with vigorous sucking. Infection and inflammation cause obstruction of the ductile system. The breast area becomes hard, inflamed, and tender if not treated early. Without treatment, the area becomes walled off and may abscess, requiring incision and drainage. It is advisable for the mother to continue breast-feeding during antibiotic therapy to prevent this.

Mastitis is not confined to the postpartum period; it can occur as a result of hormonal fluctuations, tumors, trauma, or skin infection. Cyclic inflammation of the breast occurs most frequently in adolescents, who commonly have fluctuating hormone levels. Tumors may cause mastitis secondary to skin involvement or lymphatic obstruction. Local trauma or infection may develop into mastitis because of ductal blockage of trapped blood, cellular debris, or the extension of superficial inflammation. The treatment for mastitis symptoms may include application of heat or cold, excision, aspiration, mild analgesics, antibiotics, and a supportive brassiere or breast binder.

**Ductile Disorders**

Ductal ectasia manifests in older women as a spontaneous, intermittent, usually unilateral, grayish-green nipple discharge. Palpation of the breast increases the discharge. Ectasia occurs during or after menopause and is symptomatically associated with burning, itching, pain, and a pulling sensation of the nipple and areola. The disease results in inflammation of the ducts and subsequent thickening. The treatment requires removal of the involved ductal mass.

Intraductal papillomas are benign epithelial tissue tumors that range in size from 2 mm to 5 cm. Papillomas usually manifest with a bloody nipple discharge. The tumor may be palpated in the areolar area. The papilloma is probed through the nipple, and the involved duct is removed.

**Fibrocystic Disease**

The term *fibrocystic breast disease* is the most common lesion of the breast. It is most common in women 30 to 50 years of age and is rare in postmenopausal women not receiving hormone replacement. Fibrocystic disease usually presents as nodular (i.e., “shotty”), granular breast masses that are more prominent and painful during the luteal or progesterone-dominant portion of the menstrual cycle. Discomfort ranges from heaviness to exquisite tenderness, depending on the degree of vascular engorgement and cystic distention.

Fibrocystic disease encompasses a wide variety of lesions and breast changes. Microscopically, fibrocystic disease refers to a constellation of morphologic changes manifested by (1) cystic dilation of terminal ducts, (2) relative increase in fibrous tissue, and (3) variable proliferation of terminal duct epithelial elements. Autopsy studies have demonstrated some degree of fibrocystic change in 60% to 80% of adult women in the United States. Symptomatic fibrocystic disease, in which large, clinically detectable cysts are present, is much less common, occurring in approximately 10% of the adult women between 35 and 50 years of age. Although fibrocystic disease often has been thought to increase the risk of breast cancer, only certain variants in which proliferation of the epithelial components is demonstrated represent a true risk.

Diagnosis of fibrocystic disease is made by physical examination, mammography, ultrasound, and biopsy (i.e., aspiration or tissue sample). Ultrasound is useful in differentiating a cyst from a solid mass. Because a mass caused by fibrocystic disease may be indistinguishable from carcinoma on the basis of clinical findings, suspicious lesions should undergo biopsy. Fine-needle aspiration may be used, but if a suspect mass that was nonmalignant on cytologic examination does not resolve during the course of several months, it should be removed surgically.

Treatment for fibrocystic breast disease usually is symptomatic. Aspirin, mild analgesics, and local application of heat or cold may be recommended. Women should be encouraged to wear a good supporting brassiere and advised to avoid foods that contain xanthines (e.g., coffee, cola, chocolate, and tea) in their daily diets, particularly premenstrually. Aspiration of a discrete mass indicative of a cyst may be used to relieve pain and confirm the cystic nature of the lesion. Danazol, a synthetic androgen, may be used for treatment of severe pain.

