44

The Male and Female Reproductive Systems

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. Describe the general anatomical components of the male and female reproductive system.
2. Map out the organization of the testis, with the Sertoli cells and developing sperm cells within the intralobular compartment, and the Leydig cells and capillary plexus within the interlobular/interstitial compartment.
3. Illustrate the processes of spermatogenesis and spermiogenesis.
4. List the functions of the Sertoli cell.
5. Diagram the process of testosterone synthesis within the Leydig cells, and the peripheral conversion of testosterone to estradiol or dihydrotestosterone.
6. Diagram the male hypothalamus/pituitary/testis axis, including all cell types and hormones involved.
7. Map out the organization of the ovary, and describe the various stages of follicular development, ovulation and corpus luteum formation.
8. List the stages and control of female germ cell progression from oogonia to egg.
9. Map out the steroidogenic pathways in the corresponding cell types that lead to androgen, estrogen, and progesterone synthesis.
10. Diagram the female hypothalamus/pituitary/ovarian axis during the menstrual cycle, including all cell types and hormones involved.
11. Explain changes in the female tract, with emphasis on the uterine endometrium, during the menstrual cycle.
12. List the events involved in fertilization.
13. Describe the development and function of the placenta.
14. Describe the development and function of the mammary glands.

The two most basic anatomical components of the reproductive system are the **gonads** and the **reproductive tract.** The gonads (**testes** and **ovaries**) perform an **endocrine function** that is regulated within a **hypothalamic-pituitary-gonadal axis.** The gonads are distinct from other endocrine glands in that they also perform **gametogenesis.** The reproductive tract is involved in several aspects of gamete development, function, and transport, and in women, allows fertilization, implantation, and gestation. Gametogenesis in the gonads, and development and physiology of the reproductive tract, are absolutely dependent on the endocrine function of the gonads. The clinical ramifications of this hormonal dependence include infertility in the face of low sex hormone production, ambiguous genitalia in dysregulated hormone or hormone receptor expression, and hormone-responsive cancers, especially uterine and breast cancer in women and prostate cancer in men.

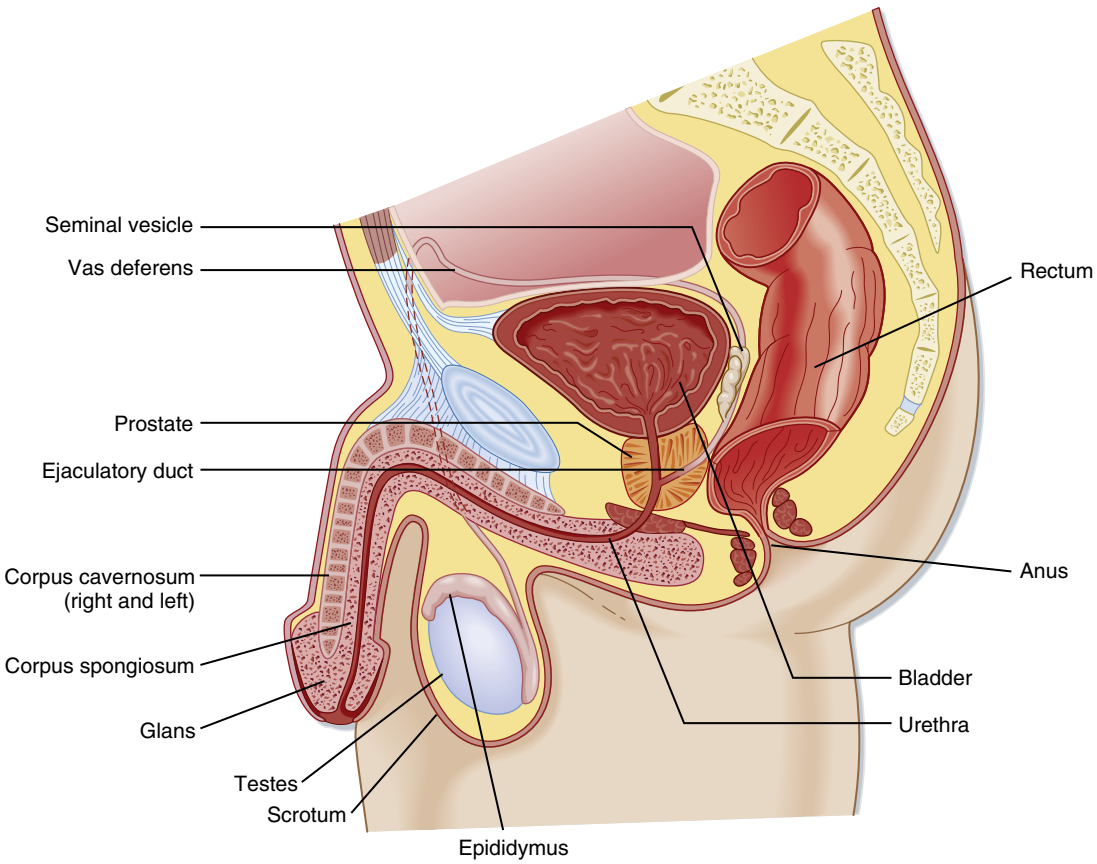
The Male Reproductive System

The male reproductive system has evolved for **continuous lifelong gametogenesis** coupled with occasional **internal insemination** with a **high density of sperm** (>60 × 10^6/mL in 3–5 mL of semen). In adult men the basic roles of gonadal hormones are (1) support of gametogenesis **(spermatogenesis),** (2) maintenance of the male reproductive tract and production of semen, and (3) maintenance of secondary sex characteristics and libido. There is no overall cyclicity of this activity in men.

The Testis

Histophysiology

Unlike the ovaries, the testes reside outside the abdominal cavity in the **scrotum** (Fig. 44.1). This location maintains testicular temperature at about 2°C lower than body temperature, which is crucial for optimal sperm development. The human **testis** is covered by a connective tissue capsule and divided into about 300 **lobules** by fibrous septa (Fig. 44.2). Within each lobule are two to four loops of **seminiferous tubules.** Each loop empties into an anastomosing network of tubules called the **rete testis.** The rete testis is continuous with small ducts, the **efferent ductules,** that lead the sperm out of the testis into the head of the **epididymis** on the superior pole of the testis (see Fig. 44.2). Once in the epididymis, the sperm pass from the **head,** to the **body,** to the **tail** of the epididymis and then to the **vas (ductus) deferens.** Viable **sperm** can be stored in the tail of the epididymis and vas deferens for several months.



• **Fig. 44.1** Anatomy of the male reproductive system. (Modified from Drake RL, Vogl W, Mitchell AWM. *Gray's Anatomy for Students.* Philadelphia: Churchill Livingstone; 2005.)

The presence of the seminiferous tubules creates two compartments within each lobule: an intratubular compartment, composed of the avascular **seminiferous epithelium** of the seminiferous tubule, and a peritubular compartment, composed of neurovascular elements, connective tissue cells, immune cells, and the **interstitial cells of Leydig,** whose main function is to produce **testosterone** (Fig. 44.3).

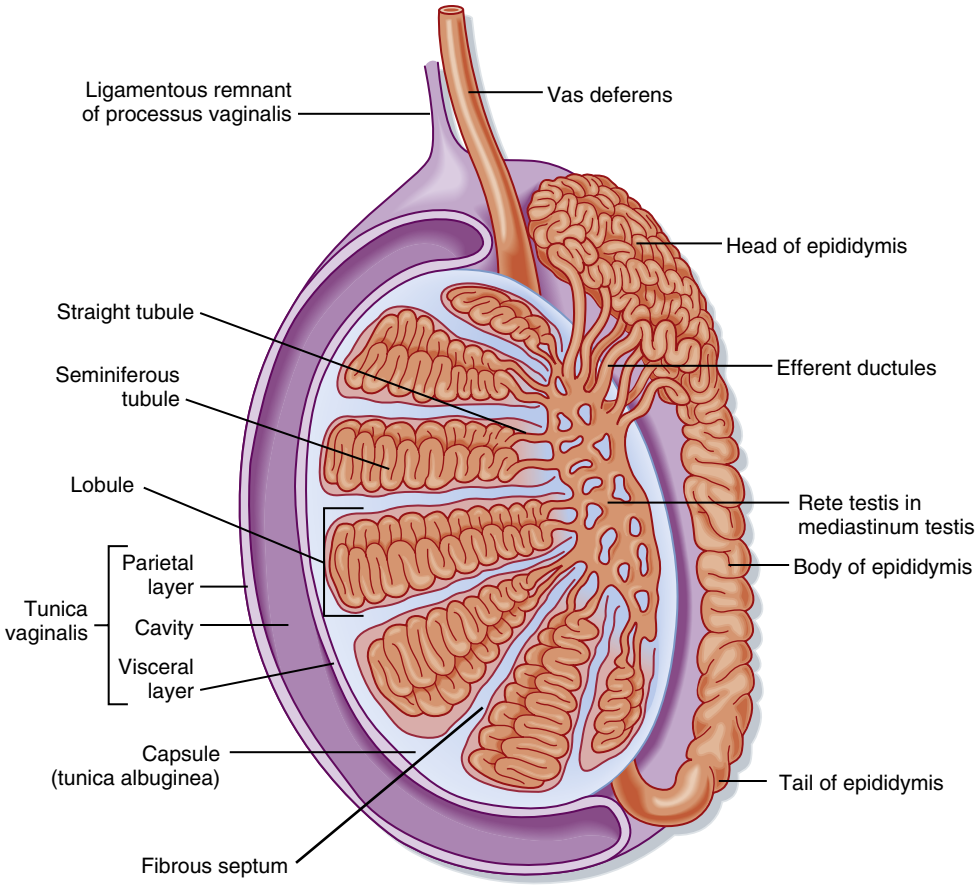
Intratubular Compartment

The seminiferous tubule is lined by a complex **seminiferous epithelium** composed of two cell types: **sperm cells** in various stages of **spermatogenesis** and **Sertoli cells** ("nurse cells") that are in intimate contact with all sperm cells (Fig. 44.4).

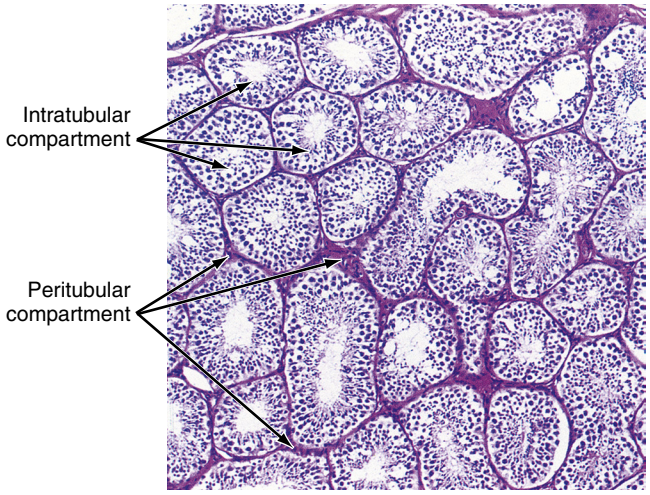
Developing Sperm Cells

Spermatogenesis involves the processes of **mitosis** and **meiosis.** Stem cells called **spermatogonia** reside at the basal level of the seminiferous epithelium (see Fig. 44.4, S_A and S_B). Spermatogonia divide mitotically to generate daughter spermatogonia **(spermatocytogenesis).** One or more spermatogonia remain within the stem cell population, firmly adherent to the basal lamina. However, the majority of these daughter spermatogonia enter meiotic division, which results in haploid spermatozoa on completion of meiosis. These divisions are accompanied by **incomplete cytokinesis** such that all daughter cells remain interconnected by a cytoplasmic bridge. This configuration contributes to the synchrony of development of a clonal population of sperm cells. Spermatogonia migrate apically away from the basal lamina as they enter the first meiotic prophase. At this time they are called **primary spermatocytes** (see Fig. 44.4, S_1). During the first meiotic prophase the hallmark processes of sexual reproduction involving chromosomal reduplication, synapsis, crossing over, and homologous recombination take place. Completion of the first meiotic division gives rise to **secondary spermatocytes,** which quickly (i.e., within 20 minutes) complete the second meiotic division. The initial products of meiosis are haploid **spermatids** (see Fig. 44.4, S_3).

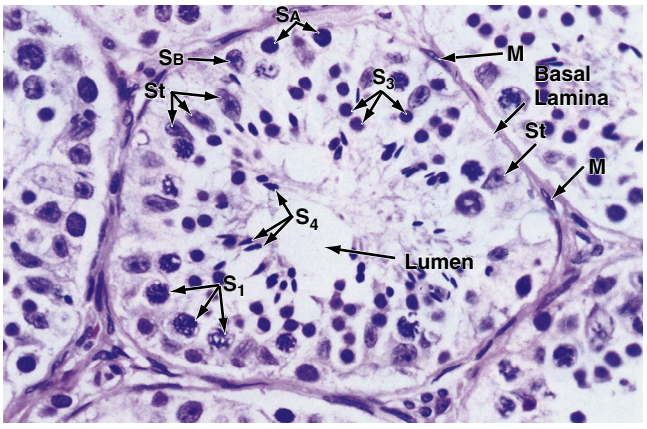
Spermatids are small round cells that undergo a remarkable metamorphosis called **spermiogenesis** (Fig. 44.5). The products of spermiogenesis are the streamlined **spermatozoa** see Fig. 44.4, S_4). As the spermatid matures into a spermatozoon, the size of the nucleus decreases and a prominent tail is formed. The tail contains microtubular structures that propel sperm, similar to a flagellum. The chromatin material in the sperm nucleus condenses, and most of the cytoplasm is lost. The **acrosome** is a membrane-enclosed structure on the head of the sperm that acts as a lysosome and contains hydrolytic enzymes that are important for fertilization. These enzymes remain inactive until the acrosomal reaction occurs (see Fertilization).



• **Fig. 44.2** Anatomy and organization of the testis. (Modified from Drake RL, Vogl W, Mitchell AWM. *Gray's Anatomy for Students.* Philadelphia: Churchill Livingstone; 2005.)

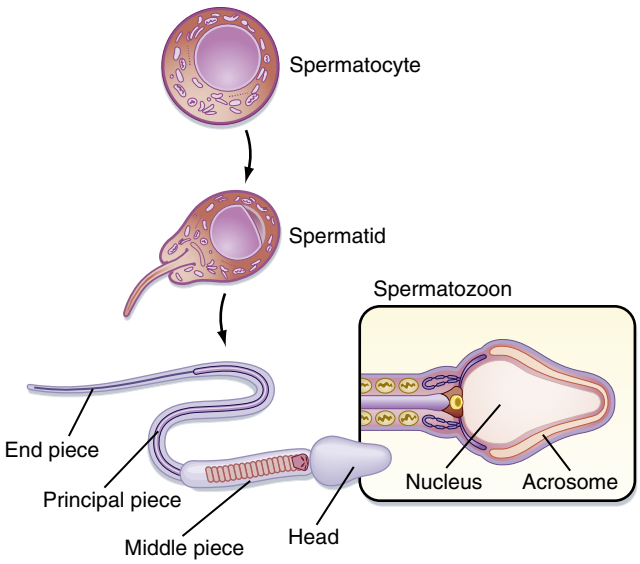


• **Fig. 44.3** Histology of a testicular lobule. (From Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology. A Text and Colour Atlas.* 5th ed. London: Churchill Livingstone; 2006.)



• **Fig. 44.4** Histology of a seminiferous tubule. *M*, Myoid cell just outside the basal lamina; S_1, primary spermatocyte; S_3, spermatid; S_4, mature spermatid or spermatozoon; S_B *and* S_A, spermatogonia; *St*, Sertoli cell. (From Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology. A Text and Colour Atlas.* 5th ed. London: Churchill Livingstone; 2006.)

Spermatozoa (see Fig. 44.4, S_4) are found at the luminal surface of the seminiferous tubule. Release of sperm, or **spermiation,** is controlled by Sertoli cells. The process of spermatogenesis takes about 72 days. A cohort of adjacent spermatogonia enter the process every 16 days so that the process is staggered at one point along a seminiferous tubule. In addition the process is staggered along the length of a seminiferous tubule (i.e., not all spermatogonia enter the process of spermatogenesis at the same time along the entire length of the tubule or in synchrony with every other



• **Fig. 44.5** Structure of sperm cells during the process of spermatogenesis and spermiogenesis.

tubule; there are about 500 seminiferous tubules per testis; see later). Because the seminiferous tubules within one testis are about 400 m in length, spermatozoa are continually being generated at many sites within the testis at any given time.

The Sertoli Cell

Sertoli cells are the true epithelial cells of the seminiferous epithelium and extend from the basal lamina to the lumen (see Fig. 44.4, St). Sertoli cells surround sperm cells and provide structural support within the epithelium, and they form adhering and gap junctions with all stages of sperm cells. Through formation and breakdown of these junctions, Sertoli cells guide sperm cells toward the lumen as they advance to later stages of spermatogenesis. Spermiation requires the final breakdown of Sertoli–sperm cell junctions.

Another important structural feature of Sertoli cells is the formation of tight junctions between adjacent Sertoli cells (Fig. 44.6). These Sertoli-Sertoli cell occluding junctions divide the seminiferous epithelium into a **basal compartment** containing the spermatogonia and early-stage primary spermatocytes and an **adluminal compartment** containing later-stage primary spermatocytes and all subsequent stages of sperm cells. As early primary spermatocytes move apically from the basal to the adluminal compartment, the tight junctions need to be disassembled and reassembled. These tight junctions form the physical basis for the **blood-testis barrier** (see Fig. 44.6), which creates a specialized immunologically safe microenvironment for developing sperm. By blocking paracellular diffusion the tight junctions restrict movement of substances between blood and the developing germ cells through a trans–Sertoli cell transport pathway. This organization enables Sertoli cells to control the availability of nutrients to germ cells.

Healthy Sertoli cell function is essential for sperm cell viability and development. In addition, spermatogenesis is absolutely dependent on testosterone produced by peritubular Leydig cells (see The Leydig Cell), yet it is the Sertoli cells that express the **androgen receptor** and respond to testosterone, not the developing sperm cells. Similarly, the pituitary hormone follicle-stimulating hormone (FSH) is also required for maximal sperm production, and again it is the Sertoli cell that expresses the **FSH receptor,** not the developing sperm. Thus testosterone and FSH support spermatogenesis indirectly through stimulation of Sertoli cell function.

Sertoli cells have multiple additional functions. They express the enzyme CYP19 (also called *aromatase*), which converts Leydig cell–derived testosterone to the potent estrogen **17β-estradiol** (see Intratesticular Androgen). This local production of estrogen may enhance spermatogenesis in humans. Sertoli cells also produce **androgen-binding protein** (ABP), which maintains a high androgen level within the adluminal compartment, the lumens of the seminiferous tubules, and the proximal part of the male reproductive tract. Sertoli cells also produce a large amount of fluid. This fluid provides an appropriate bathing medium for the sperm and assists in moving the immotile spermatozoa from the seminiferous tubule into the epididymis. Sertoli cells perform an important phagocytic function by engulfing **residual bodies,** which represent cytoplasm shed by spermatozoa during spermiogenesis.

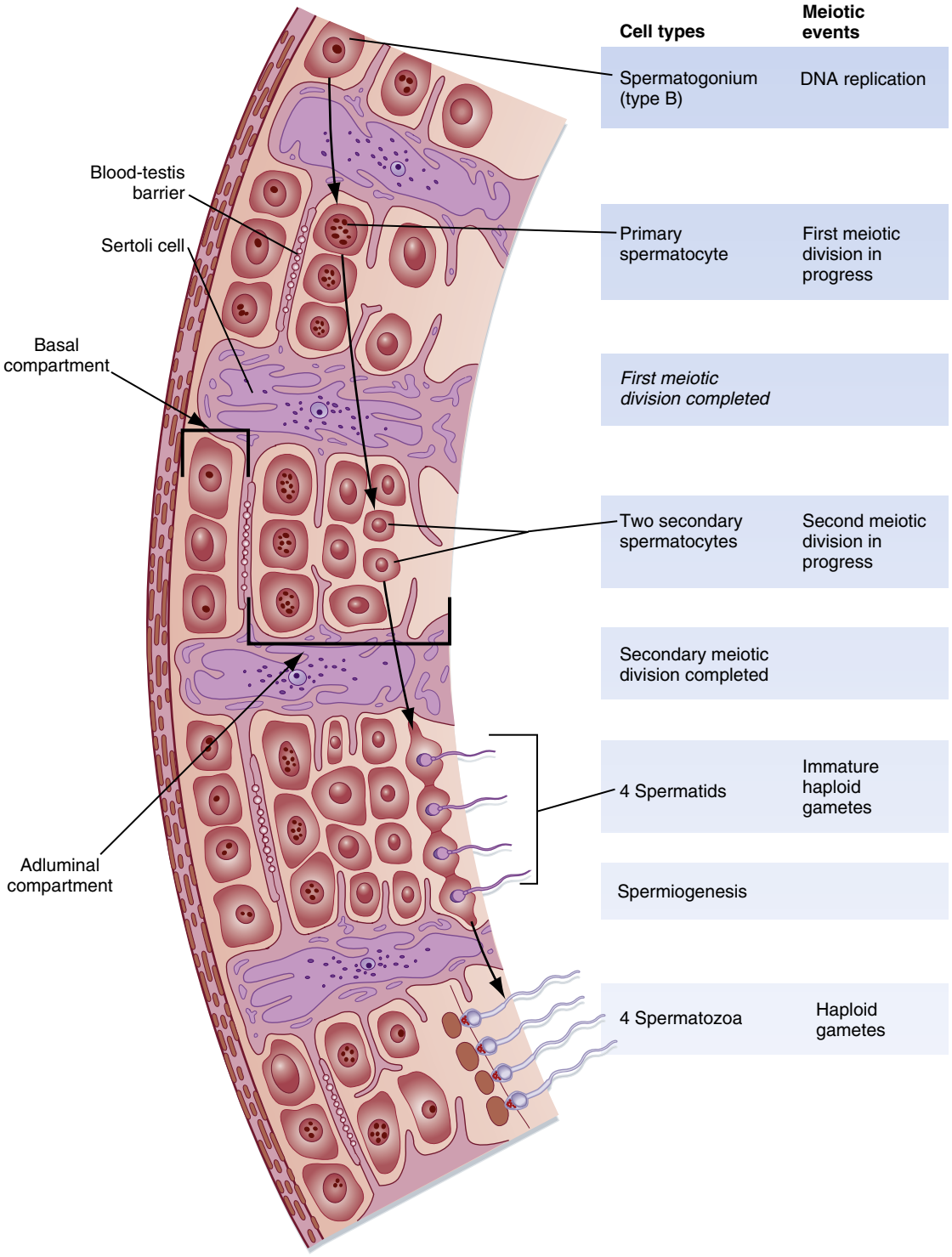
Finally, the Sertoli cell has an important endocrine role. During development, Sertoli cells produce **antimüllerian hormone (AMH;** also called **müllerian inhibitory substance**), which induces regression of the embryonic müllerian duct that is programmed to give rise to the female reproductive tract (discussed later). The Sertoli cells also produce the hormone **inhibin.** Inhibin is a heterodimer protein hormone related to the transforming growth factor-β family. FSH stimulates inhibin production, which then negatively feeds back on gonadotropes to inhibit FSH production. Thus, inhibin keeps FSH levels within a set point.

Peritubular Compartment

The peritubular compartment contains the primary endocrine cell of the testis, the **Leydig cell** (Fig. 44.7). This compartment also contains the common cell types of loose connective tissue and an extremely rich peritubular capillary network that provides nutrients to the seminiferous tubules (by way of Sertoli cells) while transporting testosterone away from the testes to the peripheral circulation.

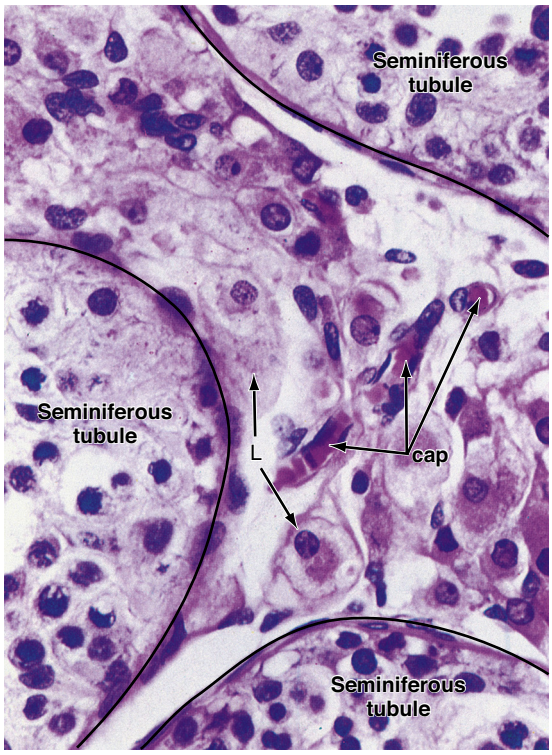
The Leydig Cell

Leydig cells are steroidogenic stromal cells. These cells synthesize cholesterol de novo, as well as acquire it through low-density lipoprotein (LDL) receptors and high-density lipoprotein (HDL) receptors (also called *scavenger receptor BI* [SR-BI]), and store cholesterol as cholesterol esters as described for adrenocortical cells (see Chapter 43). Free cholesterol is generated by a cholesterol ester hydrolase and transferred to the outer mitochondrial membrane and then



• **Fig. 44.6** Placement of germ cells within seminiferous tubule as they progress through spermatogenesis. (From Carlson BM. *Human Embryology and Developmental Biology.* Philadelphia: Mosby; 2004.)

to the inner mitochondrial membrane in a **steroidogenic acute regulatory (StAR) protein**–dependent manner. As in all steroidogenic cells, cholesterol is converted to pregnenolone by CYP11A1. Pregnenolone is then processed to progesterone, 17-hydroxyprogesterone, and androstenedione by 3β-hydroxysteroid dehydrogenase **(3β-HSD)** and **CYP17** (Fig. 44.8). Recall from Chapter 43 that CYP17 is a bifunctional enzyme with **17-hydroxylase activity** and **17,20-lyase activity.** CYP17 displays a robust level of both activities in the Leydig cell. In this respect the Leydig cell is similar to the zona reticularis cell, except that it expresses a higher level of 3β-HSD, so the **Δ4 pathway** is ultimately favored. Another major difference is that the Leydig cell expresses a Leydig cell–specific isoform of



• **Fig. 44.7** Histology of the peritubular space (between three seminiferous tubules) containing Leydig cells *(L)* and richly vascularized by peritubular capillaries *(cap)*. (Modified from Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology. A Text and Colour Atlas.* 5th ed. London: Churchill Livingstone; 2006.)

17β-hydroxysteroid dehydrogenase (17β-HSD type 3), which efficiently converts **androstenedione** to **testosterone** (see Fig. 44.8).