**Breast Cancer**

Cancer of the breast is the most common female cancer. One in eight women in the United States will have breast cancer in her lifetime. In 2000, breast cancer affected 182,800 American women and killed almost 40,800 women. Although the breast
cancer mortality rate has shown a slight decline, it is second only to lung cancer as a cause of cancer-related deaths in women. Incidence rates for carcinoma in situ have increased dramatically since the mid-1970s because of recommendations regarding mammography screening. The decline in the breast cancer mortality rate since 1989 is attributable to this earlier diagnosis as well as improvements in cancer treatments.37

Risk factors for breast cancer include sex, increasing age, personal or family history of breast cancer (i.e., at highest risk are those with multiple affected first-order relatives), history of benign breast disease (i.e., primary “atypical” hyperplasia), and hormonal influences that promote breast maturation and may increase the chance of cell mutation (i.e., early menarche, late menopause, and no term pregnancies or first child after 30 years of age).38 Most women with breast cancer have no identifiable risk factors.

Approximately 8% of all breast cancers are hereditary.38 Two breast cancer susceptibility genes—BRCA1 on chromosome 17 and BRCA2 on chromosome 13—may account for most inherited forms of breast cancer (see Chapter 5). Known carriers of these genes should begin monthly breast self-examination (BSE) at 18 years of age and begin having annual mammograms at 25 years of age.39

Breast cancer may involve the lobular or ductile structures. Invasive, or infiltrating, ductile carcinoma is the most common form of breast cancer. Invasive lobular carcinoma is the second most common form of breast cancer. It may occur alone or mixed with ductile carcinoma. Paget’s disease accounts for 1% of all breast cancers. The disease presents as an eczematoid lesion of the nipple and areola. Paget’s disease usually is associated with an infiltrating, intraductal carcinoma. Ductile carcinoma in situ (including Paget’s disease) has increased in the past several decades from less than 5% of all carcinomas before mammography screening to 15% to 20% in well-screened populations. The lesion consists of a malignant population of cells that lack the capacity to invade the basement membrane and metastasize. However, they can spread throughout the ductile system involving an entire sector of the breast.2

Detection
Cancer of the breast may manifest clinically as a mass, a puckering, nipple retraction, or unusual discharge. Many cancers are found by women themselves through BSE—sometimes when only a thickening or subtle change in breast contour is noticed. The variety of symptoms and potential for self-discovery underscore the need for regular, systematic self-examination. BSE should be done routinely by women older than 20 years of age. As an adjunct to BSE, women should have a clinical examination by a trained health professional at least every 3 years between 20 and 40 years of age, and annually after 40 years of age.

Mammography is the only effective screening technique for the early detection of clinically apparent lesions. A generally slow-growing form of cancer, breast cancer may have been present for 2 to 9 years before it reaches 1 cm, the smallest mass normally detected by palpation. Mammography can disclose lesions as small as 1 mm and the clustering of calcifications that may warrant biopsy to exclude cancer. The American Cancer Society recommends annual evaluation for women after 40 years of age. The most comprehensive approach to screening is a combination of BSE, clinical evaluation by a health professional, and mammography.

Diagnosis and Classification
Procedures used in the diagnosis of breast cancer include physical examination, mammography, ultrasonography, percutaneous needle aspiration, stereotactic needle biopsy (i.e., core biopsy), and excisional biopsy. Figure 34-17 illustrates the appearance of breast cancer on mammography. Breast cancer often manifests as a solitary, painless, firm, fixed lesion with poorly defined borders. It can be found anywhere in the breast but is most common in the upper outer quadrant. Because of the variability in presentation, any suspect change in breast tissue warrants further investigation. The diagnostic use of mammography enables additional definition of the clinically suspicious area (e.g., appearance, character, calcification). Placement of a wire marker under radiographic guidance can ensure accurate surgical biopsy of nonpalpable suspect areas. Ultrasonography is useful as a diagnostic adjunct to differentiate cystic from solid tissue in women with nonspecific thickening.

Fine-needle aspiration is a simple in-office procedure that can be performed repeatedly in multiple sites and with minimal discomfort. It can be used to identify the presence of malignant cells, but it cannot differentiate in situ from infiltrating cancers. Stereotactic needle biopsy is an outpatient procedure done with the guidance of a mammography machine. After the lesion is localized radiologically, a large-bore needle is mechanically thrust quickly into the area, removing a core of tissue. Excisional biopsy to remove the entire lump provides the only definitive diagnosis of breast cancer and often is therapeutic without additional surgery.