Fates and Actions of Androgens

Intratesticular Androgen

The testosterone produced by Leydig cells has several fates and multiple actions. Because of the proximity of Leydig cells to the seminiferous tubules, significant amounts of testosterone diffuse into the seminiferous tubules and become concentrated within the adluminal compartment by ABP (see Fig. 44.8). Testosterone levels within the seminiferous tubules that are greater than 100 times more concentrated than circulating testosterone levels are absolutely required for normal spermatogenesis. As mentioned earlier, Sertoli cells express the enzyme **CYP19 (aromatase),** which converts a small amount of testosterone into the highly potent estrogen **17β-estradiol.** Human sperm cells express at least one subtype of the **estrogen receptor,** and there is some evidence from aromatase-deficient men that this locally produced estrogen optimizes spermatogenesis in humans.

Peripheral Conversion to Estrogen

In several tissues (especially adipose tissue), testosterone is converted to estrogen (see Fig. 44.8). Studies involving men with aromatase deficiency have shown that an inability to produce estrogen results in tall stature because of the lack of epiphyseal closure in long bones, as well as osteoporosis. Thus, peripheral estrogen plays an important role in both bone maturation and maintenance in men. These studies also implicated estrogen in promoting insulin sensitivity, improving lipoprotein profiles (i.e., increasing HDL, decreasing triglycerides and LDL), and exerting negative feedback on gonadotropins at the pituitary and hypothalamus.

Peripheral Conversion to Dihydrotestosterone

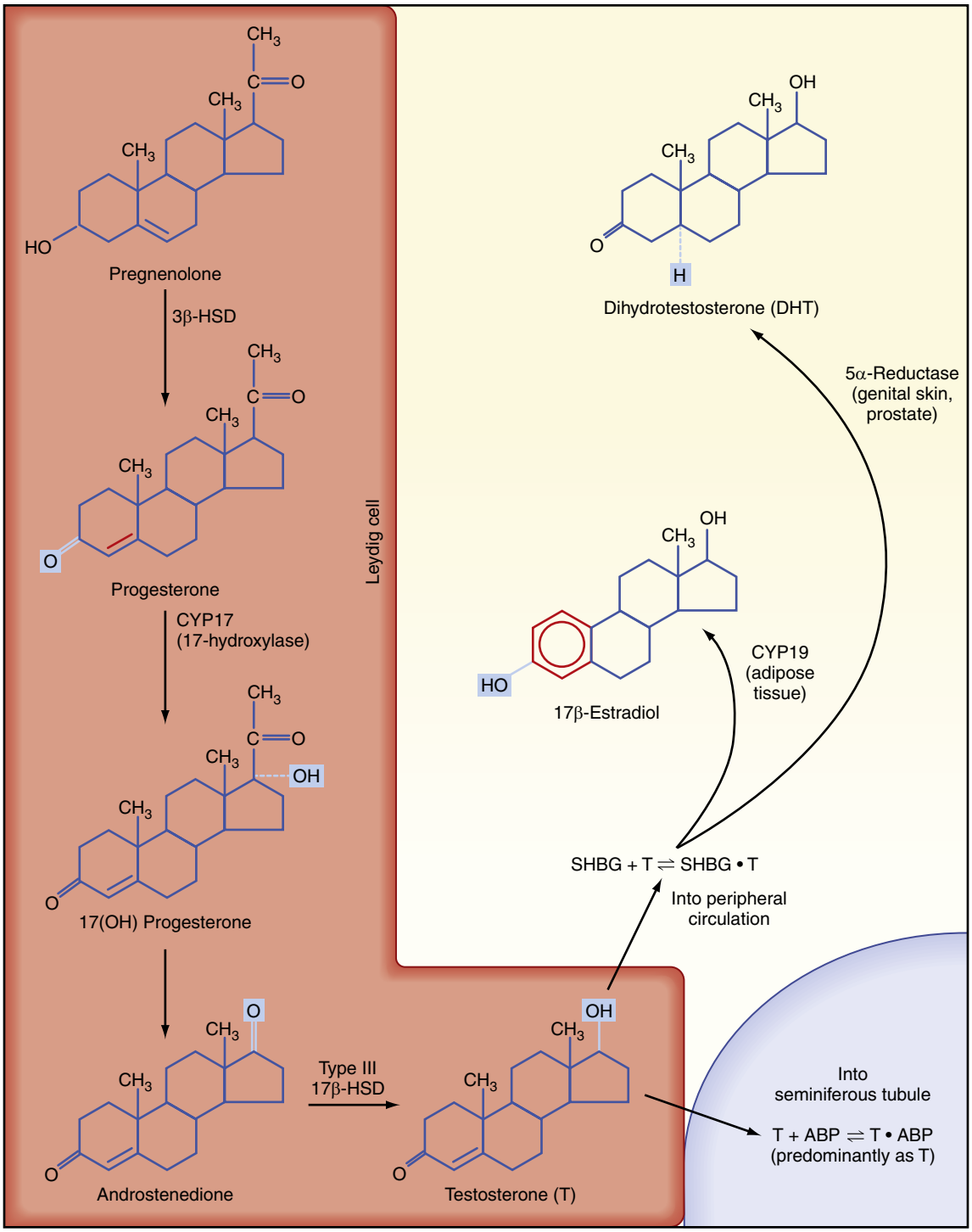
Testosterone can also be converted into a potent **nonaromatizable androgen, 5α-dihydrotestosterone (DHT),** by the enzyme **5α-reductase** (see Fig. 44.8). There are two isoforms of 5α-reductase, type 1 and type 2. Major sites of 5α-reductase 2 expression are the male urogenital tract, genital skin, hair follicles, and liver. 5α-Reductase 2 generates DHT, which is required for masculinization of the external genitalia in utero and for many of the changes associated with puberty, including growth and activity of the prostate gland (see Male Reproductive Tract), growth of the penis, darkening and folding of the scrotum, growth of pubic and axillary hair, growth of facial and body hair, and increased muscle mass (Fig. 44.9). The onset of 5α-reductase 1 expression occurs at puberty. This isozyme is expressed primarily in the skin and contributes to sebaceous gland activity and the acne associated with puberty. Because DHT has strong growth-promoting (i.e., trophic) effects on its target organs, development of **selective 5α-reductase 2 inhibitors** has proven beneficial in the treatment of prostatic hypertrophy and prostatic cancer.

Peripheral Testosterone Actions

Testosterone has a direct action (i.e., without conversion to DHT) in several cell types (see Fig. 44.9). As mentioned earlier, testosterone regulates Sertoli cell function. It induces development of the male tract from the mesonephric duct in the absence of 5α-reductase. Testosterone has several metabolic effects, including increasing very low-density lipoprotein (VLDL) and LDL while decreasing HDL, promoting deposition of abdominal adipose tissue, increasing red blood cell production, promoting bone growth and health, and exerting a protein anabolic effect on muscle. Testosterone is sufficient to maintain erectile function and libido.

Mechanism of Androgen Action

Testosterone and DHT act through the same androgen receptor (AR). The AR resides in the cytoplasm bound to chaperone proteins in the absence of ligand. Testosterone-AR binding or DHT-AR binding causes dissociation of the chaperone proteins, followed by nuclear translocation of the androgen-AR complex, dimerization, binding to an **androgen response element,** and recruitment of coactivator proteins and general transcription factors to the vicinity of a specific gene's promoter. It remains unclear how testosterone and DHT differ in their ability to activate the AR in the context of different cell types. It has been proposed that the presence of different coactivator proteins in distinct cell types may exist, which might possess different affinities

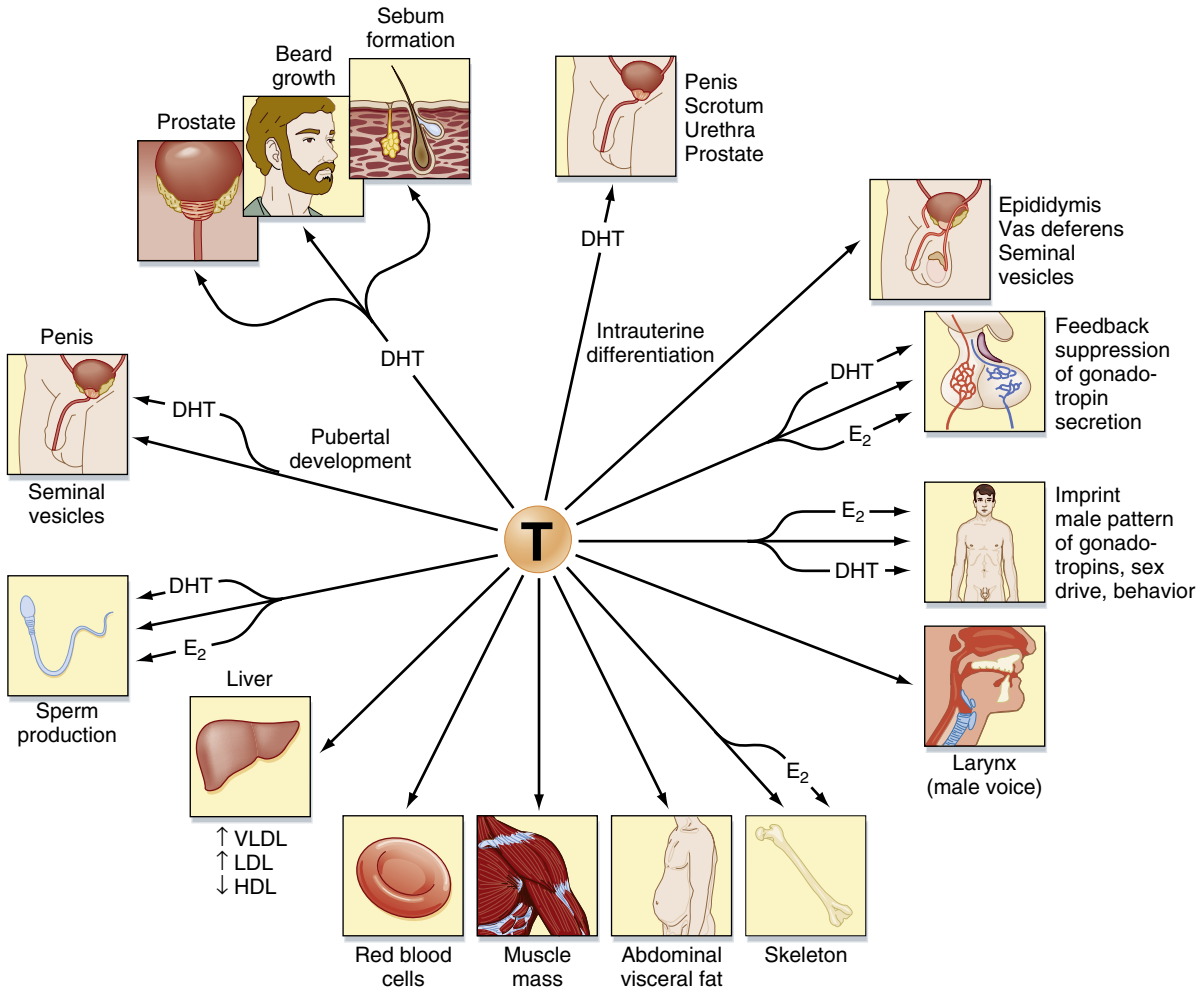


• **Fig. 44.8** Steroidogenic pathway in Leydig cells (the first step of converting cholesterol to pregnenolone is omitted). Testosterone is sequestered by binding to androgen-binding protein *(ABP)* within the seminiferous tubules or circulates within the peripheral circulation bound to sex hormone–binding globulin *(SHBG)* and can be peripherally converted to dihydrotestosterone *(DHT)* or 17β-estradiol (E_2). (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

for the testosterone-activated conformation of the AR versus the DHT-activated AR.

Transport and Metabolism of Androgens

As testosterone enters the peripheral circulation, it binds to and quickly reaches equilibrium with serum proteins. About 60% of circulating testosterone is bound to sex hormone–binding globulin (SHBG), 38% is bound to albumin, and about 2% remains as "free" hormone. Testosterone and its metabolites are primarily excreted in urine. Approximately 50% of excreted androgens are found as **urinary 17-ketosteroids,** with most of the remainder being conjugated



• **Fig. 44.9** Spectrum of effects of testosterone (T). Note that some effects result from the action of testosterone itself, whereas others are mediated by dihydrotestosterone *(DHT)* and estradiol *(E_2)* after they are produced from testosterone. *VLDL, LDL, and HDL*, Very-low-density, low-density, and high-density lipoproteins, respectively.

androgens or diol or triol derivatives. Only about 30% of the 17-ketosteroids in urine are from the testis; the rest are produced from adrenal androgens. Androgens are conjugated with glucuronate or sulfate in the liver, and these **conjugated steroids** are excreted in urine.

Hypothalamic-Pituitary-Testicular Axis

The testis is regulated by an endocrine axis (Fig. 44.10) involving parvicellular hypothalamic gonadotropin-releasing hormone (GnRH) neurons and pituitary gonadotropes that produce both luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

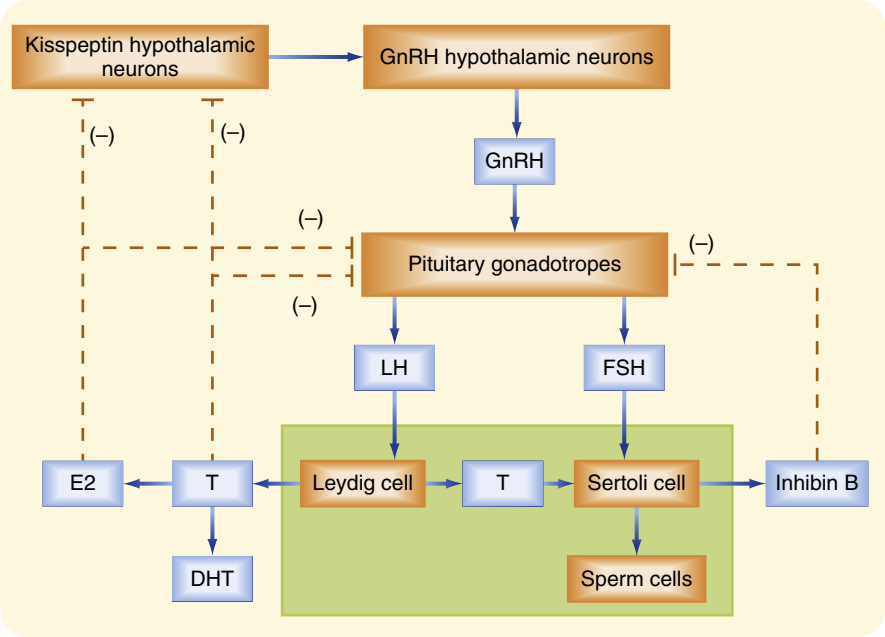
Regulation of Leydig Cell Function

The Leydig cell expresses the **LH receptor,** and LH acts on Leydig cells much like adrenocorticotropic hormone (ACTH, or corticotropin) does on zona fasciculata cells in the adrenal cortex (see Chapter 43). Rapid effects include hydrolysis of cholesterol esters and new expression of StAR protein. Less acute effects include an increase in steroidogenic enzyme gene expression and expression of the low-density lipoprotein receptor (LDLR). Over the long term, LH promotes Leydig cell growth and proliferation.

Testosterone, and estradiol produced from peripheral conversion of testosterone, negatively feedback on GnRH hypothalamic neurons indirectly through inhibition of kisspeptin-producing neurons (see Fig. 44.10). Testosterone and estradiol also negatively feedback on pituitary gonadotropes. In contrast, DHT, the other major product of peripheral conversion of testosterone, has little effect on LH or FSH levels.

Regulation of Sertoli Cell Function

The Sertoli cell is stimulated by both testosterone and FSH. In addition to stimulating synthesis of proteins involved in the "nurse cell" aspect of Sertoli cell function (e.g., ABP), FSH stimulates synthesis of the dimeric protein **inhibin.** Inhibin is induced by FSH and negatively feeds back on the gonadotrope to selectively inhibit FSH production (see Fig. 44.10).



• **Fig. 44.10** The hypothalamic-pituitary-testicular axis. *DHT,* Dihydrotestosterone; E_2, estradiol; *T*, testosterone.

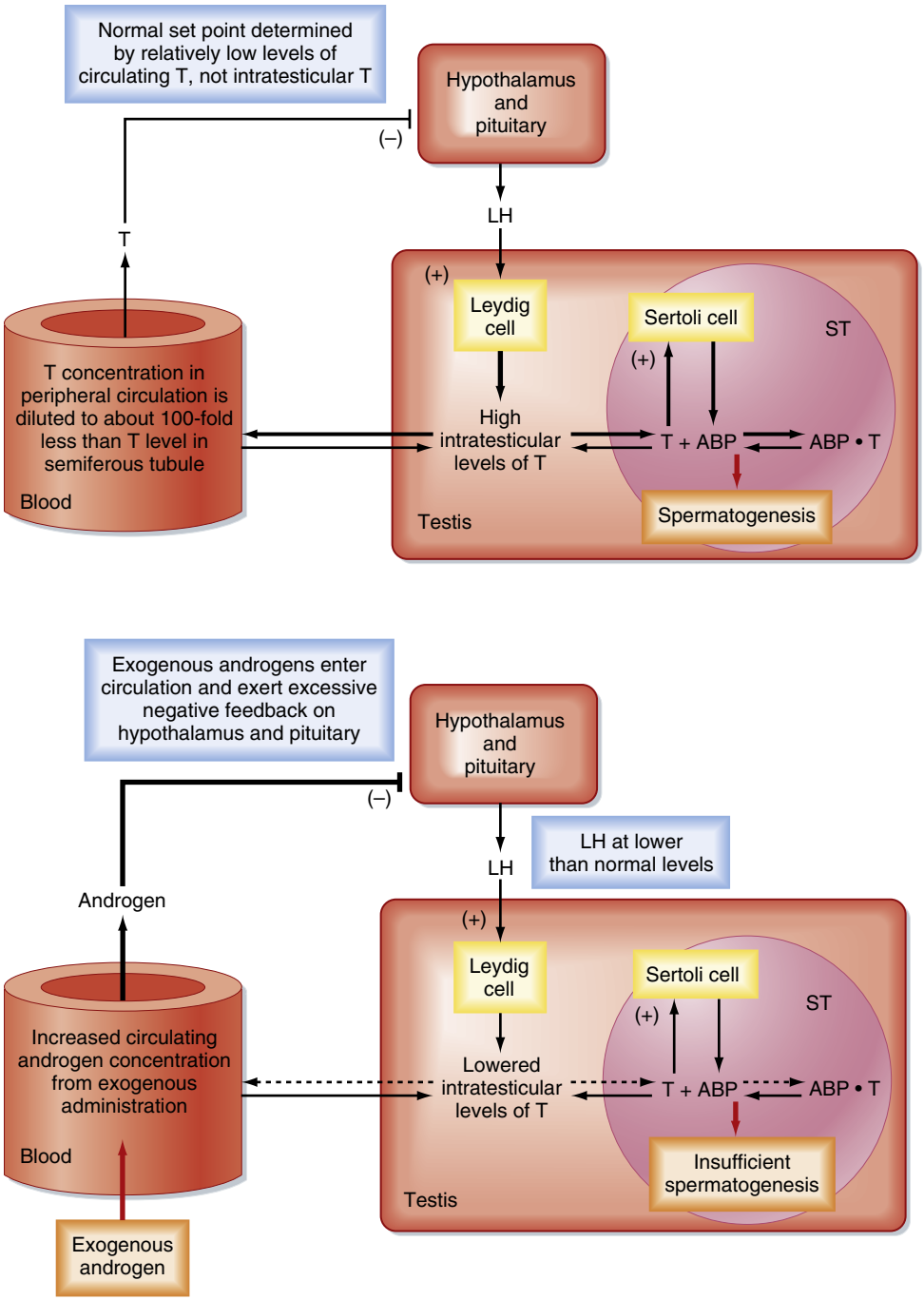
AT THE CELLULAR LEVEL

There is an important "loophole" in the male reproductive axis that is based on the fact that **intratesticular levels of testosterone** need to be greater than 100-fold higher than circulating levels of the hormone to maintain normal rates of spermatogenesis, yet it is the **circulating levels of testosterone (and estradiol)** that provide the negative feedback to the pituitary and hypothalamus. This means that exogenous administration of testosterone can raise circulating levels of testosterone and estradiol sufficient to inhibit LH but not sufficient to accumulate in the testis at the required concentration for normal spermatogenesis. However, the decreased LH levels will diminish intratesticular production of testosterone by Leydig cells, which results in reduced levels of spermatogenesis (Fig. 44.11). This "loophole" is currently being investigated as a possible strategy for developing a **male oral contraceptive.** It is also the basis for **sterility** in some cases of **steroid abuse** in men.

Male Reproductive Tract

Once spermatozoa emerge from the efferent ductules, they leave the gonad and enter the male reproductive tract (see Fig. 44.1). The segments of the tract are the: **epididymis** (**head, body,** and **tail**), **vas deferens, ejaculatory duct, prostatic urethra**, **membranous urethra**, and **penile urethra.** Unlike the female tract, there is a **contiguous lumen** from the seminiferous tubule to the end of the male tract (i.e., the tip of the penile urethra), and the male reproductive tract connects to the **distal urinary tract** (i.e., **male urethra**). In addition to conveying sperm, the primary functions of the male reproductive tract are:

1. *Sperm maturation.* Sperm spend about a month in the **epididymis**, where they undergo further maturation. The epithelium of the epididymis is secretory and adds numerous components to the seminal fluid. Spermatozoa that enter the head of the epididymis are weakly motile but are strongly unidirectionally motile by the time they exit the tail. Spermatozoa also undergo the process of **decapacitation,** which involves changes in the cell membrane to prevent spermatozoa from undergoing the acrosome reaction before contact with an egg (see later). Sperm become capacitated by the female reproductive tract within the oviduct. The function of the epididymis is dependent on both **luminal testosterone-ABP complexes** that come from the seminiferous tubules and peripheral testosterone from blood.
2. *Sperm storage and emission.* Sperm are stored in the **tail of the epididymis** and **vas deferens** for several months without loss of viability. The primary function of the vas deferens, besides providing a storage site, is to propel sperm during sexual intercourse into the male urethra. The vas deferens has a very thick muscularis that is richly innervated by sympathetic nerves. Normally in response to repeated tactile stimulation of the penis during coitus, the muscularis of the vas deferens receives bursts of sympathetic stimulation that cause peristaltic contractions. Emptying of the contents of the vas deferens into the prostatic urethra is called **emission.** Emission immediately precedes **ejaculation,** which is the propulsion of semen out of the male urethra.
3. *Production and mixing of sperm with seminal contents.* During emission, contraction of the vas deferens coincides with contraction of the muscular coats of the two accessory sex glands, the **seminal vesicles** (right and left)



• **Fig. 44.11** The difference in intratesticular testosterone versus circulating testosterone concentrations and its importance in the hypothalamic-pituitary-testis axis. *Upper panel,* Feedback loop in a normal adult man. *Lower panel,* Administration of testosterone (or an androgenic analog) increases circulating testosterone (androgen) levels, which in turn increase negative feedback on release of LH. Decreased LH levels diminish Leydig cell activity and intratesticular production of androgen. Lowered intratesticular testosterone levels result in reduced sperm production and can cause infertility. (The inhibin feedback loop has been omitted from this diagram). (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

and the **prostate gland** (which surrounds the prostatic urethra). At this point, sperm become mixed with all the components of **semen.** The seminal vesicles secrete approximately 60% of the volume. These glands are the primary source of **fructose,** a critical nutrient for sperm. The seminal vesicles also secrete **semenogelins,** which induce coagulation of semen immediately after ejaculation. The alkaline secretions of the prostate, which make up about 30% of the volume, are high in **citrate, zinc, spermine,** and **acid phosphatase. Prostate-specific antigen (PSA)** is a serine protease that liquefies coagulated semen after a few minutes. PSA can be detected

in blood under conditions of prostatic infection, benign prostatic hypertrophy, and prostatic carcinoma and is currently used as one indicator of prostatic health. The predominant buffers in semen are phosphate and bicarbonate. A third accessory gland, the **bulbourethral glands** (also called *Cowper's glands*), empty into the penile urethra in response to sexual excitement before emission and ejaculation. This secretion is high in mucus, which lubricates, cleanses, and buffers the urethra. Average sperm counts are between 60 and 100 million/mL semen. Men with sperm counts below 20 million/mL, less than 50% motile sperm, or less than 60% normally conformed sperm are usually infertile.

4. *Erection, penetration, and ejaculation.* Emission and ejaculation occur during coitus in response to a reflex arc that involves sensory stimulation from the penis (via the pudendal nerve) followed by sympathetic motor stimulation to the smooth muscle of the male tract and somatic motor stimulation to the musculature associated with the base of the penis. However, for sexual intercourse to occur in the first place, the man has to achieve and maintain an **erection** of the **penis.** The penis has evolved as an intromittent organ designed to separate the walls of the vagina, pass through the potential space of the vaginal lumen, and deposit semen at the distal end of the vaginal lumen near the cervix. This process of **internal insemination** can be performed only if the penis is stiffened from the process of erection.

Erection is a neurovascular event. The penis is composed of three erectile bodies: two **corpora cavernosa** and one **corpus spongiosum** (Fig. 44.12*A*). The penile urethra runs through the corpus spongiosum. These three bodies are composed of **erectile tissue**—an anastomosing network of potential **cavernous vascular spaces** lined with continuous endothelia within a loose connective tissue support. During the **flaccid state,** blood flow to the cavernous spaces is minimal (see Fig. 44.12*A*). This is due to vasoconstriction of the vasculature (called the *helicine arteries*) and shunting of blood flow away from the cavernous spaces. In response to sexual arousal the parasympathetic cavernous nerves innervating the vascular smooth muscle of the helicine arteries release nitric oxide (NO). NO activates guanylyl cyclase, thereby increasing cyclic guanosine monophosphate (cGMP), which decreases intracellular [Ca^{++}] and causes muscular relaxation (see Fig. 44.12*B*). Vasodilation allows blood to flow into the cavernous spaces to induce engorgement and erection. It also presses on veins in the penis and reduces venous drainage (see Fig. 44.12*B*).

Andropause

There is no distinct **andropause** in men. However, as men age, gonadal sensitivity to LH decreases and androgen production drops. As this occurs, serum LH and FSH levels rise. Although sperm production typically begins to decline after age 50, many men can maintain reproductive function and spermatogenesis throughout life.

IN THE CLINIC

Inability to achieve or maintain an erection is termed **erectile dysfunction (ED)** and is one cause of infertility in men. Multiple factors can lead to ED, including insufficient androgen production; neurovascular damage (e.g., from diabetes mellitus, spinal cord injury); structural damage to the penis, perineum, or pelvis; psychogenic factors (e.g., depression, performance anxiety); and prescribed medications and recreational drugs, including alcohol and tobacco. A major development in the treatment of some forms of erectile dysfunction is use of selective cGMP phosphodiesterase inhibitors that assist in maintaining an erection (see Fig. 44.12*B*).

The Female Reproductive System

The female reproductive system is composed of the gonads, called **ovaries,** and the female reproductive tract, which includes the **oviducts, uterus, cervix, vagina,** and **external genitalia.**

The Ovary

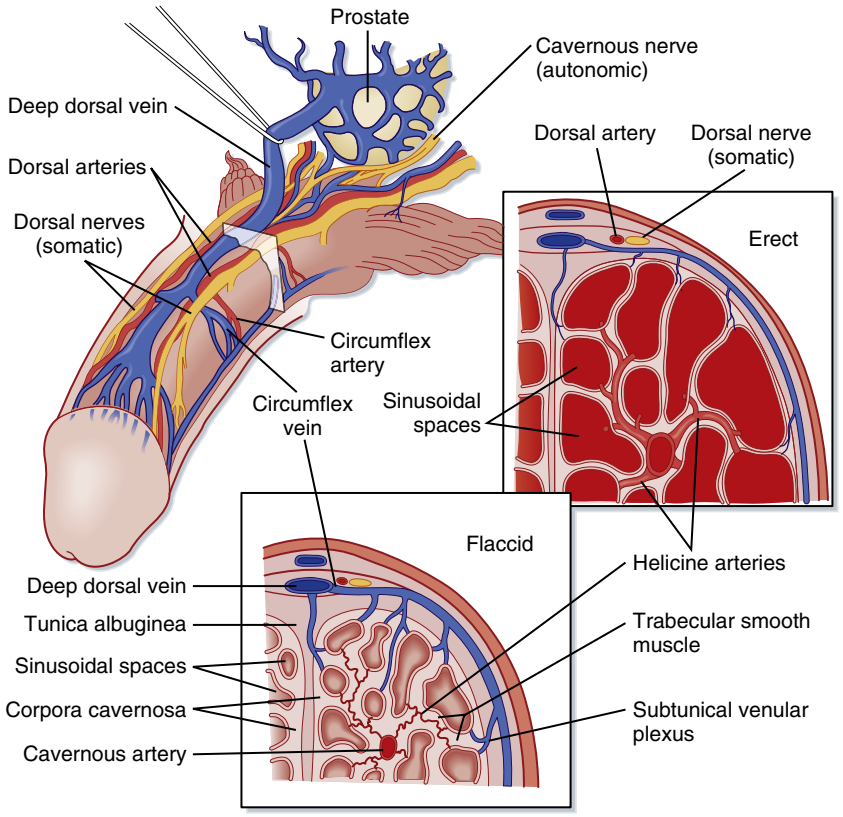
The ovary is located within a fold of peritoneum called the **broad ligament,** usually close to the lateral wall of the pelvic cavity (Fig. 44.13). Because the ovary extends into the peritoneal cavity, ovulated eggs briefly reside within the peritoneal cavity before they are captured by the oviducts.

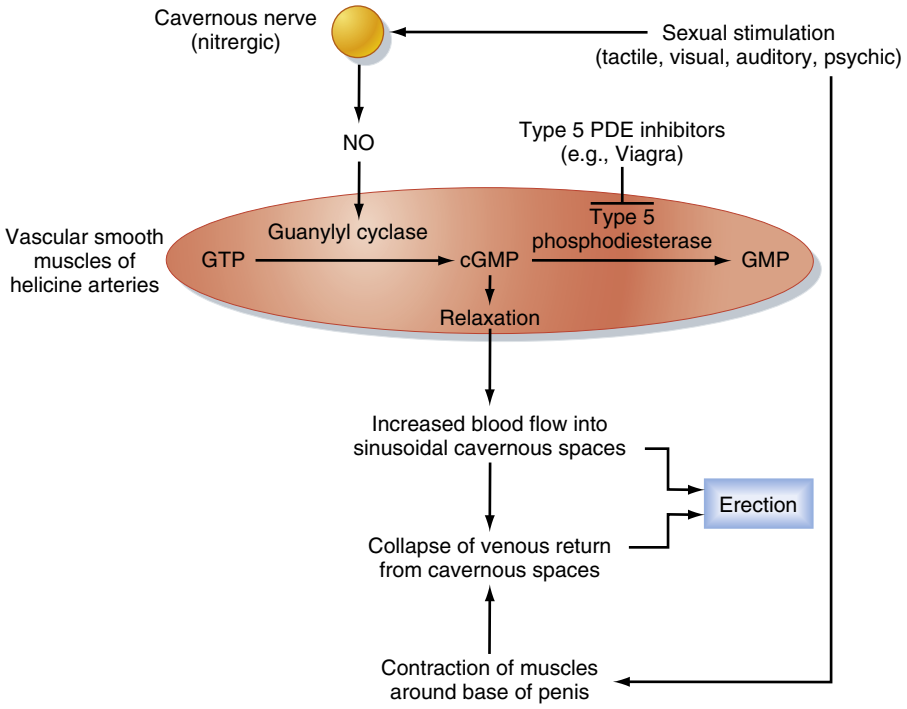
The ovary is divided into an outer cortex and inner medulla (Fig. 44.14). Neurovascular elements innervate the medulla of the ovary. The cortex of the ovary is composed of a densely cellular stroma. Within this stroma reside the **ovarian follicles** (see Fig. 44.14, F), which contain a primary oocyte surrounded by follicle cells. The cortex is covered by a connective tissue capsule, the tunica albuginea, and a layer of simple epithelium consisting of **ovarian surface epithelial cells.** There are no ducts emerging from the ovary to convey its gametes to the reproductive tract. Thus, the process of ovulation involves an inflammatory event that erodes the wall of the ovary. After ovulation the ovarian surface epithelial cells rapidly divide to repair the wall. The majority of ovarian cancer originates from this highly proliferative epithelium.

Growth, Development, and Function of the Ovarian Follicle

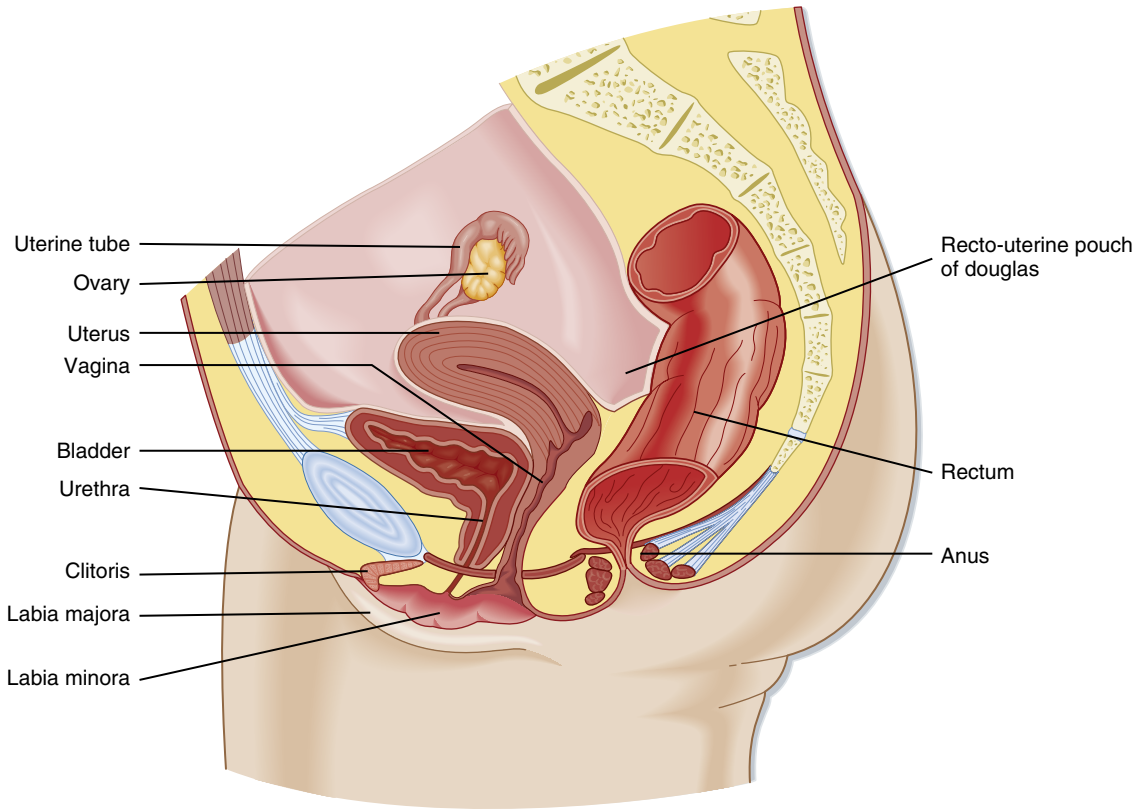
The ovarian follicle is the functional unit of the ovary, and it performs both gametogenic and endocrine functions. A histological section of the ovary from a premenopausal cycling woman contains follicular structures at many different stages of development. The life history of a follicle can be divided into the following stages:

1. Resting primordial follicle.
2. Growing preantral (primary and secondary) follicle.
3. Growing antral (tertiary) follicle.
4. Dominant (preovulatory, graafian) follicle.

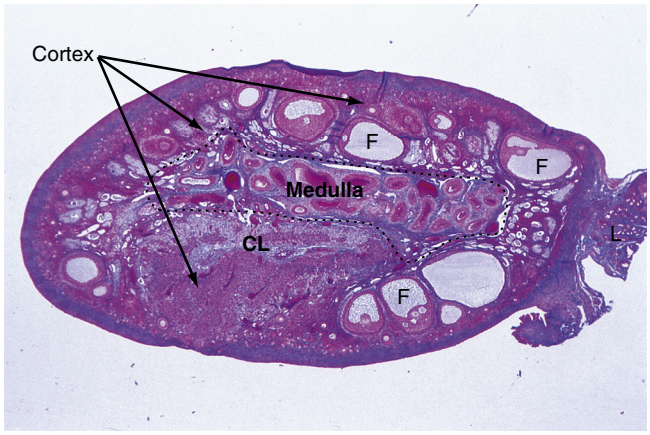




• **Fig. 44.12** **A,** Arrangement of the vasculature and cavernous tissue within the penis. During the flaccid state, blood flow into the cavernous spaces is limited by contraction of the helicine arteries. **B,** Outline of neurovascular events leading to penile erection. (**A,** From Parhon CI, Devila C. In: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2019.)



• **Fig. 44.13** Anatomy of the female reproductive system. (Modified from Drake RL, Vogl W, Mitchell AWM. *Gray's Anatomy for Students.* Philadelphia: Churchill Livingstone; 2005.)



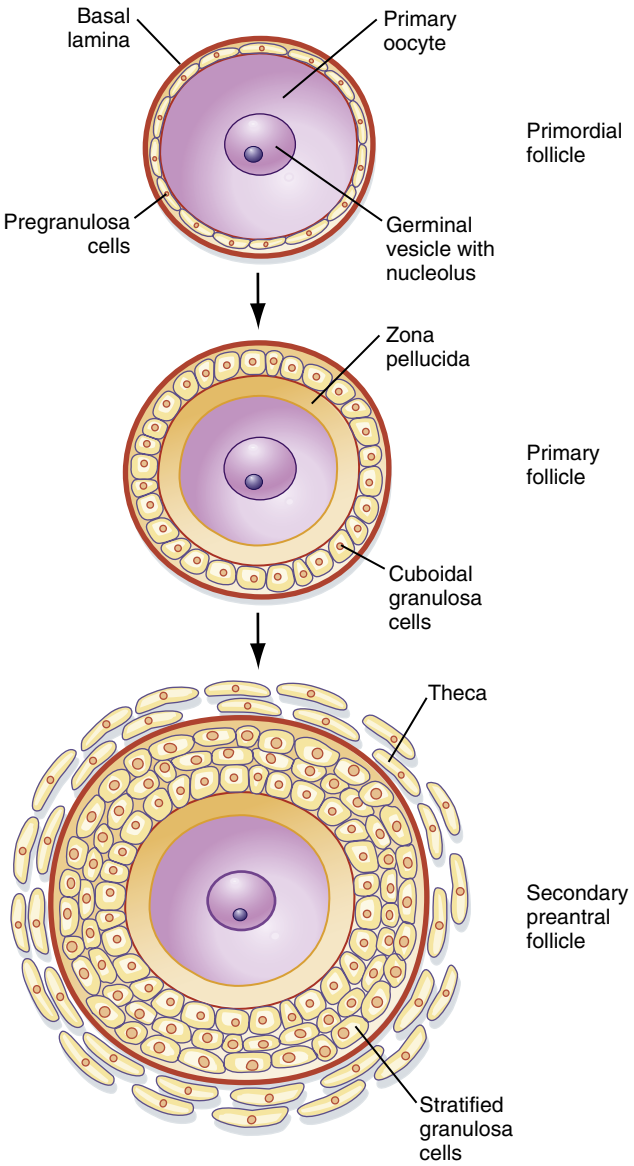
• **Fig. 44.14** Histology of the ovary. *CL*, Corpus luteum; *F*, Follicle. (Modified from Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology. A Text and Colour Atlas.* 5th ed. London: Churchill Livingstone; 2006.)

5. Dominant follicle within the periovulatory period.
6. Corpus luteum (of menstruation or of pregnancy).
7. Atretic follicles.

Resting Primordial Follicle

Growth and Structure. Resting **primordial follicles** (Fig. 44.15) represent the earliest and simplest follicular structure in the ovary. Primordial follicles appear during midgestation through the interaction of gametes and somatic cells. Primordial germ cells that have migrated to the gonad continue to divide mitotically as oogonia until the fifth month of gestation in humans. At this point the approximately 7 million oogonia enter the process of meiosis and become **primary oocytes.** During this time the primary oocytes become surrounded by a simple epithelium of somatic **follicle cells,** thereby creating the primordial follicles (see Fig. 44.15). The follicle cells establish **gap junctions** with each other and the oocyte. The follicle cells themselves represent a true avascular epithelium surrounded by a basal lamina. Similar to Sertoli cell–sperm interactions, a subpopulation of granulosa cells remains intimately attached to the oocytes throughout their development. Granulosa cells provide nutrients such as amino acids, nucleic acids, and pyruvate to support oocyte maturation.

The primordial follicles represent the **ovarian reserve** of follicles (Fig. 44.16). This reserve is reduced from a starting number of about 7 million to less than 300,000 follicles at reproductive maturity. Of these, a woman will ovulate about 450 between **menarche** (first menstrual cycle) and **menopause** (cessation of menstrual cycles). At menopause, less than 1000 primordial follicles are left in the ovary. Primordial follicles are lost primarily from death as a result of **follicular atresia.** However, a small subset of primordial follicles will enter follicular growth in waves. Because the ovarian follicular reserve represents a fixed finite number, the rate at which resting primordial follicles die or begin to develop (or both) will determine the reproductive life span



• **Fig. 44.15** Development of a primordial follicle up to a secondary preantral follicle. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

of a woman. Age at the onset of menopause has a strong genetic component but is also influenced by environmental factors. For example, cigarette smoking significantly depletes the ovarian reserve. An overly rapid rate of atresia or development will deplete the reserve and give rise to **premature ovarian insufficiency.**

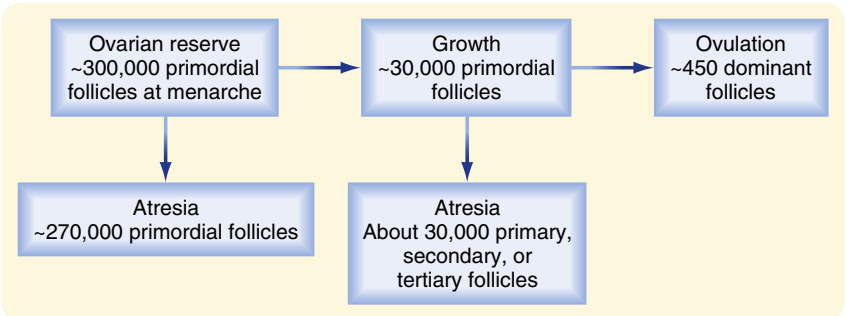
Pituitary gonadotropins maintain a normal ovarian reserve by promoting the general health of the ovary. However, the rate at which resting primordial follicles enter the growth process appears to be independent of pituitary gonadotropins. The decision of a resting follicle to enter the early growth phase is primarily dependent on intraovarian paracrine factors produced by both the follicle cells and oocytes.

The Gamete. In primordial follicles the gamete is derived from oogonia that have entered the first meiotic division; such oogonia are referred to as **primary oocytes.** Primary oocytes progress through most of prophase of the first meiotic division (termed *prophase I*) over a 2-week period and then arrest in the **diplotene stage.** This stage is characterized by the decondensation of chromatin, which supports the transcription needed for oocyte maturation. Meiotic arrest at this stage, which may last for up to 50 years. This process appears to be due to "maturational incompetence," or lack of the cell cycle proteins needed to support the completion of meiosis. The nucleus of the oocyte, called the **germinal vesicle,** remains intact at this stage.

Growing Preantral Follicles

Growth and Structure. The first stage of follicular growth is **preantral,** which refers to the development that occurs before the formation of a fluid-filled **antral cavity.** One of the first visible signs of follicle growth is the appearance of **cuboidal granulosa cells.** At this point the follicle is referred to as a **primary follicle** (see Fig. 44.15). As granulosa cells proliferate, they form a multilayered (i.e., stratified) epithelium around the oocyte. At this stage the follicle is referred to as a **secondary follicle** (see Fig. 44.15).

Once a secondary follicle acquires three to six layers of granulosa cells, it secretes paracrine factors that induce nearby stromal cells to differentiate into epithelioid **thecal cells.** Thecal cells form a flattened layer of cells around the follicle. Once a thecal layer forms, the follicle is referred to



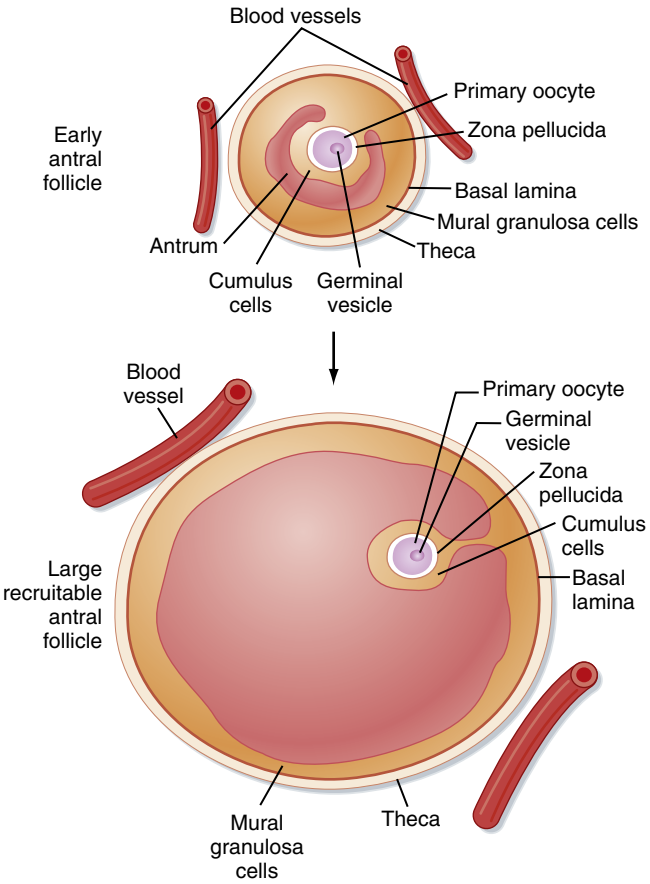
• **Fig. 44.16** Fate of ovarian follicles. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

as a **mature preantral follicle** (see Fig. 44.15). In humans it takes several months for a primary follicle to reach the mature preantral stage.

Follicular development is associated with an inward movement of the follicle from the outer cortex to the inner cortex, closer to the vasculature of the ovarian medulla. Follicles release **angiogenic factors** that induce development of one to two arterioles that form a vascular wreath around the follicle.

The Gamete. During the preantral stage, the oocyte begins to grow and produce cellular and secreted proteins. The oocyte initiates secretion of extracellular matrix glycoproteins called **ZP1, ZP2,** and **ZP3** that form the **zona pellucida** (see Fig. 44.15). The zona pellucida increases in thickness and provides a species-specific binding site for sperm during fertilization (see Pregnancy). Importantly, granulosa cells and the oocyte maintain gap junctional contact via cellular projections through the zona pellucida. The oocyte also continues to secrete paracrine factors that regulate follicle cell growth and differentiation.

Endocrine Function. Granulosa cells express the **FSH receptor** during this period, but they are primarily dependent on factors from the oocyte to grow. They do not produce ovarian hormones at this early stage of follicular development. The newly acquired thecal cells are analogous to testicular Leydig cells in that they reside outside the epithelial "nurse" cells, express the **LH receptor,** and produce **androgens.** The main difference between Leydig cells and thecal cells is that thecal cells do not express high levels of 17β-HSD. Thus the major product of theca cells is androstenedione as opposed to testosterone. Androstenedione production at this stage is minimal.



• **Fig. 44.17** Development of an early antral follicle to a mature preovulatory follicle. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

Growing Antral Follicles

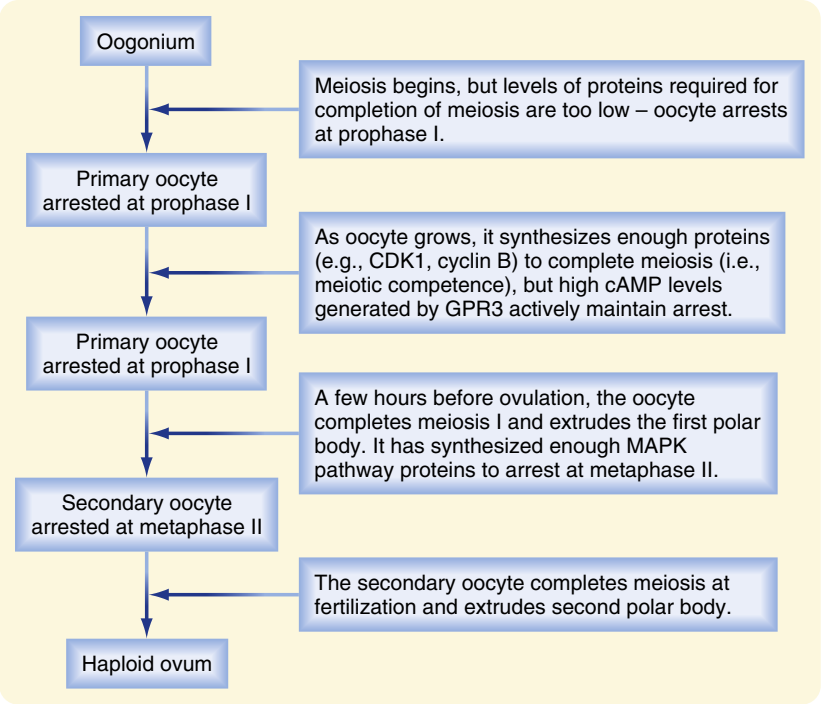
Growth and Structure. Mature preantral follicles develop into **early antral follicles** (Fig. 44.17) over a period of about 25 days, during which they grow from a diameter of about 0.1 mm to a diameter of 0.2 mm. Once the granulosa epithelium increases to six to seven layers, fluid-filled spaces appear between cells and coalesce into the **antrum.** Over a period of about 45 days, this wave of small antral follicles will continue to grow to **large recruitable antral follicles** that are 2 to 5 mm in diameter. This period of growth is characterized by about a 100-fold increase in granulosa cells (from about 10,000–1,000,000 cells). It is also characterized by swelling of the antral cavity, which increasingly divides the granulosa cells into two discrete populations: mural granulosa cells and cumulus cells (see Fig. 44.17).

Mural granulosa cells (also called the **stratum granulosum**) form the outer wall of the follicle. The basal layer is adherent to the basal lamina and in close proximity to the outer-lying thecal layers. Mural granulosa cells become highly steroidogenic and remain in the ovary after ovulation to differentiate into the corpus luteum.

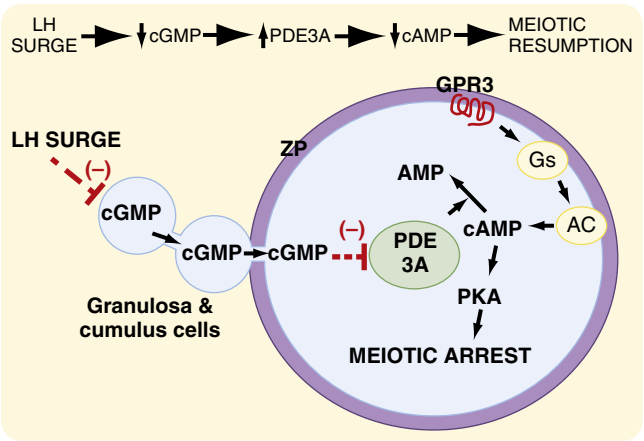
Cumulus cells are the inner cells that surround the oocyte (they are also referred to as **the cumulus oophorus** and **corona radiata**). The innermost layer of cumulus cells maintains gap and adhesion junctions with the oocyte. Cumulus cells are released with the oocyte (collectively referred to as the **cumulus-oocyte complex**) during the process of ovulation. Cumulus cells are crucial for the ability of the fimbriated end of the oviduct to "capture" and move the oocyte by a ciliary transport mechanism along the length of the oviduct to the site of fertilization (see Pregnancy).

Early antral follicles are dependent on pituitary FSH for normal growth. Large antral follicles become highly dependent on pituitary FSH for their growth and sustained viability. As discussed later, 2- to 5-mm follicles are recruited to enter a rapid growth phase via the transient increase in FSH that occurs toward the end of the previous menstrual cycle.

The Gamete. The oocyte grows rapidly in the early stages of antral follicles; growth then slows in larger follicles. In early primary and secondary follicles, the oocyte fails to complete meiosis I because of a dearth of specific meiosis-associated proteins. During the antral stage the oocyte synthesizes sufficient amounts of cell cycle components so it becomes competent to complete meiosis I at ovulation. However, larger antral follicles gain **meiotic competence** but still maintain **meiotic arrest** until the midcycle LH surge. Meiotic arrest is achieved by maintenance of **elevated cyclic adenosine monophosphate (cAMP) levels** in the



• **Fig. 44.18** Events involved in meiotic arrest and maturation of the oocyte. *MAPK*, Mitogen-activated protein kinase. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)



• **Fig. 44.19** Model of how LH surge leads to resumption of meiosis. *PDE*, phosphodiesterase.