Tumors are classified histologically according to tissue characteristics and staged clinically according to tumor size, nodal involvement, and presence of metastasis. It is recommended that estrogen and progesterone receptor analysis be performed on surgical specimens. Information about the presence or absence of estrogen and progesterone receptors can be used in predicting tumor responsiveness to hormonal manipulation. High levels of both receptors improve the prognosis and increase the likelihood of remission.

Treatment
The treatment methods for breast cancer include surgery, chemotherapy, radiation therapy, and hormonal manipulation.40 Radical mastectomy (i.e., removal of the entire breast, underlying muscles, and all axillary nodes) rarely is used today as a primary surgical therapy unless breast cancer is advanced at the time of diagnosis. Modified surgical techniques (i.e., mastectomy plus axillary dissection or lumpectomy for breast conservation) accompanied by chemotherapy or radiation therapy have achieved outcomes comparable with those obtained with radical surgical methods and constitute the preferred treatment methods.

The prognosis and need for adjuvant systemic therapy is related more to the extent of nodal involvement than to the extent of breast involvement. A newer technique for evaluating lymph node involvement is sentinel lymph node biopsy. A radioactive substance or dye is injected into the region of the tumor. In theory, the dye is carried to the first (sentinel) node to receive lymph from the tumor. This would therefore be the node most likely to contain cancer cells if the cancer has spread. If the sentinel node biopsy is positive, more nodes are removed. If it is negative, further lymph node evaluation may not be needed. It is not always possible to identify the sentinel node.41
Adjuvant systemic therapy refers to the administration of chemotherapy or hormonal therapy to women without detectable metastatic disease. The goal of this therapy depends on nodal involvement, menopausal status, and hormone receptor status. Tamoxifen is a nonsteroidal antiestrogen that binds to estrogen receptors and blocks the effects of estrogens on the growth of malignant cells in the breast. Studies have shown decreased cancer recurrence, decreased mortality rates, and increased 5-year survival rates in women with estrogen receptor-positive tissue samples who have been treated with the drug. Autologous bone marrow transplantation and peripheral stem cell transplantation are experimental therapies that may be used for the treatment of advanced disease or in women at increased risk for recurrence.

**FIGURE 34-17** Carcinoma of the breast. (A) Mammogram. An irregularly shaped, dense mass (arrows) is seen in this otherwise fatty breast. (B) Mastectomy specimen. The irregular white, firm mass in the center is surrounded by fatty tissue. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1042]. Philadelphia: Lippincott Williams & Wilkins)

In summary, the breasts are subject to benign and malignant disease. Mastitis is inflammation of the breast, occurring most frequently during lactation. Ductal ectasia and intraductal papilloma cause abnormal drainage from the nipple. Fibroadenoma and fibrocystic disease are characterized by abnormal masses in the breast that are benign. By far the most important disease of the breast is breast cancer, which is a significant cause of death of women. BSE and mammography afford a woman the best protection against breast cancer. They provide the means for early detection of breast cancer and, in many cases, allow early treatment and cure.

**REVIEW QUESTIONS**

- List the actions of estrogen and progesterone and explain the interactions among the gonadotropin-releasing hormones, LH, and FSH; ovarian follicle development; and estrogen and progesterone levels.
- Compare the extragenital abnormalities associated with Bartholin cyst and abscess, vulvar dystrophy, vulvodynia, and cancer of the vulva.
- Characterize the development of cervical cancer, from the appearance of atypical cells to the development of invasive cervical cancer, and the role of the Pap smear in early detection.
- State the proposed relationship between unopposed estrogen stimulation of the endometrium and endometrial cancer.
- List the common causes and symptoms of pelvic inflammatory disease.
- State the underlying cause of ovarian cysts.
- Differentiate benign ovarian cyst from polycystic ovary syndrome.
- State the reason that ovarian cancer may be difficult to detect at an early stage.
- Describe the manifestations of cystocele, rectocele, and enterocoele.
- Compare the symptoms of primary dysmenorrhea with those of secondary dysmenorrhea.
Characterize the manifestations of the premenstrual syndrome, its possible causes, and the methods of treatment.

Describe the physiology of normal menopause.

Describe changes in breast function that occur with mastitis and ductal ectasia.

Describe the manifestations of fibrocystic disease and state why it is often referred to as a “catchall” for breast irregularities.

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

REFERENCES