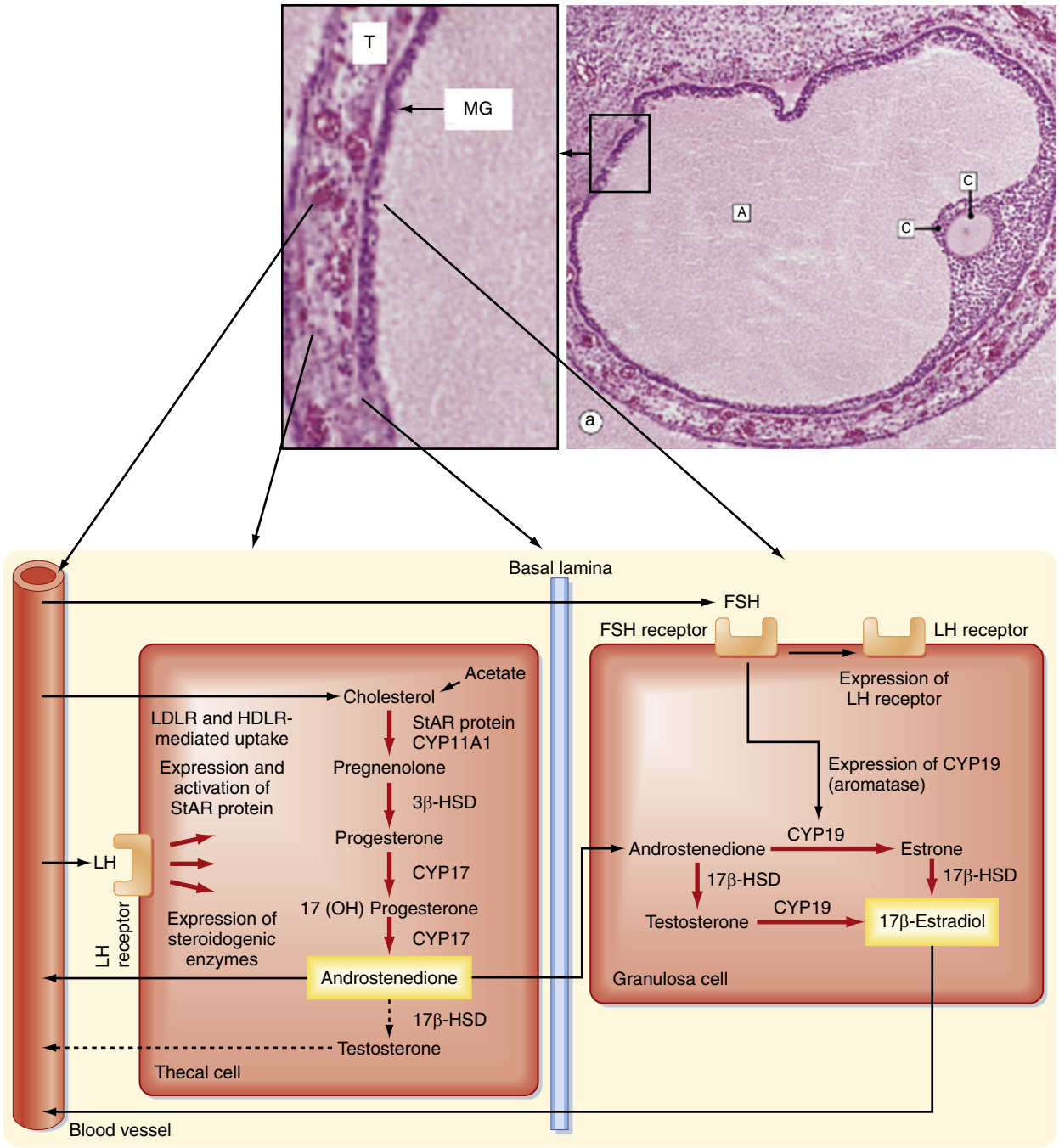
mature oocyte (Figs. 44.18 and 44.19). The constitutively active (i.e., not requiring a ligand) Gs protein-coupled receptor **GPR3** maintains high cAMP. The oocyte-specific phosphodiesterase PDE3A degrades cAMP to inactive AMP. Before the LH surge, PDE3A is inhibited by cGMP, which is produced within cumulus and granulosa cells and enters the oocyte via gap junctions. Note that the human egg arrests after ovulation at a second point, metaphase II, until it is fertilized by sperm (see Fig. 44.18).

Endocrine Function. The thecal cells of large antral follicles produce significant amounts of **androstenedione** and less testosterone. Androgens are converted to **17β-estradiol** by the granulosa cells (Fig. 44.20). At this stage, FSH stimulates proliferation of granulosa cells and induces the expression of **CYP19 (aromatase)** required for estrogen synthesis. Additionally, the mural granulosa cells of the large antral follicles produce increasing amounts of **inhibin** during the early follicular phase. Low levels of estrogen and inhibin negatively feedback on FSH secretion, thereby contributing to selection of the follicle with the most highly FSH-responsive cells.

Dominant Follicle

Growth and Structure. As already discussed, at the end of a previous menstrual cycle, a crop of large (2–5 mm) antral follicles (see Fig. 44.17) are **recruited by a rise in FSH** to begin rapid gonadotropin-dependent development. The total number of recruited follicles in both ovaries can be as high as 20 in a younger woman (<33 years old) but rapidly declines at older ages. The number of recruited follicles is reduced to the **ovulation quota** (one in humans) by the process of **selection.** As FSH levels decline the rapidly growing follicles progressively undergo atresia until one follicle is left. Generally the largest follicle with the most FSH receptors of the recruited crop becomes the **dominant follicle.** Selection occurs during the early follicular phase. By midcycle the dominant follicle becomes a large **preovulatory follicle** that is 20 mm in diameter and contains about 50 million granulosa cells by the midcycle gonadotropin surge.

The Gamete. The oocyte is competent to complete meiosis I but remains arrested in the dominant follicle until the



• **Fig. 44.20** Two-cell model for steroidogenesis in the dominant follicle. *Top panel: MG*, Mural granulosa; *T*, theca. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

LH surge. Growth of the oocyte continues but at a slower rate until the oocyte reaches a diameter of about 140 μm by ovulation (i.e., ≈20 times the diameter of an erythrocyte).

Endocrine Function. The newly selected follicle emerges as a significant steroidogenic "gland." Ovarian steroidogenesis requires both theca and granulosa cells. As discussed earlier, **thecal cells** (see Fig. 44.20, T) express **LH receptors** and produce primarily androstenedione. Basal levels of LH stimulate expression of steroidogenic enzymes in thecal cells. The thecal cells are richly vascularized and thus have access to cholesterol within the lipoprotein particles LDL and HDL. LH promotes expression of the **LDL receptor and HDL receptor (SR-B1),** which import cholesterol. LH also promotes robust expression of **CYP11A1** (side chain cleavage enzyme), **3β-HSD, and CYP17** with both 17-hydroxylase activity and 17,20-lyase activity. Androgens (primarily **androstenedione** but also some **testosterone**) released from the theca diffuse into the **mural granulosa cells** or enter the vasculature surrounding the follicle.

The **mural granulosa cells** (see Fig. 44.20, MG) of the selected follicle have a high number of **FSH receptors** and are very sensitive to FSH, which upregulates **CYP19**

(aromatase) gene expression and activity. CYP19 converts androstenedione to the weak estrogen **estrone** and converts testosterone to the potent estrogen **17β-estradiol.** Granulosa cells express activating isoforms of **17β-HSD,** which converts the less active estrone to highly active 17β-estradiol. In addition, FSH induces expression of **inhibin B** during the follicular phase.

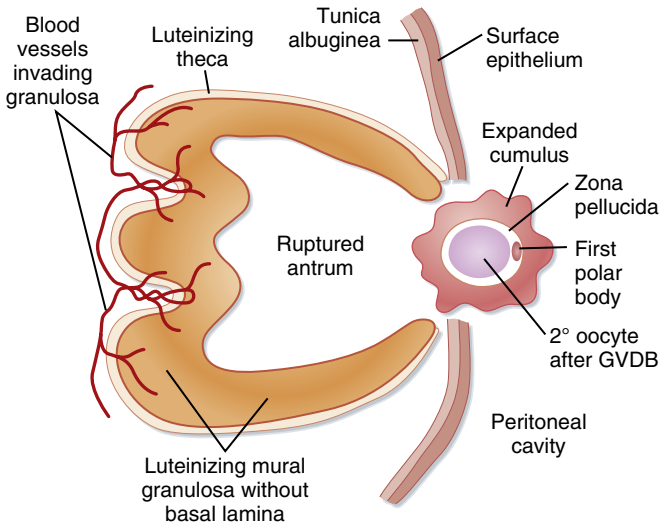
Importantly, FSH also induces expression of **LH receptors** in mural granulosa cells during the second half of the follicular phase (see Fig. 44.20). Thus mural granulosa cells acquire the ability to respond to LH, which allows these cells to maintain high levels of CYP19 in the face of declining FSH levels. Acquisition of LH receptors also ensures that mural granulosa cells respond to the LH surge.

The Dominant Follicle During the Periovulatory Period

The **periovulatory period** is defined as the time from the onset of the LH surge to expulsion of the cumulus-oocyte complex out of the ovary (i.e., ovulation). This process lasts for 32 to 36 hours in women. Starting at the same time and superimposed on the process of ovulation is a change in the steroidogenic function of theca and mural granulosa cells. This process is called **luteinization** and culminates in formation of a **corpus luteum** that is capable of producing high amounts of **progesterone,** along with estrogen, within a few days after ovulation. Thus the LH surge induces the onset of complex processes during the periovulatory period that complete the gametogenic function of the ovary for a given month and switches the endocrine function to prepare the female reproductive tract for implantation and gestation.

Growth and Structure. The LH surge induces dramatic structural changes in the dominant follicle that involves its rupture, ovulation of the cumulus-oocyte complex, and biogenesis of a new structure called the **corpus luteum** from the remaining thecal and mural granulosa cells. Major structural changes occur during this transition:

1. Before ovulation the large preovulatory follicle presses against the ovarian surface and generates a poorly vascularized bulge of the ovarian wall called the **stigma.** The LH surge induces release of inflammatory cytokines and hydrolytic enzymes from the theca and granulosa cells. These secreted components lead to breakdown of the follicle wall, tunica albuginea, and surface epithelium in the vicinity of the stigma (Fig. 44.21). At the end of this process the antral cavity becomes continuous with the peritoneal cavity.
2. The attachment of the cumulus cells to the mural granulosa cells degenerates, and the cumulus-oocyte complex becomes free-floating within the antral cavity (see Fig. 44.21). Cumulus cells also respond to the LH surge by secreting hyaluronic acid and other extracellular matrix components. These substances enlarge the entire cumulus-oocyte complex, a process called **cumulus expansion** (see Fig. 44.21). This enlarged cumulus-oocyte complex is more easily captured and transported by the oviduct. The expanded cumulus also makes the cumulus-oocyte complex easier for spermatozoa to find. Sperm express a **membrane hyaluronidase** that allows them to penetrate the expanded cumulus. The cumulus-oocyte complex is released through the ruptured stigma through a relatively slow process.
3. The basal lamina of mural granulosa cells is broken down so that blood vessels and outer-lying theca cells can push into the granulosa cells. Granulosa cells secrete **angiogenic factors** such as vascular endothelial growth factor, angiopoietin 2, and basic fibroblast growth factor (bFGF), which significantly increase the blood supply to the new corpus luteum.

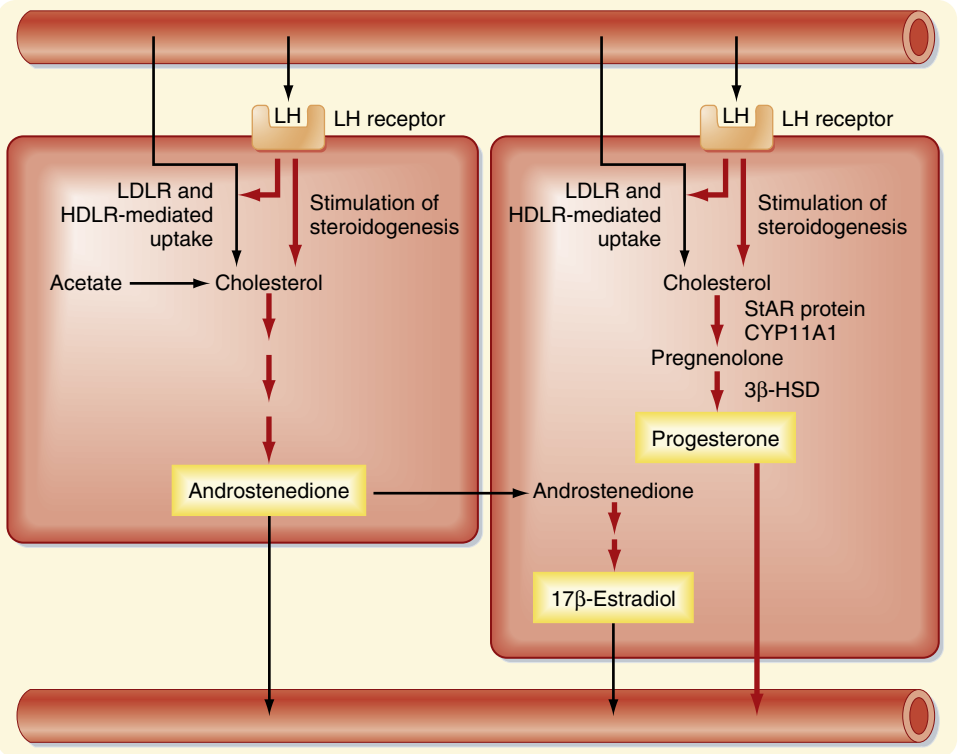


• **Fig. 44.21** Ovulation. *GVBD*, Germinal vesicle breakdown. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

The Gamete. Before ovulation the primary oocyte is competent to complete meiosis, but it is arrested in prophase I (see Fig. 44.18). The LH surge inhibits production of cGMP by granulosa and cumulus cells, thereby removing inhibition of the oocyte-specific PDE3A. PDE3A proceeds to degrade cAMP to inactive AMP, thereby removing the brake on meiotic progression (Fig. 44.19). The oocyte then progresses to metaphase II and subsequently arrests at metaphase II until fertilization.

Endocrine Function. Both theca and mural granulosa cells express LH receptors at the time of the LH surge. The LH surge induces differentiation of the granulosa cells—a process that continues for several days after ovulation. During the periovulatory period, the LH surge induces the following shifts in steroidogenic activity of the mural granulosa cells (that are now turning into granulosa lutein cells).

1. *Transient inhibition of CYP19 expression and consequently estrogen production.* The rapid decline in estrogen helps turn off the positive feedback on LH secretion.
2. *Breakdown of the basal lamina and vascularization of the granulosa cells.* This makes LDL and HDL cholesterol accessible to these cells for steroidogenesis. The LH surge also increases expression of the LDL receptor and HDL receptor (SR-BI) in granulosa cells.



• **Fig. 44.22** Steroidogenic pathways in the corpus luteum. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

3. *Onset of expression of StAR protein, CYP11A1 (side chain cleavage enzyme), and 3β-HSD* (Fig. 44.22). Expression of these enzymes is key to the onset of production of high levels of progesterone by these cells. As discussed later, high progesterone synthesis is absolutely necessary for maintenance of pregnancy. Because CYP17 activity, especially its 17,20-lyase function, is largely absent in granulosa lutein cells, progesterone is not further metabolized to another steroid but instead exits the cells and enters the circulation.

The Corpus Luteum

Growth and Structure. After ovulation the remnant of the antral cavity fills with blood from damaged blood vessels in the vicinity of the stigma. This gives rise to a **corpus hemorrhagicum.** Within a few days, red blood cells and debris are removed by macrophages, and fibroblasts fill in the antral cavity with a hyaline-like extracellular matrix. In the mature corpus luteum the granulosa cells, now called **granulosa lutein cells,** enlarge and become filled with lipid (cholesterol esters). The enlarged granulosa lutein cells collapse into and partially fill in the old antral cavity. The theca along with blood vessels, mast cells, macrophages, leukocytes, and other resident connective tissue cells infiltrate the granulosa layer at multiple sites.

The human corpus luteum is programmed to live for 14 days, plus or minus 2 days **(corpus luteum of menstruation),** unless "rescued" by the LH-like hormone **human chorionic gonadotropin (hCG),** which originates from an implanting embryo. If rescued, the **corpus luteum of pregnancy** will remain viable during the pregnancy (usually ≈9 months). The mechanism by which the corpus luteum of menstruation regresses in 14 days is not fully understood. The corpus luteum appears to become progressively less sensitive to basal levels of LH, so that hCG binding to the LH receptor is needed for continued health and function of the corpus luteum. Regression appears to involve release of the **prostaglandin $PGF_{2\alpha}$** from both granulosa lutein cells and the uterus in response to declining levels of progesterone during the second week of the luteal phase. Several paracrine factors (endothelin, monocyte chemotactic protein-1) from immune and vascular cells are likely to play a role in the demise and removal of granulosa lutein cells. The corpus luteum is ultimately turned into a scarlike body called the **corpus albicans,** which sinks into the medulla of the ovary and is slowly absorbed.

The Gamete. The LH surge induces two parallel events, ovulation and luteinization. If ovulation occurs normally, the corpus luteum is devoid of a gamete.

Endocrine Function. Before the LH surge, the granulosa cells have very low capacity to convert cholesterol into a steroid hormone. The LH surge induces the onset of expression of CYP11A1, 3β-HSD and StAR protein, allowing granulosa lutein cells to convert cholesterol into progesterone. Because CYP17 expression is extremely low, progesterone accumulates and moves out of the granulosa lutein cells and enters the vasculature. Progesterone production by the corpus luteum (see Fig. 44.22) increases steadily from the

onset of the LH surge and peaks during the midluteal phase. The main purpose of this timing is to transform the uterine lining into an adhesive and supportive structure for implantation and early pregnancy. As discussed later, the midluteal phase is synchronized with early embryogenesis so the uterus is optimally primed when a blastocyst enters the uterus around day 22 of the menstrual cycle. Estradiol continues to be produced by theca lutein cells and granulosa lutein cells. Estrogen production transiently decreases in response to the LH surge but then rebounds and peaks at the midluteal phase. Estradiol induces the progesterone receptor in progesterone target cells, such as the uterine endometrium, and thereby ensures a full response to progesterone.

Luteal hormonal output is absolutely dependent on basal LH levels (see Fig. 44.22). In fact, progesterone output is closely correlated with the pulsatile pattern of LH release in women. Both FSH and LH are reduced to basal levels during the luteal phase by negative feedback from progesterone and estrogen. In addition, granulosa lutein cells secrete **inhibin,** which selectively represses FSH secretion.

The corpus luteum must generate large amounts of progesterone to support implantation and early pregnancy. Accordingly, the life of the corpus luteum is very regular, and a shortened luteal phase typically leads to infertility. The quality of the corpus luteum is largely dependent on the size and health of the dominant follicle from which it developed, which in turn is dependent on normal hypothalamic and pituitary stimulation during the follicular phase. Numerous factors that perturb hypothalamic and pituitary output during the follicular phase, including heavy exercise, starvation, high prolactin levels, and abnormal thyroid function, can lead to **luteal phase deficiency** and **infertility.**

Atretic Follicles

Follicular atresia refers to the demise of an ovarian follicle. During atresia the granulosa cells and oocytes undergo **apoptosis.** The thecal cells typically persist and repopulate the cellular stroma of the ovary. The thecal cells retain LH receptors and the ability to produce androgens and are collectively referred to as the **"interstitial gland"** of the ovary. Follicles can undergo atresia at any time during development.

Follicular Development With Respect to the Monthly Menstrual Cycle

The **human menstrual cycle** strictly refers to the monthly discharge of discarded uterine lining as **menstrual blood** or **menstrual flow** (a period referred to as **menses**) through the process of **menstruation** (see later). In fact, it is the onset or lack thereof of menses, as detected by the woman herself, that is the primary evidence for the cessation of menstruation (e.g., due to pregnancy or menopause) or a change in the duration and/or frequency of the menstrual cycle. However, it is useful from an endocrinological perspective to consider the human menstrual cycle as having an ovarian cycle and a uterine cycle, with the latter being driven by the former. As discussed later, there are also hypothalamic, pituitary, oviductal, and vaginal components of the human menstrual cycle. The reproductive function of the menstrual cycle is the collective orchestration by ovarian hormones of the functions of the hypothalamus, pituitary, uterus, oviduct, cervix, and vagina—and even the ovary itself—to: (1) produce a fertilizable gamete (egg); (2) provide a supportive environment for intercourse, reception of sperm, fertilization of egg and early embryogenesis; (3) prepare the uterine lining for implantation, placentation and pregnancy; and (4) minimize the possibility of a superimplantation (i.e., a second implantation) from occurring and/or prevent an ascending infection from moving up to the uterus from the vagina.

The first half of the monthly menstrual cycle is referred to as the **follicular phase** of the **ovary** and is characterized by recruitment and growth of a large antral follicle, selection of the dominant follicle, and growth of the dominant follicle until ovulation. The dominant follicle must contain a fully developed oocyte and somatic follicle cells that secrete high levels of estrogen.

The second (post-ovulatory) half of the monthly menstrual cycle is referred to as the **luteal phase** of the ovary and is dominated by hormonal secretions of the **corpus luteum**. The corpus luteum must secrete both **progesterone** and **estradiol** for progression of the normal cycle.

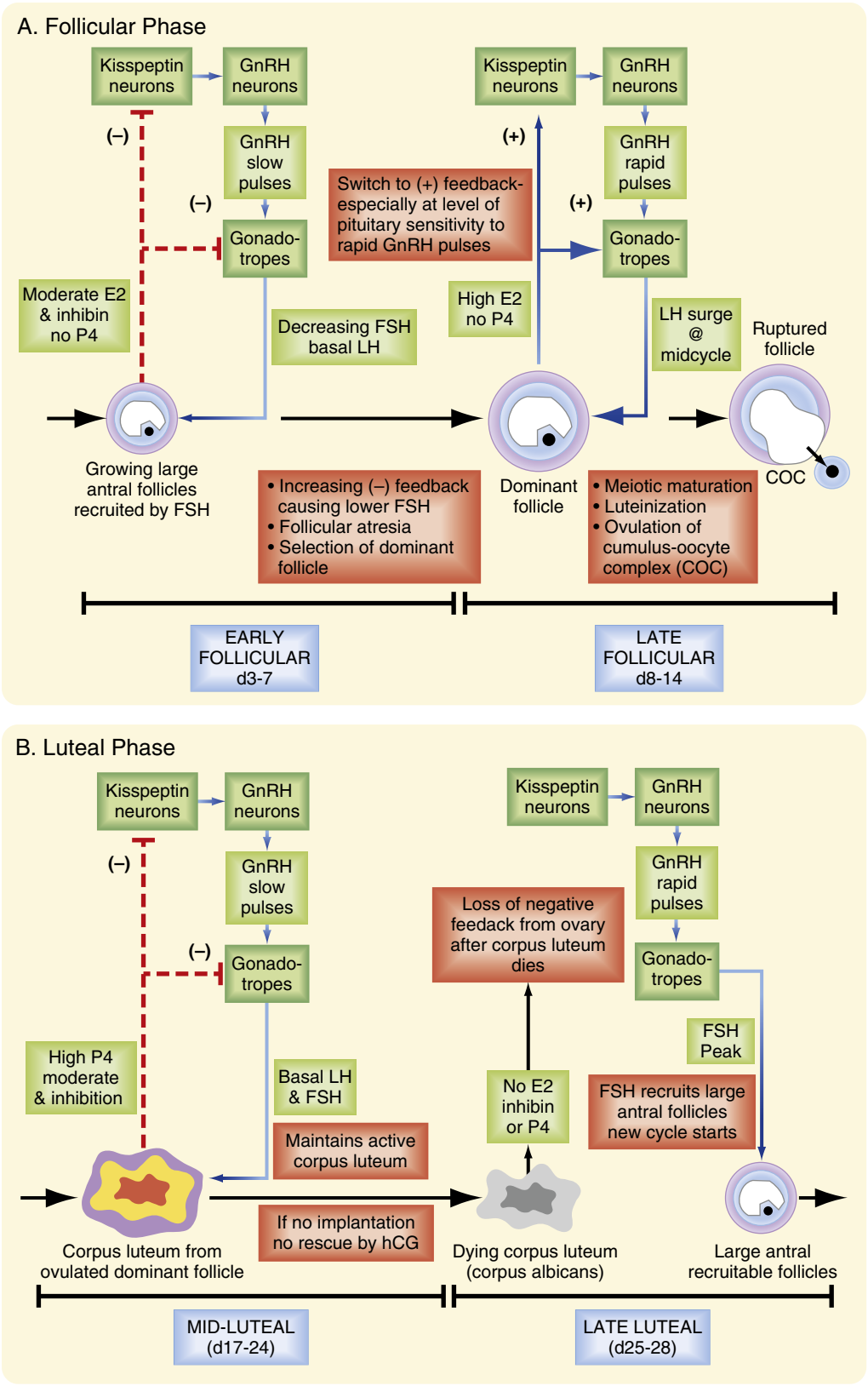
Regulation of Late Stages of Follicular Development, Ovulation, and Luteinization: The Human Menstrual Cycle

As stated earlier, late stages of follicular development and luteal function are absolutely dependent on normal hypothalamic and pituitary function. As in the male, hypothalamic neurons secrete **GnRH** in a **pulsatile** manner. GnRH in turn stimulates LH and FSH production by pituitary gonadotropes. A high frequency of GnRH pulses (1 pulse per 60–90 minutes) selectively promotes LH production, whereas a slow frequency promotes FSH production. One major difference between the male and female reproductive axes is the midcycle gonadotropin surge, which is dependent on a constant high level of estrogen coming from the dominant follicle.

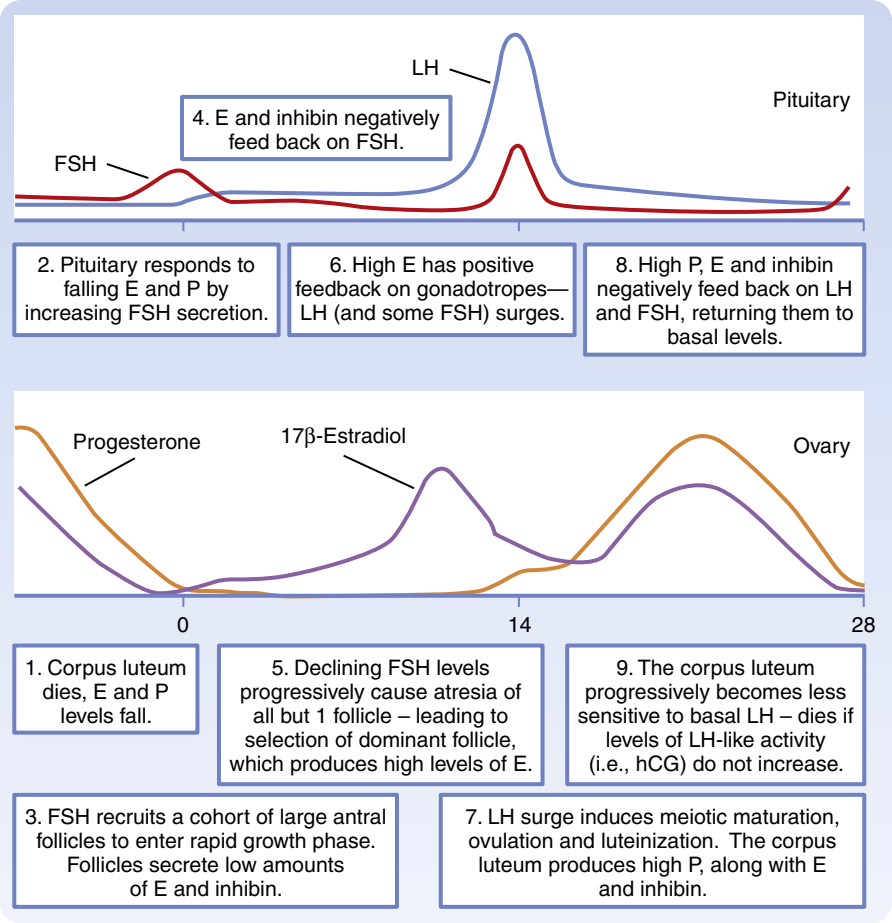
A highly dynamic "conversation" occurs among the ovary, pituitary, and hypothalamus in which the events of the menstrual cycle are orchestrated, beginning with the ovary at the end of the luteal phase of a previous nonfertile cycle (Fig. 44.23). Events that follow are numbered according to Fig. 44.24:

Event 1: In the absence of fertilization and implantation, the **corpus luteum regresses and dies** (called **luteolysis**). This leads to a dramatic **decline** in levels of **progesterone, estrogen, and inhibin** by day 24 of the menstrual cycle.

Event 2: The **pituitary gonadotrope** perceives the end of luteal function as a release from negative feedback (see Fig. 44.23*B*, Late Luteal Phase). This leads to an **increase** in **FSH** about 2 days before the onset of menstruation. The basis for the selective increase in FSH is incompletely



• **Fig. 44.23** **A,** Endocrine signaling leading to the ovulation of a dominant follicle at the end of the follicular phase of the menstrual cycle. **B,** Endocrine signaling during the luteal phase of a nonpregnant menstrual cycle leading to the death of the corpus luteum and recruitment of follicles to begin next cycle.



• **Fig. 44.24** The human menstrual cycle, with emphasis on the "dialogue" between ovary and pituitary gonadotropes. Note that the relative changes in the levels of E_2 and inhibin are shown by the same line.

understood, but it may be due to the slow frequency of GnRH pulses during the luteal phase, which in turn is due to high progesterone levels.

Event 3: The rise in FSH levels recruits a crop of **large (2–5 mm in diameter) antral follicles** to begin rapid, highly gonadotropin-dependent growth. These follicles produce **low levels of estrogen and inhibin B.**

Event 4: The gonadotrope responds to the slowly rising levels of estrogen and inhibin B by **decreasing FSH secretion** (see Fig. 44.23*A*, Early Follicular Phase). The absence of progesterone promotes an **increase** in the **frequency of GnRH pulses,** thereby selectively **increasing LH** synthesis and secretion by the gonadotrope. Thus the **LH:FSH ratio slowly increases** throughout the follicular phase.

Event 5: The ovary's response to declining FSH levels is **follicular atresia of all of the recruited follicles** except for one dominant follicle (see Fig. 44.23*A*, Early Follicular Phase). Thus the process of **selection** is driven by an extreme dependency of follicles on FSH in the face of declining FSH secretion. Usually only the largest follicle with the most FSH receptors and best blood supply can survive. This follicle produces **increasing amounts of 17β-estradiol and inhibin B**. A critical action of FSH at this time is induction of the expression of **LH receptors** in the **mural granulosa cells** of the dominant follicle (see Fig. 44.23*A*, Late Follicular Phase).

Event 6: Once the dominant follicle causes **circulating estrogen levels to exceed 200 pg/mL for about 50 hours** in women, estrogen exerts a **positive feedback** on the gonadotrope to produce the **midcycle LH surge**. This is enhanced by the small amount of progesterone secreted at midcycle. The exact mechanism of the positive feedback is unknown. However, it requires changes at the level of the pituitary, as **GnRH receptors** and the sensitivity to GnRH signaling increase dramatically in the gonadotropes. The hypothalamus contributes to the gonadotropin surge by increasing the frequency of GnRH pulses. There appears to be a role for midcycle progesterone in priming the hypothalamus.

Event 7: The LH surge drives **meiotic maturation, ovulation**, and **differentiation of granulosa cells** into progesterone-producing cells (see Fig. 44.23*A*, Late Follicular Phase).

Event 8: **Rising levels of progesterone, estrogen, and inhibin A** by the mature **corpus luteum** negatively feedback on pituitary gonadotropes. Even though estradiol levels exceed the 200 pg/mL threshold for positive

feedback, the high progesterone levels now produced by the corpus luteum block any positive feedback of estradiol. Consequently, both **FSH and LH levels decline** to basal levels (see Fig. 44.23*B*, Mid-Luteal Phase).

Event 9: **Basal levels of LH** (but not FSH) are absolutely required for **normal corpus luteum function.** However, the corpus luteum becomes progressively insensitive to LH signaling and will die unless LH-like activity (i.e., hCG from an implanted embryo) increases. In a nonfertile cycle the corpus luteum of menstruation will regress in 14 days, and progesterone and estrogen levels will start to decline by about 10 days, thereby cycling back to event 1 (see Fig. 44.23*B*, Late Luteal Phase).

From this sequence of events, it is evident that the **ovary is the primary clock for the menstrual cycle.** The timing of the two main pituitary-based events—the transient rise in FSH that recruits large antral follicles and the LH surge that induces ovulation—is determined by two ovarian events. These are: (1) the highly regular life span of the corpus luteum and its demise after 14 days; and (2) growth of the dominant follicle to the point at which it can maintain a sustained high production of estrogen that induces a switch to positive feedback at the pituitary. In essence the dominant follicle tells the pituitary it is ready to undergo ovulation and luteinization.

The Oviduct

Structure and Function

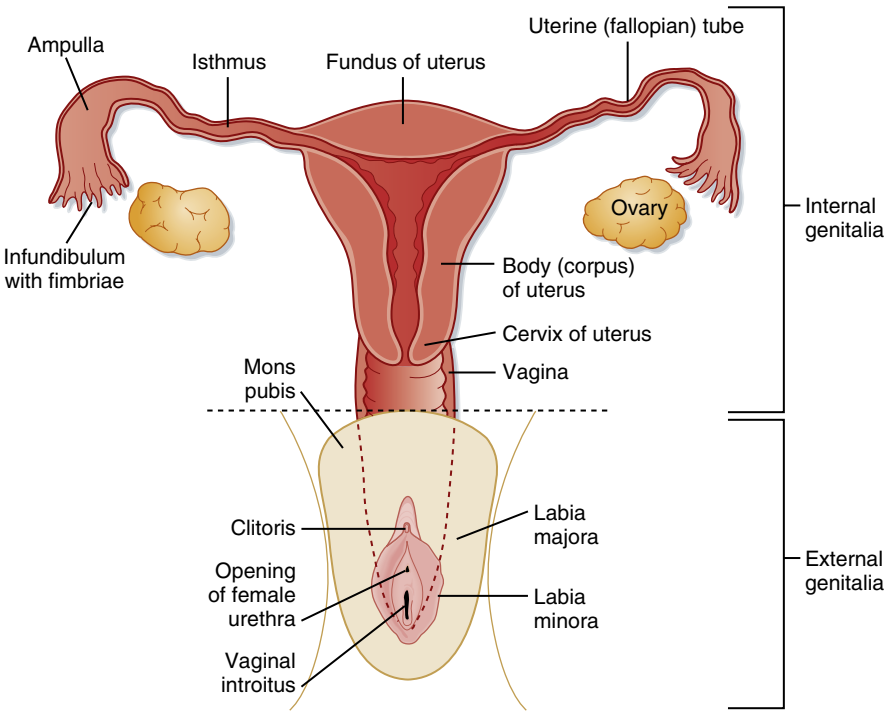
The **oviducts** (also called the **uterine tubes** and the **fallopian tubes**) are muscular tubes with the distal ends close to the surface of each ovary and the proximal ends traversing the wall of the uterus. The oviducts are divided into four sections (going from distal to proximal): the **infundibulum,** or open end of the oviduct, which has fingerlike projections called **fimbriae** that sweep over the surface of the ovary; the **ampulla,** which has a relatively wide lumen and extensive folding of the mucosa; the **isthmus,** which has a relatively narrow lumen and less mucosal folding; and the **intramural** or **uterine segment,** which extends through the uterine wall at the superior corners of the uterus (Fig. 44.25).

The main functions of the oviducts are to:

1. Capture the **cumulus-oocyte complex** at ovulation and transfer the complex to a midway point (the **ampullary-isthmus junction**), where **fertilization** takes place. Oviductal secretions coat and infuse the cumulus-oocyte complex and are likely required for viability and fertilizability.
2. Provide a site for **sperm storage.** Women who ovulate up to 5 days after sexual intercourse can get pregnant. Sperm remain viable by adhering to the epithelial cells lining the isthmus. The secretions of the oviduct also induce **capacitation** and **hyperactivity of sperm.**
3. Secrete fluids that provide nutritional support to the **preimplantation embryo.**

The timing of movement of the embryo into the uterus is critical because the uterus has an implantation window of about 3 days. The oviduct needs to hold the early embryo until it reaches the blastocyst stage (5 days after fertilization) and then allow it to pass into the uterine cavity.

The wall of the oviduct is composed of a mucosa (called the **endosalpinx**), a two-layered muscularis (called the



• **Fig. 44.25** Schematic of the female reproductive system. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

myosalpinx), and an outer-lying connective tissue (the **perisalpinx**). The endosalpinx is thrown into many folds, almost to the extent that the lumen is obliterated. The lining is composed of a simple epithelium made up of two cell types: **ciliated cells** and **secretory cells.** The cilia are most numerous at the infundibular end and propel the cumulus-oocyte complex toward the uterus. The cilia on the fimbriae are the sole mechanism for transport of the ovulated cumulus-oocyte complex. Once the complex passes through the ostium of the oviduct and enters the ampulla, it is moved by both cilia and peristaltic contractions of the muscularis.

The secretory cells of the endosalpinx produce a protein-rich mucus that is conveyed along the oviduct to the uterus by the cilia. This ciliary-mucus escalator maintains a healthy epithelium, moves the cumulus-oocyte complex toward the uterus, and may provide directional cues for swimming sperm. Movement of the cumulus-oocyte complex slows at the ampullary-isthmus junction, where fertilization normally takes place. This appears to be due in part to thick mucus produced by the isthmus and increased tone of the muscularis of the isthmus. The composition of oviductal secretions is complex and includes growth factors, enzymes, and oviduct-specific glycoproteins. Note that the clinical process of in vitro fertilization has shown that secretions of the oviduct are not absolutely necessary for fertility. However, normal oviductal function is absolutely required for both fertilization and implantation after in vivo insemination (i.e., natural sexual intercourse). Normal oviductal function also minimizes the risk of **ectopic implantation** and **ectopic pregnancy,** which occurs most often within the oviduct.

Hormonal Regulation During the Menstrual Cycle

In general, estrogen secreted during the follicular phase increases epithelial cell size and height in the endosalpinx. Estrogen increases blood flow to the lamina propria of the oviducts, promotes production of oviduct-specific glycoproteins (whose functions are poorly understood), and increases ciliogenesis throughout the oviduct. Estrogen promotes secretion of thick mucus in the isthmus and increases the tone of the muscularis of the isthmus, thereby keeping the cumulus-oocyte complex at the ampullary-isthmus junction for fertilization. In addition, it should be noted that oviductal epithelial cells express the LH receptor, which may synergize with estrogen to optimize oviductal function during the periovulatory period. Following ovulation, high progesterone, along with estrogen, during the early luteal to midluteal phase decreases epithelial cell size and function. Progesterone further promotes deciliation, decreases the secretion of thick mucus, and relaxes the tone in the isthmus.

The Uterus

Structure and Function

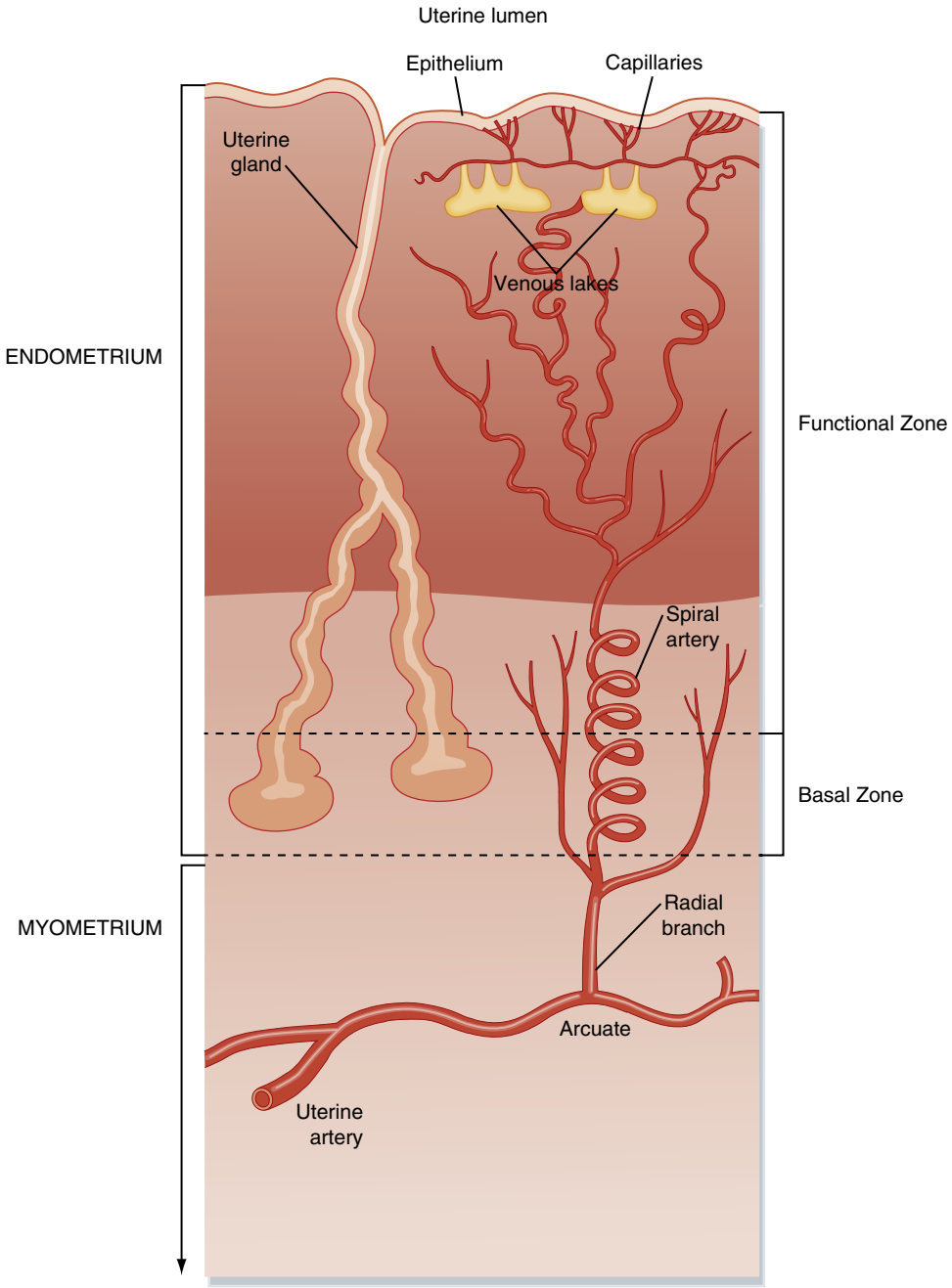
The **uterus** is a single organ that sits in the midline of the pelvic cavity between the bladder and the rectum. The mucosa of the uterus is called the **endometrium,** the three-layered thick muscularis is called the **myometrium,** and the outer connective tissue and serosa are called the **perimetrium.** The parts of the uterus are (1) the **fundus,** which is the portion that rises superiorly from the entrance of the oviducts; (2) the **body** of the uterus, which makes up most of the uterus; (3) the **isthmus,** a short, narrowed part of the body at its inferior end; and (4) the **cervix,** which extends into the **vagina** (see Figs. 44.13 and 44.25). Because the cervical mucosa is distinct from the rest of the uterus and does not undergo the process of menstruation, it will be discussed separately later.

The established functions of the uterus are all related to fertilization and pregnancy (discussed later). The main functions of the uterus are to:

1. Assist movement of sperm from the vagina to the oviducts.
2. Provide a suitable site for attachment and implantation of the blastocyst, including a thick nutrient-rich stroma.
3. Limit the invasiveness of the implanting embryo so it stays in the endometrium and does not reach the myometrium.
4. Provide a maternal side of the mature placental architecture, including the basal plate to which the fetal side attaches, and large intervillous spaces that become filled with maternal blood after the first trimester.
5. Grow and expand with the growing fetus so it develops within an aqueous nonadhesive environment.
6. Provide strong muscular contractions to expel the fetus and placenta at term.

To understand the function of the uterus and uterine changes during nonfertile menstrual cycles, the fine structure of the endometrium and the relationship of uterine blood supply to the endometrium will be reviewed (Fig. 44.26). The luminal surface of the endometrium is covered with a simple cuboidal/columnar epithelium. The epithelium is continuous with mucosal glands (called **uterine glands**) that extend deep into the endometrium. The mucosa is vascularized by **spiral arteries,** which are branches of the **uterine artery** that run through the myometrium. The terminal arterioles of the spiral arteries project just beneath the surface epithelium. These arterioles give rise to a subepithelial plexus of capillaries and venules that have ballooned thin-walled segments called **venous lakes** or **lacunae.** The lamina propria itself is densely cellular. The stromal cells of the lamina propria play important roles during both pregnancy and menstruation.

About two-thirds of the luminal side of the endometrium is lost during menstruation and is called the **functional zone** (also called the **stratum functionalis**) (see Fig. 44.26). The basal third of the endometrium that remains after menstruation is called the **basal zone** (also called the **stratum basale**). The basal zone contains all the cell types of the endometrium (i.e., epithelial cells from the remaining tips of glands, stromal cells, and endothelial cells). Blood supply is provided by straight arteries that are separate from the spiral arteries.



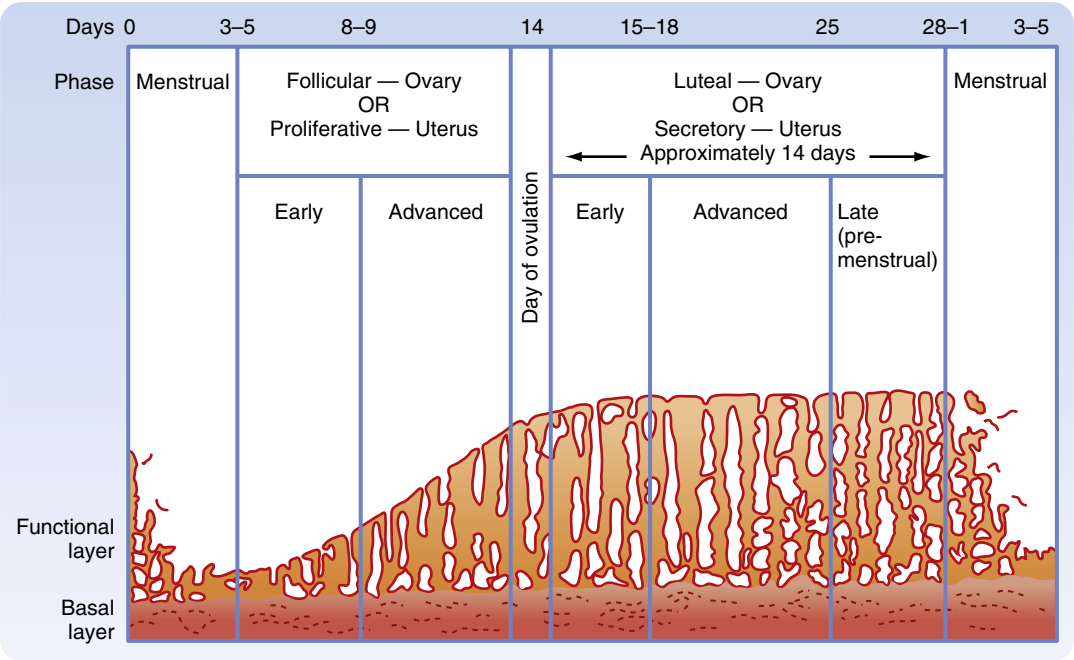
• **Fig. 44.26** Diagram of the organization of glands and blood flow within the uterine endometrium. (From Straus III. In: Yen SSC, et al, eds. *Reproductive Endocrinology.* 4th ed. Philadelphia: Saunders; 1999.)

Hormonal Regulation of the Uterine Endometrium During the Menstrual Cycle

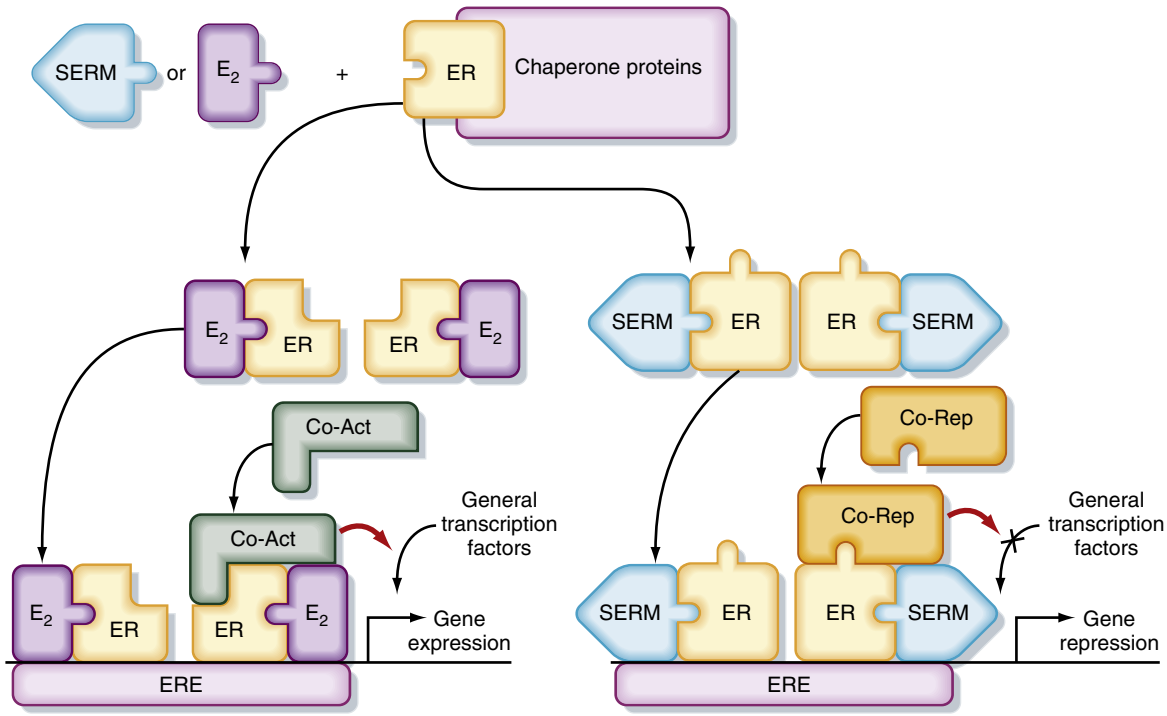
Proliferative Phase

Monthly oscillations in ovarian steroids induce the uterine endometrium to enter different stages. At the time of selection of the dominant follicle and its elevating production of estradiol, the uterine endometrium is just ending menstruation. The stratum functionalis has been shed and only the stratum basale remains (Fig. 44.27). The rising levels of estrogen during the mid to late follicular phase of the ovary induce the **proliferative phase** of the uterine endometrium.

Estrogen induces all cell types in the stratum basale to grow and divide. In fact the definition of an **"estrogenic"** compound has historically been one that is **"uterotropic."** Estrogen increases cell proliferation directly through its cognate receptors (ER-α and ER-β), which regulate gene expression (Fig. 44.28). Estrogen also controls uterine growth indirectly through local production of growth factors. In addition, estrogen induces expression of **progesterone receptors,** thereby "priming" the uterine endometrium so it can respond to progesterone during the luteal phase of the ovary.



• **Fig. 44.27** The menstrual cycle of the uterine endometrium. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)



• **Fig. 44.28** Molecular mechanism by which the estrogen receptor *(ER)* regulates gene expression. *Left,* 17β-Estradiol binds to the ER and changes its conformation so that it binds as a dimer to estrogen-response element *(ERE)* and recruits coactivator proteins *(Co-Act)*, which leads to stimulation of gene expression. *Right,* Selective estrogen receptor modulators *(SERMs)*, such as tamoxifen in the breast, alter ER conformation so that it recruits co-repressor proteins *(Co-Rep)*, thereby inhibiting gene expression. In this case the SERM acts as an ER antagonist, but in some tissues the same SERM can act as an ER agonist. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

Secretory Phase

By ovulation, the thickness of the stratum functionalis has been reestablished under the proliferative actions of 17β-estradiol (see Fig. 44.27). After ovulation the corpus luteum produces high levels of progesterone along with 17β-estradiol. As a consequence of these hormones, the luteal phase of the ovary switches the proliferative phase of the uterine endometrium to the **secretory phase.** Although the proliferative effects of estradiol decline, as discussed above, estradiol facilitates the actions of progesterone by upregulation of progesterone receptors. In general, progesterone inhibits further endometrial growth and induces differentiation of epithelial and stromal cells. Progesterone induces the uterine glands to secrete a nutrient-rich product that supports blastocyst viability. As the secretory phase proceeds, the mucosal uterine glands become corkscrewed and sacculated (see Fig. 44.27). Progesterone also induces changes in adhesivity of the surface epithelium, thereby generating the "window of receptivity" for implantation of an embryo (see Pregnancy). Additionally, progesterone promotes differentiation of stromal cells into **"predecidual cells,"** which must be prepared to form the **decidua** of pregnancy or to orchestrate menstruation in the absence of pregnancy.

Menstrual Phase

In a nonfertile cycle, death of the corpus luteum results in sudden withdrawal of progesterone, which leads to changes in the uterine endometrium that result in loss of the stratum functionalis (see Fig. 44.27). **Menstruation** normally lasts for 4 to 5 days (called a **period**), and the volume of blood loss ranges from 25 to 35 mL. Menstruation coincides with the early follicular phase of the ovary.

AT THE CELLULAR LEVEL

Progesterone opposes the proliferative actions of 17β-estradiol and downregulates the estrogen receptor (ER). Progesterone also induces **inactivating isoforms of 17β-HSD,** thereby converting the active 17β-estradiol into the inactive estrone. This opposition of the mitogenic actions of 17β-estradiol by progesterone is important to protect the uterine endometrium from estrogen-induced uterine cancer. In contrast, administration of **"unopposed estrogen"** to women significantly increases the risk for uterine cancer.

Drugs called **selective estrogen receptor modulators (SERMs)** have been developed that inhibit ER function in a tissue-specific manner (see Fig. 44.28). For example, the SERM **tamoxifen** is used as an ER antagonist for the treatment of ER-positive breast cancer, whose early progression is promoted by estrogen. Binding of SERM to the ER induces conformational changes that allow co-repressors to bind to the ER or promote degradation of the ER (or both; see Fig. 44.28). Because tamoxifen possesses uterotropic activity (i.e., makes uterine endometrial tissue grow), newer SERMs such as **raloxifene** have been developed which display ER antagonist activity on the breast, beneficial ER agonist activity on bone (see later), and no activity or ER antagonistic activity on the uterine endometrium.

Hormonal Regulation of the Myometrium

The smooth muscle cells of the myometrium are also responsive to changes in steroid hormones. Peristaltic contractions of the myometrium favor movement of the luminal contents from the cervix to the fundus at ovulation, and these contractions probably play a role in rapid bulk transport of ejaculated sperm from the cervix to the oviducts. During menstruation, contractions propagate from the fundus to the cervix, thereby promoting expulsion of sloughed stratum functionalis. The size and number of smooth muscle cells are determined by estrogen and progesterone. Healthy cycling women maintain a robust myometrium, whereas the myometrium progressively thins in postmenopausal women. The most drastic changes are seen during pregnancy, when the smooth muscle cells increase from 50 to 500 μm in length. The pregnant myometrium also has a greater number of smooth muscle cells and more extracellular matrix.

IN THE CLINIC

Disorders of menstruation are relatively common and include **menorrhagia** (heavy menstrual flow leading to loss of more than 80 mL of blood), **metrorrhagia** (irregular and sometimes prolonged menstrual flow between normal periods), and **dysmenorrhea** (painful periods). The existence of a few irregular periods, called **oligomenorrhea,** and the absence of periods, called **amenorrhea,** are often due to dysfunction of the hypothalamic-pituitary-ovarian axis as opposed to local pelvic pathophysiology.

Because endometrial tissue is naturally sloughed in fragments that contain viable cells, endometrial tissue occasionally gains access to other parts of the female tract (e.g., oviducts, ovary), as well as the lower part of the abdomen and associated structures (e.g., rectouterine pouch of Douglas, as shown in Fig. 44.13). These transplants give rise to **endometriosis**—a foci of hormonally responsive endometrial tissue outside the uterus. The spread of endometriosis may be due to reflux of menstrual tissue into the oviducts or movement of tissue through lymphatics, or both. Endometriosis frequently exhibits cyclic bleeding and is associated with infertility, pain on defecation, pain on urination, pain with sexual intercourse, or generalized pelvic pain.

The Cervix

Structure and Function

The cervix is the inferior extension of the uterus that projects into the vagina (see Fig. 44.25). It has a mucosa that lines the **endocervical canal,** which has a highly elastic lamina propria and a muscularis that is continuous with the myometrium. The part of the cervix that extends into the vaginal vault is called the **ectocervix,** whereas the part surrounding the endocervical canal is called the **endocervix.** The openings of the endocervical canal at the uterus and vagina are called the **internal cervical os** and the **external cervical os,**

respectively. The cervix acts as a gateway to the upper female tract—at midcycle the endocervical canal facilitates sperm viability and entry. During the luteal phase the endocervical canal impedes passage of sperm and microbes, thereby inhibiting **superimplantation** of a second embryo or ascending infection into the placenta, fetal membranes, and fetus. The cervix physically supports the weight of the growing fetus. At term, **cervical softening and dilation** allow passage of the newborn and placenta from the uterus into the vagina.

Hormonal Regulation of Cervical Mucus During the Menstrual Cycle

The endocervical canal is lined by simple columnar epithelium that secretes **cervical mucus** in a hormonally responsive manner. Estrogen stimulates production of a copious quantity of thin, watery, slightly alkaline mucus that is an ideal environment for sperm. Progesterone stimulates production of a scant, viscous, slightly acidic mucus that is hostile to sperm. During the normal menstrual cycle the conditions of the cervical mucus are ideal for sperm penetration and viability at the time of ovulation.

The Vagina

Structure and Function

The vagina is one of the copulatory structures in women and acts as the birth canal (see Figs. 44.13 and 44.25). Its mucosa is lined by a nonkeratinized stratified squamous epithelium. The mucosa has a thick lamina propria enriched with elastic fibers and is well vascularized. There are no glands in the vagina, so lubrication during intercourse comes from (1) cervical mucus (especially with intercourse that occurs midcycle), (2) a transudate (i.e., ultrafiltrate) from the blood vessels of the lamina propria, and (3) the vestibular glands. The mucosa is surrounded by a relatively thin (i.e., relative to the uterus and cervix) two-layered muscularis and an outer connective tissue. The vaginal wall is innervated by branches of the pudendal nerve, which contribute to sexual pleasure and orgasm during intercourse.

Hormonal Regulation During the Menstrual Cycle

The superficial cells of the vaginal epithelium are continually desquamating, and the nature of these cells is influenced by the hormonal environment. Estrogen stimulates proliferation of the vaginal epithelium and increases its glycogen content (referred to as **"cornification"**—but in humans, true cornification or keratinization does not occur). The glycogen is metabolized to lactic acid by commensal lactobacilli, thereby maintaining an acidic environment. This inhibits infection by noncommensal bacteria and fungi. Progesterone increases the desquamation of epithelial cells.

The External Genitalia

Structure and Function

The female external genitalia are surrounded by the **labia majora** (homologues of the scrotum) laterally and the **mons pubis** anteriorly (see Fig. 44.25). The **vulva** collectively refers to an area that includes the labia majora and mons pubis plus the **labia minora,** the **clitoris,** the **vestibule of the vagina,** the **vestibular bulbs** (glands), and the **external urethral orifice.** The vulva is also referred to as the **pudendum** by clinicians. The structures of the vulva serve the functions of sexual arousal and climax, directing the flow of urine, and partially covering the opening of the vagina, thereby inhibiting entry of pathogens.

The clitoris is the embryological homologue of the penis and is composed of two **corpora cavernosa,** which attach the clitoris to the ischiopubic rami, and a **glans.** These structures are composed of erectile tissue and undergo the process of erection in essentially the same manner as the penis. Unlike the penis, clitoral tissue is completely separate from the urethra. Thus, the clitoris is involved in sexual arousal and climax at orgasm. The vagina is likewise involved in sexual satisfaction but also serves as the copulatory organ and birth canal.

Hormonal Regulation During the Menstrual Cycle

The structures of the vulva do not show marked changes during the menstrual cycle. However, the health and function of these structures are dependent on hormonal support. The external genitalia and vagina are responsive to androgens (testosterone and dihydrotestosterone) and estrogen. Androgens also act on the central nervous system (CNS) to increase libido in women.

Biology of 17β-Estradiol and Progesterone

Biological Effects of Estrogen and Progesterone

17β-Estradiol and progesterone fluctuate during the menstrual cycle, and they have multiple effects that can be categorized according to whether they are directly related to the reproductive system or not. Both hormones have profound effects on the ovary, oviduct, uterus, cervix, vagina, and external genitalia and on the hypothalamus and pituitary. Estrogen and progesterone also have important effects on nonreproductive tissues:

Bone: Estrogen is required for closure of the epiphyseal plates of long bones in both sexes. 17β-Estradiol has a **bone anabolic** and **calciotropic effect** (see Chapter 40). It stimulates intestinal Ca^{++} absorption. 17β-Estradiol is also one of the most potent regulators of osteoblast and osteoclast function. Estrogen promotes survival of osteoblasts and apoptosis of osteoclasts, thereby favoring bone formation over resorption. Low estrogen levels associated with menopause leads to bone loss and **osteoporosis.**

Liver: The overall effect of 17β-estradiol on the liver is to improve circulating lipoprotein profiles. Estrogen increases expression of the **LDL receptor,** thereby increasing clearance of cholesterol-rich **LDL** particles by the liver. Estrogen also increases circulating levels of **HDL.** Estrogen regulates hepatic production of several

transport proteins, including cortisol-binding protein, thyroid hormone–binding protein, and SHBG.

Cardiovascular organs: Premenopausal women have significantly less cardiovascular disease than men or postmenopausal women do. Estrogen promotes vasodilation through increased production of **nitric oxide,** which relaxes vascular smooth muscle and inhibits platelet activation. Single-nucleotide polymorphisms in the estrogen receptor have been associated with increased cardiovascular disease.

Integument: Estrogen and progesterone maintain healthy smooth skin with normal epidermal and dermal thickness. Estrogen stimulates proliferation and inhibits apoptosis of keratinocytes. In the dermis, estrogen and progesterone increase collagen synthesis and inhibit breakdown of collagen by suppressing matrix metalloproteinases. Estrogen also increases glycosaminoglycan production and deposition in the dermis and promotes wound healing.

CNS: Estrogen is neuroprotective—that is, it inhibits neuronal cell death in response to hypoxia or other insults. Estrogen's positive effects on angiogenesis may account for some of the beneficial and stimulant-like actions of estrogen on the CNS. Progesterone acts on the hypothalamus to increase the set point for thermoregulation, thereby elevating body temperature approximately 0.5°F. This is the basis for using body temperature measurements to determine whether ovulation has occurred. Progesterone is a CNS depressant. The loss of progesterone upon demise of the corpus luteum of menstruation is the basis for **premenstrual dysphoria (premenstrual syndrome [PMS]).** Progesterone also acts on the brainstem to sensitize the ventilatory response to P_{CO_2} so that ventilation increases and P_{CO_2} decreases.

Adipose tissue: Estrogen decreases adipose tissue by decreasing lipoprotein lipase activity and increasing hormone-sensitive lipase (i.e., it has a lipolytic effect). Loss of estrogen results in accumulation of adipose tissue, especially in the abdomen.

Transport and Metabolism of Ovarian Steroids

Steroid hormones are hydrophobic and are transported while bound to plasma proteins in blood. Approximately 60% of the estrogen is transported bound to **SHBG,** 20% is bound to albumin, and 20% is in the free form. Progesterone binds primarily to **cortisol-binding globulin (transcortin)** and albumin. Because it has relatively low binding affinity for these proteins, its circulating half-life is about 5 minutes.

Although the ovary is the primary site of estrogen production, peripheral aromatization of androgens to estrogens can generate locally high levels of 17β-estradiol in some tissues. Peripheral conversion of adrenal and ovarian androgens serves as an important source of estrogen after menopause (discussed later). The fact that CYP19 (aromatase) is expressed in the breast is the basis for the use of **aromatase inhibitors** in the treatment of estrogen-dependent breast cancer in postmenopausal women.

Estrogens and progestins are degraded in the liver to inactive metabolites, conjugated with sulfate or glucuronide, and excreted in urine. Major metabolites of estradiol include estrone, estriol, and catechol estrogens (2-hydroxyestrone and 2-methoxyestrone). The major metabolite of progesterone is pregnanediol, which is conjugated with glucuronide and excreted in urine.

Ontogeny of the Reproductive Systems

Unlike most other organ systems, the reproductive systems undergo significant changes in their activity during the life span of a man or woman (Fig. 44.29). Development of the reproductive systems occurs in utero and results in female or male fetuses. After birth and during infancy, the reproductive systems are largely quiescent. At puberty the hypothalamic-pituitary-gonadal axes "awaken" and the gonads begin producing sex steroids, which in turn induce the sexually dimorphic changes in appearance and behavior associated with men and women. The reproductive life span of women is set by their ovarian reserve and degree of follicular development (see earlier) and ends at menopause, usually in the fifth decade of life. Loss of estrogen production by the ovaries has a clear clinical impact on many postmenopausal women. Men continue to produce sperm throughout life but can experience a decline in androgen production (andropause), which is associated with its own clinical sequelae.

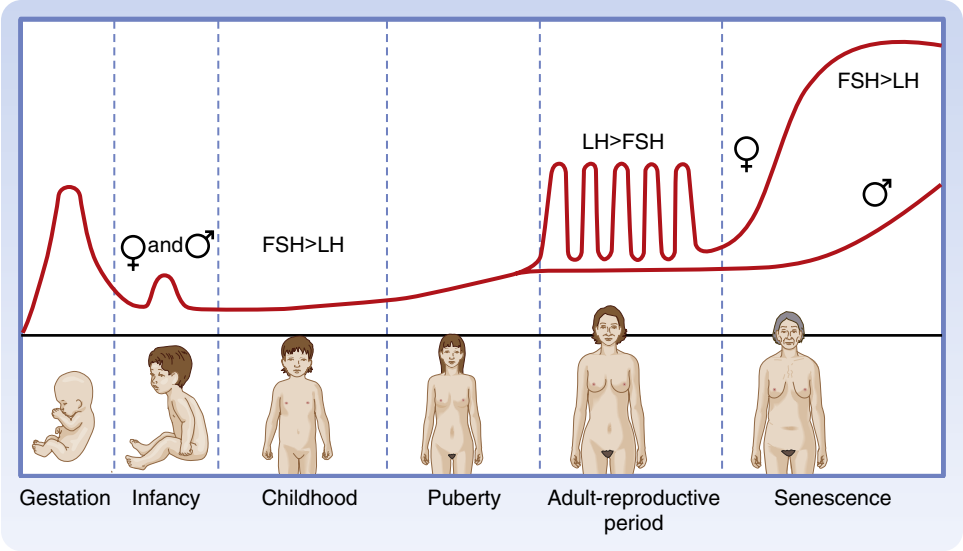
Pregnancy

The reproductive system of women undergoes dramatic changes during pregnancy. Production of gonadotropin and gonadal steroids is switched from the maternal hypothalamic-pituitary-ovarian axis, which is strongly repressed during pregnancy, to the **fetal placenta.** Indeed, it is the endocrine function of fetal placental tissue that (1) maintains a quiescent gravid uterus, (2) alters maternal physiology to ensure fetal nutrition in utero, (3) alters maternal pituitary function and mammary gland development to ensure ongoing fetal nutrition after birth, and (4) determines the time of labor and delivery (also called **parturition**). The placenta also plays an important role in fetal testosterone production and male differentiation of the reproductive system before the fetal hypothalamus and pituitary develop into a functional axis.

Fertilization, Early Embryogenesis, Implantation, and Placentation

Synchronization With Maternal Ovarian and Reproductive Tract Function

Fertilization, early embryogenesis, implantation, and early gestation are all synchronized with the human menstrual cycle (Fig. 44.30). Just before ovulation the ovary is in the late follicular stage and produces high levels of estrogen. Estrogen promotes growth of the uterine endometrium and induces expression of the progesterone receptor. Estrogen



• **Fig. 44.29** Pattern of gonadotropin secretion throughout life. Note the transient peaks during gestation and early infancy and the low levels thereafter in childhood. Women subsequently have monthly cyclic bursts, with luteinizing hormone *(LH)* exceeding follicle-stimulating hormone *(FSH)*; men do not. Both genders show increased gonadotropin production after age 50, with FSH exceeding LH.

ultimately induces the LH surge, which in turn induces meiotic maturation of the oocyte and ovulation of the cumulus-oocyte complex.

The events between fertilization and implantation take about 6 days to complete, so implantation occurs at about day 22 of the menstrual cycle. At this time the ovary is in the midluteal phase and secreting large amounts of progesterone. Progesterone stimulates secretion from the uterine glands, which provide nutrients to the embryo. This is referred to as *histiotropic nutrition* and is an important mode of maternal-to-fetal transfer of nutrients for about the first trimester of pregnancy, after which it is replaced by hemotropic nutrition (see later). Progesterone inhibits myometrial contraction and prevents release of paracrine factors (e.g., cytokines, prostaglandins, chemokines, and vasoconstrictors) that lead to menstruation. Progesterone induces the **"window of receptivity"** in the uterine endometrium, which exists from about day 20 to day 24 of the menstrual cycle. This receptive phase is associated with increased adhesivity of the endometrial epithelium and involves formation of cellular extensions called **pinopodes** on the apical surface of endometrial epithelia, along with increased expression of adhesive proteins (e.g., integrins, cadherins) and decreased expression of antiadhesive proteins (e.g., mucins) in the apical cell membrane.

When a fertilized egg implants in the uterus, the uterine endometrium is at its full thickness, is actively secreting, and is capable of tightly adhering to the implanting embryo.

Fertilization

Fertilization accomplishes both recombination of genetic material to form a new genetically distinct organism and initiation of events that begin embryonic development. Several steps must occur to achieve successful (unassisted) fertilization (Fig. 44.31):

Step 1: Penetration of the expanded cumulus by the sperm. This involves digestion of the extracellular matrix of the cumulus by a membrane hyaluronidase, PH-20.

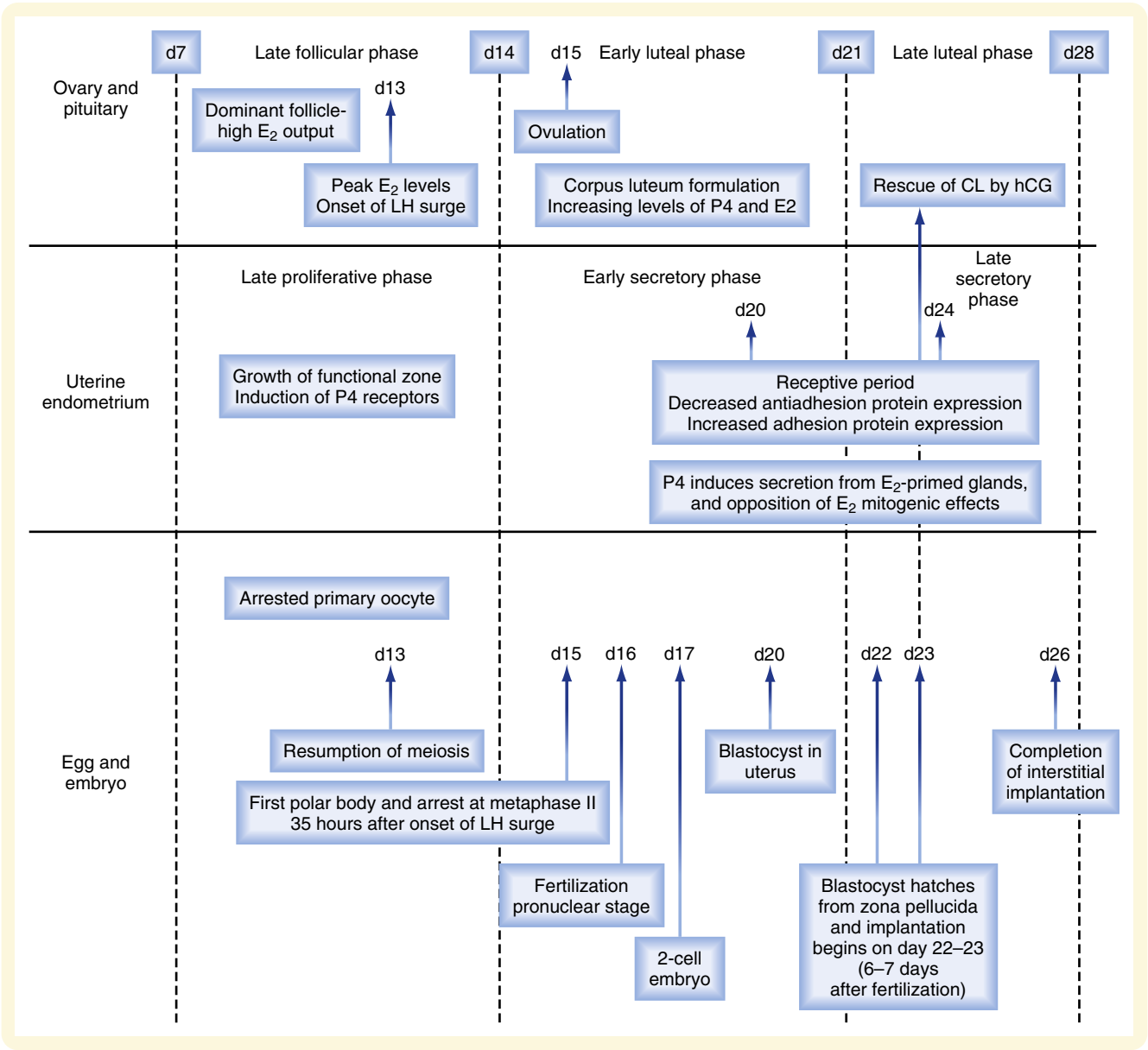
Step 2: Penetration of the zona pellucida by the sperm. This involves binding of the sperm to the zona protein ZP3 (step 2a), which induces release of acrosomal enzymes (called the **acrosomal reaction)** (step 2b). The sperm secondarily bind to another zona protein, ZP2 (step 2c), as the zona pellucida is digested and the sperm swims through to the egg (step 2d).

Step 3: Fusion of the sperm and egg membrane takes place.

Step 4: A Ca^{++} signaling cascade (see Chapter 3) occurs.

Step 5: The signaling cascade activates the exocytosis of enzyme-filled vesicles called **cortical granules** that reside in the outermost, or cortical, region of the unfertilized egg. The enzymes contained in the cortical granules are released to the outside of the egg upon exocytosis. These enzymes modify both ZP2 and ZP3 of the zona pellucida such that ZP2 can no longer bind acrosome-reacted sperm, and ZP3 can no longer bind capacitated acrosome-intact sperm. Thus only one sperm usually enters the egg. Occasionally, more than one sperm does enter the egg. This results in a **triploid** cell that is unable to develop further. Therefore prevention of polyspermy is critical for normal development of the fertilized egg.

Step 6: The entire sperm enters the egg during fusion. The flagellum and mitochondria disintegrate, so most of the mitochondrial DNA in cells is maternally derived. Once inside the egg, decondensation of the sperm DNA occurs. A membrane called the *pronucleus* forms around the sperm DNA as the newly activated egg completes the second meiotic division.



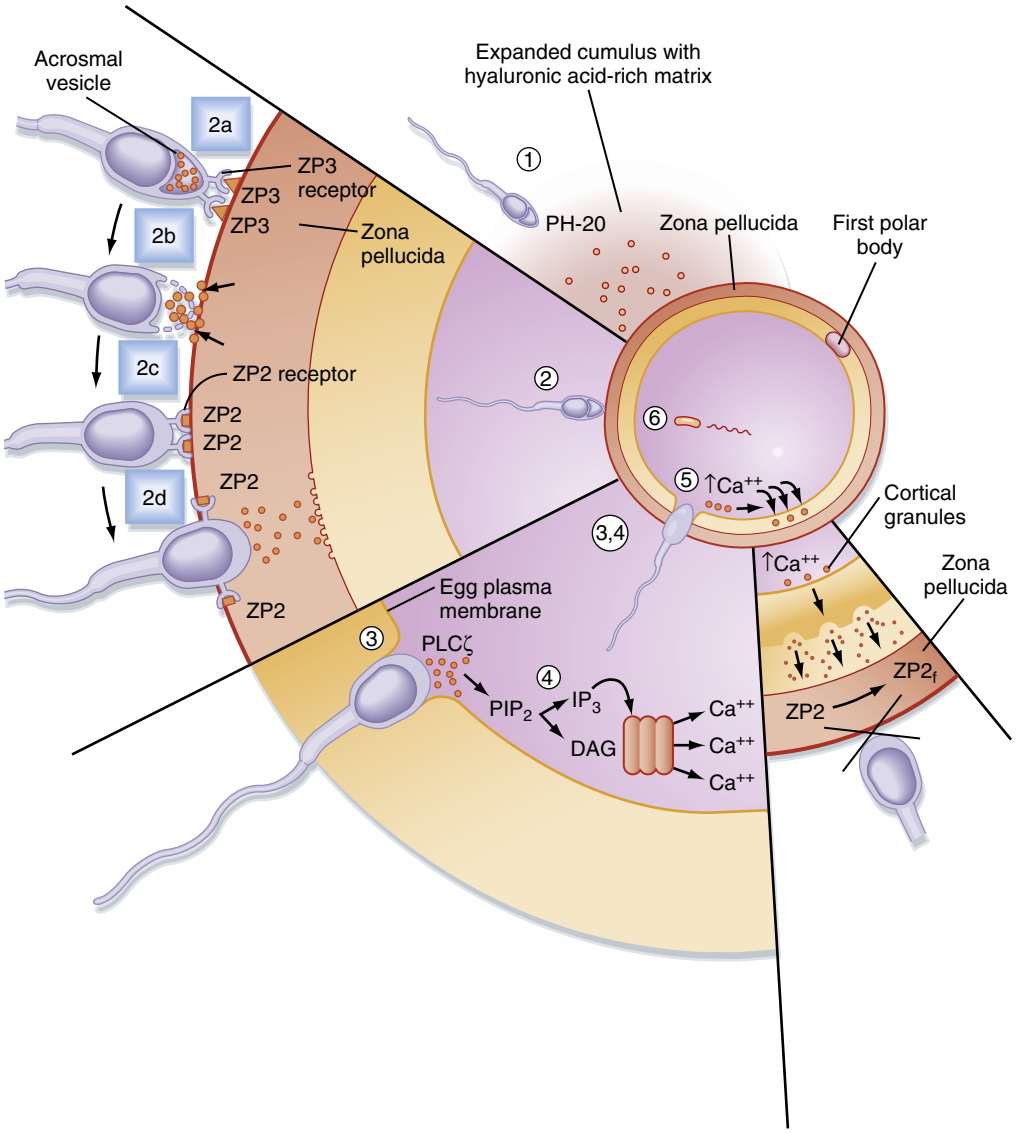
• **Fig. 44.30** Synchronization of events of the menstrual cycle (ovary and endometrium) with fertilization, early embryonic development within the oviduct, and implantation of embryo (blastocyst) into the uterine endometrium. *E_2*, Estradiol; *P4*, Progesterone. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

In mammalian eggs a large initial release of Ca^{++} is followed by a series of subsequent smaller Ca^{++} oscillations that can last for hours. A major consequence of this signaling pathway is that it "awakens" the metabolically quiescent egg so it can resume meiosis and begin embryonic development. This process is called **egg activation.**

The activated egg completes the second meiotic division as the sperm DNA decondenses and a pronucleus forms around it (Fig. 44.32). Once the egg has completed meiosis, a pronucleus forms around the female chromosomes as well. A **centrosome** contributed by the sperm becomes a microtubule organizing center from which microtubules extend until they contact the female pronucleus. The male and female DNA replicate as the two pronuclei are pulled together. Once the pronuclei contact each other, the nuclear membranes break down, the chromosomes align on a common metaphase plate, and the first cleavage occurs.

Early Embryogenesis and Implantation

Fertilization typically occurs on day 16 to 17 of the menstrual cycle, and implantation occurs about 6 days later. Thus the first week of embryogenesis takes place within the lumens of the oviduct and uterus. For most of this time the embryo remains encapsulated by the zona pellucida. The first two cleavages take about 2 days, and the embryo reaches a 16-cell **morula** by 3 days. The outer cells of the

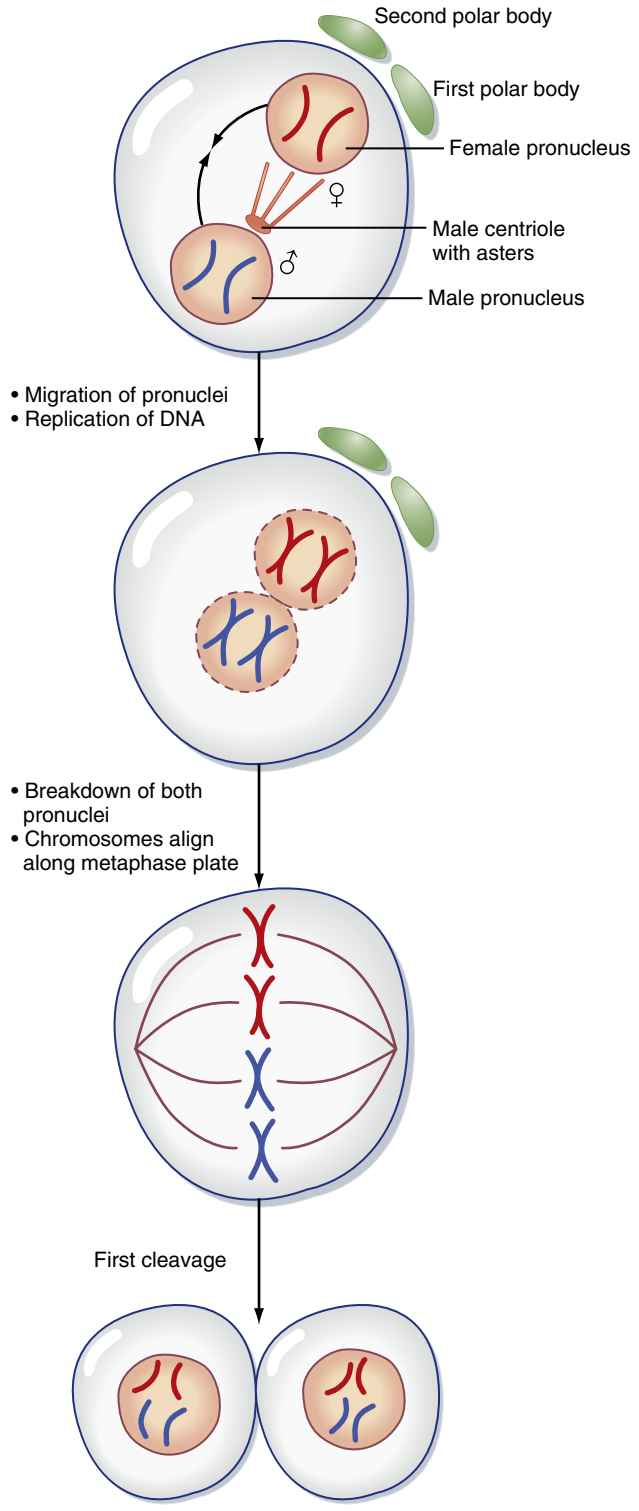


• **Fig. 44.31** Events involved in fertilization (see text for details). (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

morula become tightly adhesive with each other and begin transporting fluid into the embryonic mass. During days 4 and 5 the transport of fluid generates a cavity called the *blastocyst cavity,* and the embryo is now called a **blastocyst** (Fig. 44.33). The blastocyst is composed of two subpopulations of cells: an eccentric **inner cell mass** and an outer epithelial-like layer of **trophoblasts.** The region of the trophoblast layer immediately adjacent to the inner cell mass is referred to as the **embryonic pole,** and it is this region that attaches to the uterine endometrium at implantation (see Fig. 44.33).

The embryo resides within the oviduct during the first 3 days and then enters the uterus. By 5 to 6 days of development the trophoblasts of the blastocyst secrete proteases that digest the outer-lying zona pellucida. At this point, corresponding to about day 22 of the menstrual cycle, the **"hatched" blastocyst** is able to adhere to and implant into the receptive uterine endometrium (see Fig. 44.33).

At the time of attachment and implantation the trophoblasts differentiate into two cell types: an inner layer of **cytotrophoblasts** and an outer layer of multinuclear/multicellular **syncytiotrophoblasts** (see Fig. 44.33). The cytotrophoblasts initially provide a feeder layer of continuously dividing cells. Syncytiotrophoblasts initially perform three general types of function: adhesive, invasive, and endocrine. Syncytiotrophoblasts express adhesive surface proteins (i.e., cadherins and integrins) that bind to uterine surface epithelia and, as the embryo implants, to components of the uterine extracellular matrix. In humans the embryo completely burrows into the superficial layer of the endometrium (see Fig. 44.33). This mode of implantation, called **interstitial implantation,** is the most invasive among placental mammals. Invasive implantation involves adhesion-supported migration of syncytiotrophoblasts into the endometrium, along with the breakdown of extracellular matrix by secretion of matrix metalloproteinases and other hydrolytic enzymes.



• **Fig. 44.32** Overview of genetic events after fertilization up to the first embryonic cleavage. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

The endocrine function begins with the onset of implantation, when syncytiotrophoblasts start secreting the LH-like protein **hCG,** which maintains the viability of the corpus luteum and thus progesterone secretion. Syncytiotrophoblasts also become highly steroidogenic. By 10 weeks the syncytiotrophoblasts acquire the ability to make progesterone at sufficient levels to maintain pregnancy independently of a corpus luteum. Syncytiotrophoblasts produce several other hormones as well as enzymes that modify hormones.

As implantation and placentation progress, syncytiotrophoblasts take on the important functions of phagocytosis (during histiotropic nutrition) and bidirectional placental transfer of gases, nutrients, and wastes. Exchange across the syncytiotrophoblasts involves diffusion (e.g., gases), facilitated transport (e.g., GLUT1-mediated transfer of glucose), active transport (e.g., amino acids by specific transporters), and pinocytosis/transcytosis (e.g., of iron-transferrin complexes).

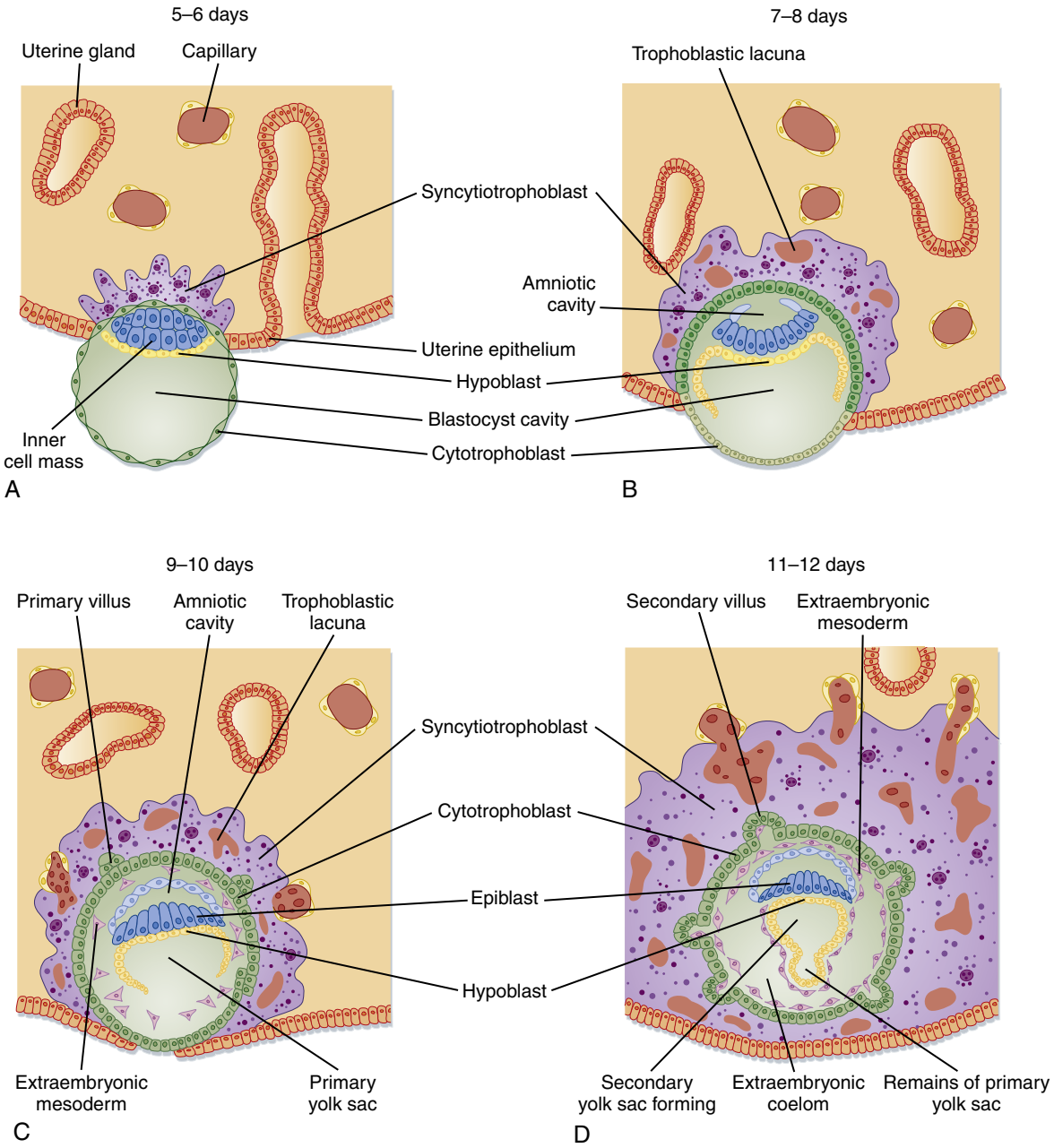
There is also a maternal response to implantation, termed **decidualization**, that involves transformation of the endometrial stroma. Decidualization involves an enlargement of stromal cells as they become lipid- and glycogen-filled decidual cells, and at this time the endometrium is referred to as the **decidua**. The decidua forms an epithelial-like sheet with adhesive junctions that inhibit migration of the implanting embryo. The decidua also secretes factors such as **tissue inhibitors of metalloproteinases (TIMPs)** that moderate the activity of syncytiotrophoblast-derived hydrolytic enzymes in the endometrial matrix. Consequently, decidualization allows regulated invasion during implantation. Normally the implanting embryo and placenta do not extend to and involve the myometrium.

IN THE CLINIC

Placenta accreta is the burrowing of the embryo completely through the endometrium and adhesion of the placenta to the myometrium, a condition associated with potentially life-threatening **postpartum hemorrhage.** The decidual response occurs only in the uterus. Thus the highly invasive nature of the human embryo poses considerable risk to the mother in the case of **ectopic implantation.** *Ectopic implantation* refers to implantation of an embryo at a site other than the uterus, and *ectopic pregnancy* refers to a developing embryo at a site of ectopic implantation. Most ectopic pregnancies (>90%) occur within the oviducts (called **tubal pregnancies**), but they can also occur in the ovary and abdominal cavity. Implantation in the oviducts is often associated with long-term infection and inflammation (called **pelvic inflammatory disease**) and obstruction of the tube. In a tubal pregnancy the highly invasive nature of the human syncytiotrophoblast, which is normally moderated by the uterine decidual response, usually leads to burrowing of the implanted embryo through the wall of the oviduct. Although abdominal pregnancies can proceed to term, undetected oviductal pregnancies usually lead to rupture of the oviductal wall. The resulting internal hemorrhage can be catastrophic to the mother and requires immediate surgical intervention.

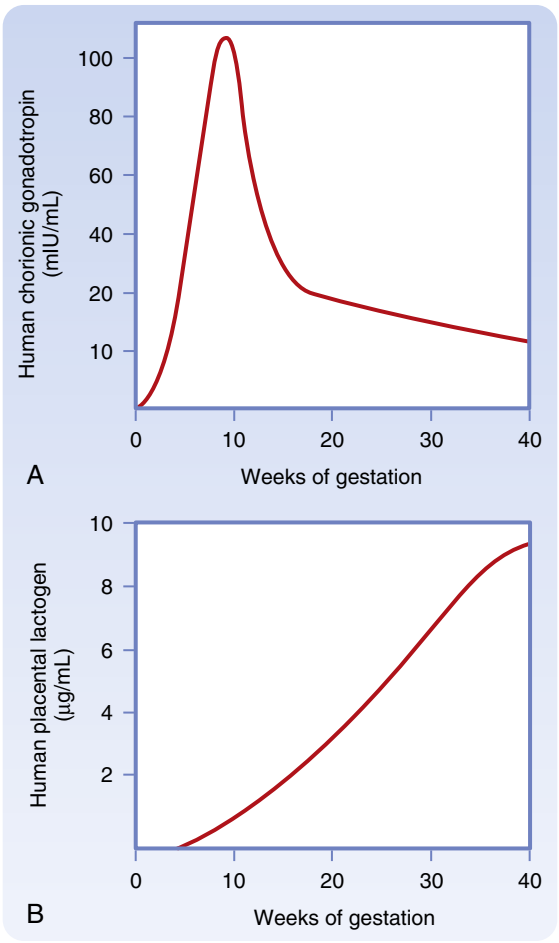
Placental Endocrinology

Human Chorionic Gonadotropin. The first hormone produced by syncytiotrophoblasts is hCG, which is structurally related to the pituitary glycoprotein hormones (see Chapter 41). As such, hCG is composed of a common



• **Fig. 44.33 A,** Beginning of implantation. The trophoblast has differentiated into cytotrophoblast and syncytiotrophoblast layers. **B,** As the syncytiotrophoblast layer increases in size and invades deeper, this layer begins to surround and erode maternal vessels, forming lacunae filled with maternal blood. **C,** Interstitial implantation is almost complete. Extensions of cytotrophoblasts have formed that will become covered by a layer of syncytiotrophoblast. At this point, they are called "primary villi." **D,** Interstitial implantation is complete. Extraembryonic mesodermal has developed from the epithelial layers (amnion, primary yolk sac), and will form an inner layer of the villi, forming "secondary villi." Ultimately, the mesoderm will give rise to umbilical blood vessels within the core of the villus, thereby forming tertiary villi. (From Carlson BM. *Human Embryology and Developmental Biology.* Philadelphia: Mosby; 2004.)

α-glycoprotein subunit (α-GSU) and a **hormone-specific β subunit (β-hCG).** Antibodies used to detect hCG (i.e., in laboratory assays and over-the-counter pregnancy tests) are designed to specifically detect the β subunit. hCG is most similar to LH and binds with high affinity to the LH receptor. The β subunit of hCG is longer than that of LH and contains more sites for **glycosylation,** which greatly increases the half-life of hCG to 24 to 30 hours. The stability of hCG allows it to rapidly accumulate in the maternal circulation such that hCG is detectable within maternal serum within 24 hours of implantation. Serum hCG levels double every 2 days for the first 6 weeks and peak at about 10 weeks. Serum hCG then declines to a constant level at about 50% of the peak value (Fig. 44.34*A*).



• **Fig. 44.34** Circulating levels of human chorionic gonadotropin (hCG) and human placental lactogen (hPL) in maternal blood during pregnancy. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

The primary action of hCG is to stimulate LH receptors on the corpus luteum. This prevents luteolysis and maintains a high level of luteal-derived progesterone production during the first 10 weeks. The rapid increase in hCG is responsible for the nausea of **"morning sickness"** associated with early pregnancy. A small amount (i.e., 1%–10%) of hCG enters the fetal circulation. hCG stimulates fetal Leydig cells to produce testosterone before the fetal gonadotropic axis is fully mature. hCG also stimulates the fetal adrenal cortex (see later) during the first trimester.

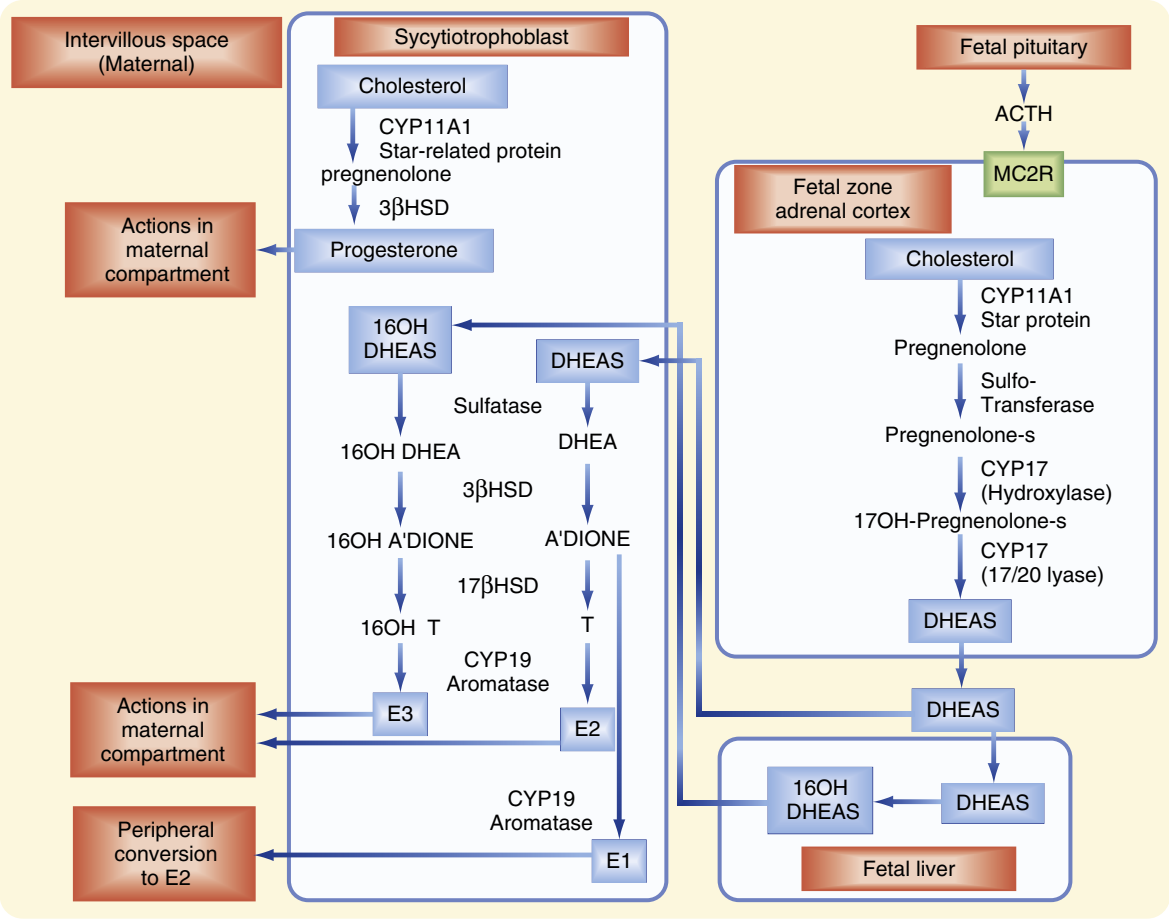
Progesterone. The placenta produces a high amount of progesterone, which is absolutely required to maintain a quiescent myometrium and a pregnant uterus. Progesterone production by the placenta is largely unregulated—the placenta produces as much progesterone as the supply of cholesterol and the levels of CYP11A1 and 3β-HSD allow (Fig. 44.35). Notably, placental steroidogenesis differs from that in the adrenal cortex, ovaries, and testis in that cholesterol is transported into the placental mitochondria by a mechanism that is independent of **StAR protein.** Thus this first step in steroidogenesis is not a regulated rate-limiting step in the placenta as it is in other steroidogenic glands. This means that fetuses with an inactivating mutation in StAR protein will develop **lipoid congenital adrenal hyperplasia** (see Chapter 43) and **hypogonadism** but will have normal progesterone levels produced by their placenta. Progesterone production by the placenta does not require fetal tissue. Consequently, progesterone levels are largely independent of fetal health and cannot be used as a measure of fetal health. Maternal progesterone levels continue to increase throughout pregnancy.

Progesterone is released primarily into the maternal circulation and is required for implantation and maintenance of pregnancy. Progesterone also has several effects on maternal physiology including breast growth and differentiation, immunosuppression, and elevation of core body temperature. The switch from corpus luteum–derived progesterone to placental-derived progesterone (referred to as the **luteal-placental shift**) is complete at about the eighth week of pregnancy. Progesterone (and pregnenolone) are used by the transitional zone of the fetal cortex to make cortisol late in pregnancy.

Estrogen. Estrogens are also produced by syncytiotrophoblasts. Syncytiotrophoblasts are similar to ovarian granulosa cells in that they lack CYP17 and are dependent on another cell type to provide 19-carbon androgens for aromatization (see Fig. 44.35). The ancillary androgen-producing cells reside in the **fetal adrenal cortex.**

The fetal adrenal cortex contains an outer **definitive zone,** a middle **transitional zone,** and an inner **fetal zone.** The definitive and transitional zones give rise to the zona glomerulosa and zona fasciculata, respectively. Aldosterone synthesis is initiated close to parturition. Synthesis of cortisol begins at about 6 months and increases during late gestation. The fetal zone is the predominant portion of the adrenal cortex in the fetus; it constitutes as much as 80% of the bulk of the large fetal adrenal and is the site of most fetal adrenal steroidogenesis. The fetal zone strongly resembles the zona reticularis in that it expresses little or no 3β-HSD (see Fig. 44.35). The fetal zone primarily releases the sulfated form of the inactive androgen **dehydroepiandrosterone sulfate** (DHEAS) throughout most of gestation. Production of DHEAS from the fetal adrenal is absolutely dependent on fetal ACTH from the fetal pituitary by the end of the first trimester.

The DHEAS released from the fetal zone has two fates. First, DHEAS can go directly to the syncytiotrophoblast, where it is desulfated by a placental **steroid sulfatase** and used as a 19-carbon substrate for the synthesis of 17b-estradiol and estrone (see Fig. 44.35). The second fate of DHEAS is **16-hydroxylation** in the fetal liver by the enzyme CYP3A7. 16-Hydroxyl-DHEAS is then converted by syncytiotrophoblasts to the major estrogen of pregnancy, **estriol** (see Fig. 44.35). In X-linked ichthyosis, the steroid sulfatase is low or missing, resulting in loss of active (i.e., desulfated) estrogen production by the fetoplacental unit. Pregnancy is normal, but because estrogens promote parturition, the pregnancy is prolonged and usually ends with



• **Fig. 44.35** Production of progesterone by syncytiotrophoblast and estrogens by fetoplacental unit.

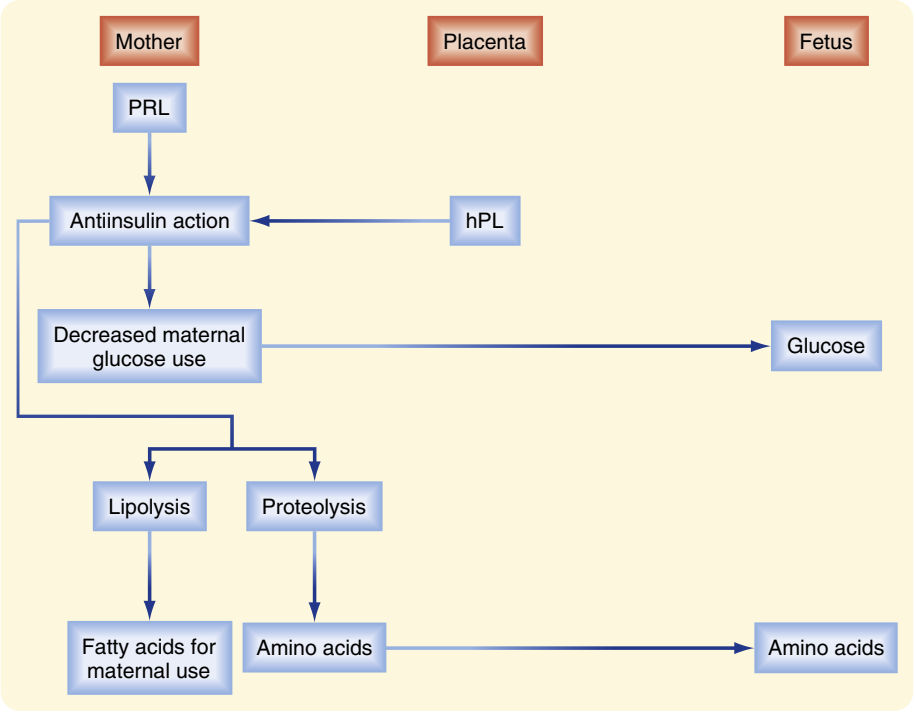
physician-induced labor. The baby boy is born with a skin disorder of varying degrees of severity that is called *ichthyosis* (scaly skin), owing to buildup of layers of shed cells within the stratum corneum. This form of ichthyosis is readily treatable by topical creams.

Maternal estrogen levels increase throughout pregnancy. Because estrogen production is dependent on a healthy fetus, estriol levels can be used as one measure of fetal health. The collective term used for the placental syncytiotrophoblasts and fetal organs in the context of estrogen production is the **fetoplacental unit.** Estrogens increase uteroplacental blood flow, enhance LDL receptor expression in syncytiotrophoblasts, and induce several components (e.g., prostaglandins, oxytocin receptors) involved in parturition. Estrogens increase breast growth directly and indirectly through stimulation of maternal pituitary prolactin production. Estrogens also increase lactotrope size and number, thereby increasing overall pituitary mass by more than twofold by term. Estrogens also affect several other aspects of maternal physiology.

Human Placental Lactogen. Human placental lactogen (hPL), also called **human chorionic somatomammotropin (hCS),** is a 191–amino acid protein hormone produced in the syncytiotrophoblast that is structurally similar to growth hormone (GH) and prolactin (PRL). Its function overlaps those of both GH and PRL. It can be detected within the syncytiotrophoblast by 10 days after conception and in maternal serum by 3 weeks' gestation (see Fig. 44.34). Maternal serum levels rise progressively throughout the remainder of the pregnancy. The quantity of hormone produced is directly related to the size of the placenta, such that as the placenta grows during gestation, hPL secretion increases. As much as 1 g/day of hPL can be secreted late in gestation.

Like GH, hPL is protein anabolic and lipolytic. Its antagonistic action to insulin is the major basis for the diabetogenicity of pregnancy. Like PRL, it stimulates mammary gland growth and development. Mammary gland development in pregnancy results from the actions of hPL, PRL, estrogens, and progestins. hPL inhibits maternal glucose uptake and use, thereby increasing serum glucose levels. Glucose is a major energy substrate for the fetus, and hPL increases fetal glucose availability.

As with hCG, far less hPL is found in the fetal circulation than in the maternal circulation. This suggests that the hormones may play a more important role in the mother than in the fetus. hPL is not essential for the pregnancy and delivery of a healthy child.



• **Fig. 44.36** Overview of energy use by the maternal and fetal compartments. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

Both hPL and PRL act as fetal GHs and stimulate production of the fetal growth-promoting hormones insulin-like growth factor IGF-1 and IGF-2. Ironically, fetal GH does not appear to regulate growth, and anencephalic infants and GH-deficient children typically have normal birth weight.

Diabetogenicity of Pregnancy

Pregnancy represents an **insulin-resistant state** (Fig. 44.36). During the last half of pregnancy when hPL levels are highest, maternal energy metabolism shifts from an anabolic state, in which nutrients are stored, to a catabolic state. In this catabolic state, sometimes described as **accelerated starvation,** maternal energy metabolism shifts toward fat utilization with sparing of glucose. As maternal use of glucose for energy decreases, lipolysis increases and fatty acids become major energy sources. Peripheral responsiveness to insulin decreases and pancreatic insulin secretion increases. Beta cell hyperplasia occurs in pregnancy. Although this does not usually lead to a clinical condition, pregnancy aggravates existing diabetes mellitus, and diabetes can develop for the first time in pregnancy. If the diabetes resolves spontaneously with delivery, the condition is referred to as **gestational diabetes.** Other hormones contributing to the diabetogenicity of pregnancy are estrogens and progestins, because both these hormones decrease insulin sensitivity.

Parturition

Human pregnancy lasts an average of 40 weeks from the beginning of the last menstrual period (gestational age). This corresponds to an average fetal age of 38 weeks. **Parturition** is the process whereby uterine contractions lead to childbirth. **Labor** consists of three stages: strong uterine contractions that force the fetus against the cervix, with dilation and thinning of the cervix (several hours); delivery of the fetus (<1 hour); and delivery of the placenta, along with contractions of the myometrium to halt bleeding (<10 minutes).

Control of parturition in humans is complex, and the exact mechanisms underlying its control are not well understood.

Placental CRH and the Fetal Adrenal Axis

The placenta produces **corticotropin-releasing hormone (CRH),** which is identical to the 41–amino acid peptide produced by the hypothalamus. Placental CRH production and maternal serum CRH levels increase rapidly during late pregnancy and labor. Moreover, circulating CRH is either in the form of free CRH, which is bioactive, or complexed to a CRH-binding protein. Maternal levels of CRH-binding protein plummet during late pregnancy and labor, so free CRH levels increase. Placental CRH also accumulates in the fetal circulation and stimulates fetal ACTH secretion. ACTH stimulates both fetal adrenal cortisol production and fetoplacental estrogen production. In contrast to the inhibitory effect of cortisol on hypothalamic CRH production, cortisol stimulates placental CRH production. This establishes a self-amplifying positive feedback. CRH itself promotes myometrial contractions by sensitizing the uterus to oxytocin and prostaglandins (see Oxytocin, Prostaglandins).

Estrogens also directly and indirectly stimulate myometrial contractility. In addition to the role of the CRH-ACTH axis in parturition, this model correlates the onset of parturition with cortisol-induced maturation of fetal systems, including the lungs and gastrointestinal tract.

Estrogen and Progesterone Secretion

Although a rise in maternal serum estrogen and a drop in progesterone levels occur late in gestation in some species, no change in the ratio of the two hormones is seen in human serum. However, "functional" progesterone withdrawal, involving changes in uterine progesterone receptor and progesterone metabolism, has been proposed.

Oxytocin

Oxytocin is secreted from the **pars nervosa (posterior pituitary)** (see Chapter 41). Oxytocin, which stimulates powerful uterine contractions, plays a major role in progression and completion of parturition. Oxytocin is released in response to stretch of the cervix through a **neuroendocrine reflex,** and its release stimulates uterine contractions and thereby facilitates delivery. Uterine sensitivity to oxytocin increases before parturition, and oxytocin can be used to induce parturition. Because maternal serum oxytocin levels do not increase until after parturition has begun, oxytocin is not thought to initiate parturition, but rather promote contractions post initiation. Progesterone inhibits and estrogen stimulates synthesis of oxytocin receptors. Although maternal serum progesterone levels do not decrease immediately before human parturition, estrogen levels rise and oxytocin receptor synthesis increases in a manner sufficient to facilitate oxytocin sensitivity.

Prostaglandins

Because estrogens stimulate prostaglandin synthesis in the uterus, amnion, and chorion, the rising estrogen levels late in gestation can increase uterine prostaglandin formation before parturition. Although the role of prostaglandin in initiating parturition is not known, prostaglandins and other cytokines increase uterine motility, and levels of these compounds increase during parturition, thereby facilitating delivery. Prostaglandin levels in amniotic fluid, fetal membranes, and uterine decidua increase before the onset of labor. **Prostaglandin $F_{2\alpha}$** and **prostaglandin E_2** increase uterine motility, and large doses of these agents have been used to induce labor.

Uterine Size

Uterine size is thought to be a factor regulating parturition. Stretch of smooth muscle, including the uterine myometrium, increases muscle contraction. In addition, uterine stretch stimulates uterine prostaglandin production, further increasing motility. Multiple births generally occur prematurely. The tendency for early delivery can be a result of increased uterine size, increased fetal production of chemicals stimulating delivery, or both.

Mammogenesis and Lactation

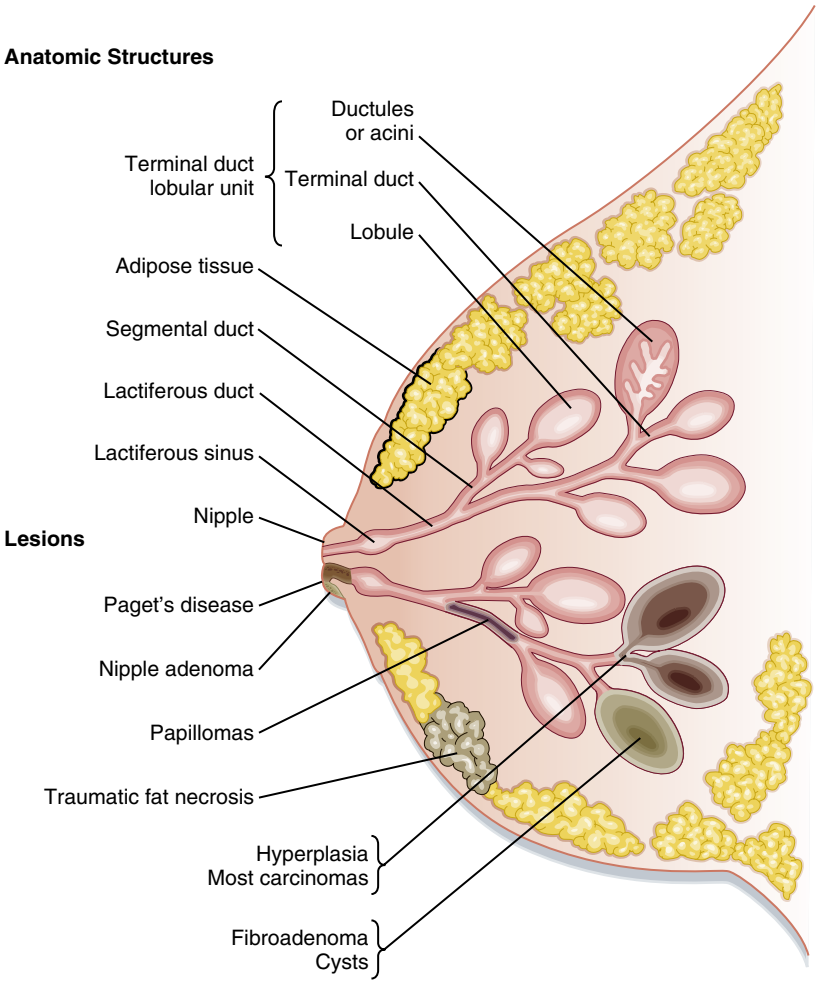
Structure of the Mammary Gland

The **mammary gland** is composed of 15 to 20 lobes, each with an excretory **lactiferous duct** that opens at the nipple (Fig. 44.37). The lobes in turn are composed of several lobules that contain secretory structures called **alveoli** at the terminal portions of the **ducts.** The epithelium of the alveoli and ducts is composed of two cell layers: apical **luminal epithelial cells** and basal **myoepithelial cells.** There is strong evidence for the presence of adult mammary stem cells within this epithelium. The luminal epithelial cells of the alveoli are the producers of milk, and the luminal cells of the ducts convey and modify the secreted milk. Myoepithelial cells are stellate smooth muscle–like cells, and contraction of these cells in response to a stimulus (i.e., milk let-down) expels milk from the lumens of the alveoli and ducts. Lobes and lobules are supported within a connective tissue matrix. The other major tissue component of the breast is adipose tissue. The lactiferous ducts empty at the **nipple,** a highly innervated hairless protrusion of the breast designed for suckling by an infant. The nipple is surrounded by a pigmented hairless areola that is lubricated by sebaceous glands. Protrusion of the nipple, called **erection,** is mediated by sympathetic stimulation of smooth muscle fibers in response to suckling and other mechanical stimulation, erotic stimulation, and cold.

Hormonal Regulation of Mammary Gland Development

At **puberty, estrogen** increases ductal growth and branching. With onset of the luteal phases of the ovary, **progesterone and estrogen** induce ductal growth and formation of rudimentary alveoli. During nonpregnant cycles the breasts develop somewhat and then regress. Estrogen also increases deposition of **adipose tissue,** which makes a major contribution to breast size and overall form. Adipose tissue expresses **CYP19/aromatase,** so accumulation of this tissue in the breast increases local production of estrogens from circulating androgens.

Breast development is facilitated by pregnancy, during which extensive ductal growth and branching and lobuloalveolar development occur. The parenchymal growth of the breast during development occurs at the expense of stroma, which is degraded to make room for enlarging lobuloalveolar structures. Several placental hormones stimulate breast development, including **estrogen, progesterone, placental lactogen,** and a **growth hormone variant (GH-V).** Estrogen acts on the breast both directly and indirectly through increasing maternal **pituitary PRL.** Estrogen increases PRL secretion from pituitary lactotropes. Estrogen also stimulates **lactotrope hypertrophy and proliferation,** which accounts for the twofold increase in pituitary volume during pregnancy in humans. Although epithelial cells express genes encoding milk protein and enzymes involved in milk production, progesterone inhibits the onset of milk production and secretion **(lactogenesis).**

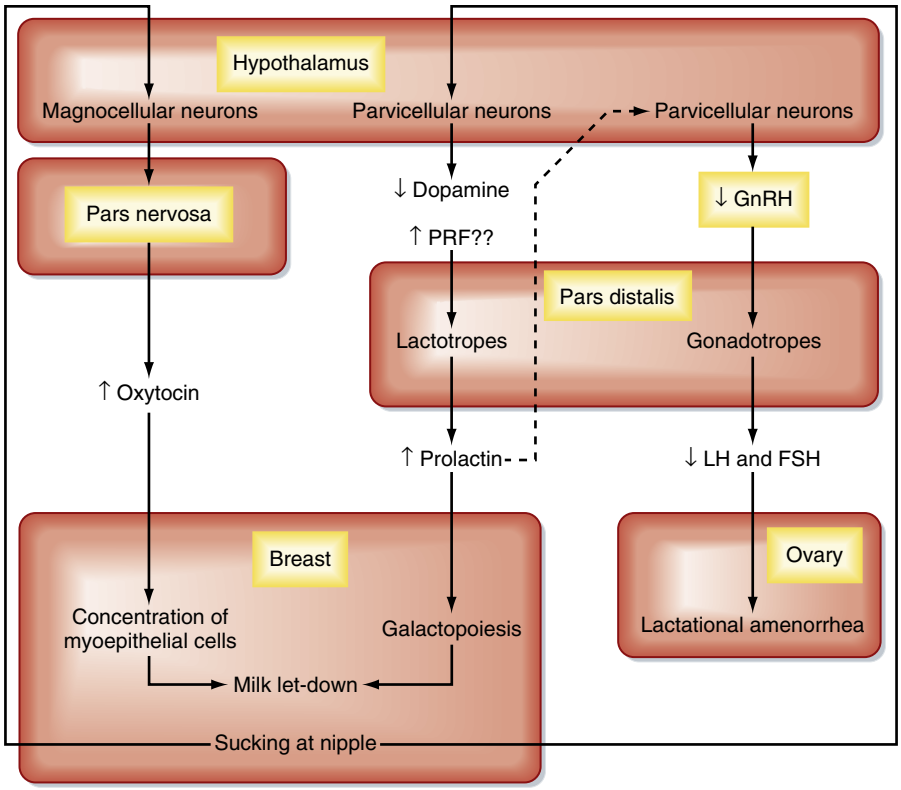


• **Fig. 44.37** Diagram of the structure of the breast, along with some pathological conditions of the breast and where they occur. (From Crum CP, et al. In: Kumar V, Cotran RS, Robbins SL, eds. *Robbins Basic Pathology.* 7th ed. Philadelphia: Saunders; 2003.)

After parturition, the human breast produces **colostrum,** which is enriched with antimicrobial and anti-inflammatory proteins. In the absence of placental progesterone postdelivery, normal breast milk production occurs within a few days. The lobuloalveolar structures produce milk, which is subsequently modified by the ductal epithelium. **Lactogenesis** and maintenance of milk production **(galactopoiesis)** require stimulation by pituitary PRL in the presence of normal levels of other hormones, including insulin, cortisol, and thyroid hormone. Although placental estrogen stimulates PRL secretion during pregnancy, the stimulus for PRL secretion during the nursing period is suckling by the infant (Fig. 44.38). Levels of PRL are directly correlated with frequency and duration of suckling at the nipple. The link between suckling at the nipple and PRL secretion involves a neuroendocrine reflex in which dopamine secretion at the median eminence is inhibited (the PRL release inhibitory factor; see Chapter 41). It is also possible suckling increases secretion of unidentified PRL-releasing hormones.

PRL also inhibits release of GnRH, and consequently, nursing can be associated with **lactational amenorrhea** (see Fig. 44.38). This effect of prolactin has been called "nature's contraceptive," and it may play a role in spacing out pregnancies. However, only regular nursing over a 24-hour period is sufficient to induce a PRL-induced anovulatory state in the mother. Thus, lactational amenorrhea is not an effective or reliable form of birth control for most women. Inhibition of GnRH by high levels of PRL is important clinically. A **prolactinoma** is the most common form of hormone-secreting pituitary tumor, and **hyperprolactinemia** is a significant cause of infertility in both sexes. Hyperprolactinemia can likewise be associated with **galactorrhea** (inappropriate flow of breast milk) in men and women.

Suckling at the nipple also stimulates release of **oxytocin** from the pars nervosa (see Chapter 41) through a neuroendocrine reflex (see Fig. 44.38). Contraction of myoepithelial cells induces **milk let-down,** or expulsion of milk from the alveolar and ductal lumens. Thus, the nursing infant does not gain milk by applying negative pressure to the breast during suckling. Rather, milk is actively ejected through a neuroendocrine reflex. Oxytocin release and milk let-down can be induced by psychogenic stimuli such as the mother hearing a baby crying on television or thinking about her baby. Such psychogenic stimuli do not affect PRL release.



• **Fig. 44.38** Neuroendocrine reflex caused by suckling at the nipple and leading to secretion of oxytocin and prolactin. In turn these hormones induce continued milk production (galactopoiesis) and milk let-down. Prolactin also induces lactational amenorrhea. (Modified from White BA, Porterfield SP. *Endocrine Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

IN THE CLINIC

Invasive breast cancer (IBC) is a major cancer in women and can be classified into several categories. Most newly diagnosed IBC is classified as **luminal A,** which is usually derived from luminal cells of terminal ducts or alveoli. Luminal A IBC displays some epithelial organization, including E cadherin–mediated cell-cell contacts, and is poorly motile and poorly aggressive. This form also expresses the **estrogen receptor α (ERα)** and is dependent on estrogenic stimulation for growth. Early diagnosis of luminal A IBC confers a good prognosis. Treatment for early small tumors that are "node-negative" (i.e., have not spread to nearby lymph nodes) typically involves surgical removal ("lumpectomy"), followed by radiation treatment, followed by 5 years of daily tamoxifen treatment. Tamoxifen is a SERM that opposes estrogen in the breast.

Menopause

Though related to depletion of ovarian follicles, the causes and process of **menopause** are poorly understood. Age-related changes in the CNS, including critical patterns of GnRH secretion, precede follicular depletion and may play an important role in menopause. Because follicles do not develop in response to LH and FSH secretion, estrogen and progesterone levels drop. Loss of the negative-feedback inhibition of estrogen on GnRH and LH/FSH results in a marked rise in serum LH and FSH. FSH levels rise more than LH levels. This could result from loss of ovarian inhibin.

Menopause typically occurs between 45 and 55 years of age. It extends over a period of several years. Initially the cycles become irregular and are periodically anovulatory. The cycles tend to shorten, primarily in the follicular phase. Eventually the woman ceases to cycle altogether. Serum estradiol levels drop to about a sixth of the mean levels for younger cycling women, and progesterone levels drop to about a third those in the follicular phase of younger women. Production of these hormones does not cease entirely, but the primary source of these hormones in postmenopausal women becomes the adrenal, although interstitial cells of the ovarian stroma continue to produce some steroids. Most circulating estrogens are now produced peripherally from androgens. Because estrone is the primary estrogen produced in adipose tissue, it becomes the predominant estrogen in postmenopausal women.

Most symptoms associated with menopause result from **estrogen deficiency.** The vaginal epithelium atrophies and becomes dry, and bone loss is accelerated and may lead

IN THE CLINIC

There are multiple behavioral methods of **contraception.** Total abstinence is the most effective way to avoid getting pregnant. Two other behavioral methods include withdrawal before ejaculation (**coitus interruptus)** and the rhythm method. The rhythm method relies on abstinence from sexual intercourse during fertile periods around the time of ovulation, including three to four days before the time of ovulation until three to four days afterward. Both these methods have higher failure rates (20%–30%) than **barrier methods** (2%–12%), **intrauterine devices (IUDs)** (<2%), and **oral contraceptives** (<1%) do. Barriers such as **condoms** or **diaphragms** are more effective when used with **spermicidal jellies.** Of all methods, only condoms provide effective protection from sexually transmitted diseases in sexually active individuals. IUDs are relatively effective, and these agents prevent implantation by locally producing an inflammatory response in the endometrium. Some forms of IUDs contain copper, zinc, or progestins, which inhibit sperm transport or viability in the female reproductive tract.

Oral contraceptives have been marketed in the United States since the early 1960s. The doses of steroids used today are significantly lower than those used 35 years ago. Properly used, oral contraceptives have a low failure rate. Many forms of oral contraceptives are marketed today. The trend over the years has been to decrease the dosage of steroids used because the side effects are dose-dependent. All oral steroidal contraceptives contain either a combination of an estrogen and a progestin or a progestin alone. Oral contraceptives work through multiple mechanisms. Most block the LH surge that triggers ovulation. However, some pills (e.g., progestin-only minipill) do not prevent LH surges. In general, oral contraceptives also block fertility by changing the nature of cervical mucus, altering endometrial development, or regulating fallopian tube motility. Because these contraceptives suppress FSH, they also impair early follicular development.

Emergency contraception involves hormone or IUD treatment designed to inhibit or delay ovulation, inhibit corpus luteum function, disrupt the function of the oviducts and uterus, or any combination of these mechanisms. For example, candidates for emergency contraception include women who are sexually assaulted or who experienced failure of a barrier method (e.g., ruptured condom). There are more than 20 types of commercially available "morning-after" pills. The currently preferred medication is **levonorgestrel (Plan B),** which is a synthetic progestin-only pill. The efficacy of the pill is inversely correlated with the time it is taken after intercourse, although the exact mechanism of action is not known. Treatment has no effect if implantation has occurred. The most effective type of emergency contraceptive is the **ParaGard copper IUD**, which is inserted within five days of unprotected intercourse. The copper acts as a spermicide and the device alters the endometrial environment in a manner that prevents implantation.

Medical **(hormonal) termination** of pregnancy (abortion) can be achieved up to 49 days' gestation by administration of **mifepristone (RU-486),** a progesterone receptor antagonist that induces collapse of the pregnant endometrium. Mifepristone is followed 48 hours later by ingestion or vaginal insertion of a **synthetic prostaglandin E** (e.g., misoprostol), which induces myometrial contractions.

to osteoporosis. The incidence of coronary artery disease increases markedly after menopause. **Hot flashes** result from periodic increases in core temperature, which produces peripheral vasodilation and sweating. Hot flashes are thought to be linked to increases in LH release and are probably associated not with the pulsatile rise in LH secretion but rather with central mechanisms controlling GnRH release. Hot flashes typically subside within 1 to 5 years of the onset of menopausal symptoms.

Key Concepts

1. The reproductive systems are composed of gonads, an internal reproductive tract with associated glands, and external genitalia. Mammary glands are accessory reproductive glands in women.
2. Gonads have two main functions: production of gametes and production of hormones. Hormones (primarily sex steroids) are absolutely necessary for normal function of the reproductive system, and their production is regulated by a hypothalamic-pituitary-gonadal axis.
3. Seminiferous tubules in the testis contain Sertoli cells and developing sperm cells.
4. *Spermatogenesis* refers to the progression of sperm cells from spermatogonia through the processes of meiosis and spermiogenesis to form mature spermatozoa.
5. Testosterone and pituitary FSH are required for normal sperm production. Only Sertoli cells express the androgen receptor and the FSH receptor, so these hormones regulate spermatogenesis indirectly through their actions on Sertoli cells. Sertoli cells produce the hormone inhibin, which negatively feeds back on pituitary FSH production.
6. Sertoli cells have many functions, including production of androgen-binding protein (ABP) and fluid and creation of the blood-testis barrier.
7. Leydig cells are stromal cells that reside outside the seminiferous tubules. They respond to LH by producing testosterone.
8. Testosterone is an active androgen. It can be converted peripherally to DHT, which is more active in certain tissues (e.g., prostate), or to estradiol.
9. Leydig cells are regulated within a hypothalamic-pituitary-testicular axis. The hypothalamus produces GnRH, which stimulates pituitary gonadotropes to

secrete LH and FSH. Testosterone, DHT, and estradiol negatively feedback at the pituitary and hypothalamus and inhibit LH more than FSH secretion. Inhibin from the Sertoli cells selectively inhibits FSH.

10. Testosterone, DHT, and estradiol have numerous actions on the male reproductive tract, external genitalia, and male secondary sex characteristics, as well as on other organ systems (e.g., blood cell production, lipoprotein production, bone maturation).
11. The male tract includes tubal structures (epididymis, ductus deferens, and male urethra), accessory sex glands (seminal vesicles, prostate), and the penis. The seminal vesicles and the prostate produce most of the ejaculate, which nourishes, buffers, and protects sperm.
12. Penile erection involves a complex neurovascular response leading to engorgement of the erectile tissue within the penis base and shaft with blood.
13. The follicle is the functional unit of the ovary. Follicles contain epithelial cells (granulosa and cumulus) and outer stromal cells (thecal). All these cells surround a primary oocyte that remains arrested in the first meiotic prophase until just before ovulation.
14. Follicles develop from the smallest (primordial) to a large antral follicle over a period of months. The latter part of follicular development requires gonadotropins.
15. The *menstrual cycle* refers to an approximately 28-day cycle that is driven by the following ovarian events: development of one large antral follicle to a preovulatory follicle (follicular phase), ovulation, and formation and death of a corpus luteum of menstruation (luteal phase).
16. The follicular phase of the ovary corresponds to the menstrual and proliferative phases of the uterine endometrium. The luteal phase of the ovary corresponds to the secretory phase of the uterine endometrium.
17. One dominant follicle is selected per menstrual cycle—usually the largest follicle with the most FSH receptors.
18. High levels of estradiol occur around midcycle and exert positive feedback on gonadotropin secretion. This induces the LH (and a smaller FSH) surge. The midcycle gonadotropin surge induces (a) meiotic maturation of the primary oocyte so that it progresses to a secondary oocyte (with one polar body) arrested at metaphase of the second meiotic division, (b) breakdown of the ovarian and follicular wall so that the oocyte-cumulus complex is extruded (called *ovulation*), and (c) differentiation of the remaining follicular cells into a corpus luteum. The corpus luteum produces high levels of progesterone, estradiol, and inhibin.
19. If pregnancy does not occur, the corpus luteum will die in 14 days. This constitutes the luteal phase of the menstrual cycle.
20. The oviducts capture the ovulated cumulus-oocyte complex and transport it medially into the oviduct and toward the uterus. Estrogen promotes ciliation and transport; progesterone inhibits transport.
21. The uterine mucosa, called the *endometrium,* is the normal site of embryonic implantation. The mucosa is increased in thickness in preparation for implantation and is sloughed away if no pregnancy occurs.
22. During the mid to late follicular phase (days 6–14 of the menstrual cycle), the ovary produces estradiol, which induces all cells of the endometrium to proliferate (called the *proliferative phase* of the uterus).
23. After ovulation the ovary enters the luteal phase (days 16–28) and produces progesterone. Progesterone promotes glandular differentiation and stimulates secretion from the uterine glands (called the *secretory phase* of the uterus).
24. In the absence of an implanting embryo the corpus luteum dies, progesterone production ceases, and the uterine endometrium is sloughed (called the *menstrual phase,* or *period*, of the uterus—this corresponds to days 1 to 5 of the follicular phase of the ovary).
25. The cervix is the lower portion of the uterus. Cervical mucus is hormonally regulated so that at midcycle, in response to estrogen, cervical mucus promotes entry of sperm into the uterus from the vagina. During the luteal phase, in response to progesterone, cervical mucus becomes thick and poses a barrier to entry of sperm and microbes into the uterus.
26. Fertilization is a complex series of events that occur in the oviduct and lead to penetration of the oocyte by sperm.
27. Early embryogenesis (up to day 6 after fertilization) occurs in the oviduct and gives rise to a blastocyst that hatches from the zona pellucida.
28. The placenta develops from the outer extraembryonic trophoblast. The endocrine function of the placenta includes production of hCG, progesterone, estrogens, and placental lactogen. Estrogen production requires placental cells (syncytiotrophoblasts) as well as the fetal adrenal and liver—collectively called the *fetoplacental unit.*
29. Pregnancy and the hormones of pregnancy induce major changes in maternal physiology, including an increase in insulin resistance, an increase in the use of free fatty acids by the mother, and development of the mammary glands. Mammary gland development (but not lactation) is promoted by estrogen, progesterone, and placental lactogen but also by maternal pituitary prolactin, whose secretion is stimulated by placental estrogens.
30. Oxytocin is a pituitary hormone that promotes contraction of certain smooth muscles, including myometrial contractions during labor and myoepithelial contractions in the breasts that lead to let-down of milk in response to suckling.
31. Menopause results from exhaustion of the ovarian reserve and is characterized by low ovarian hormones and elevated gonadotropin levels.

Acknowledgment

We wish to thank Dr. Lisa Mehlmann for her advice on this chapter, and especially for help in drawing Figs. 44.31 and 44.32.