

## 9.9 Female Reproductive Physiology

### Learning Objectives

- Identify vagina, cervix, uterus, fallopian tube, fimbria, infundibulum, and ovary and summarize their functions
- Describe when oogonia arise and when the first and second meiotic divisions occur
- Draw on a graph the approximate relative levels of LH, FSH, estrogen, and progesterone during the menstrual cycle and indicate when ovulation occurs
- List the three phases of the menstrual cycle
- Describe the general changes in the endometrium during the menstrual cycle
- Name the enzyme that converts testosterone and androstenedione to estradiol and estrone
- Describe the requirements for positive feedback of estrogen on gonadotrophs
- Define GnRH and indicate its site of origin
- Explain why the LH surge is greater than the FSH surge immediately prior to ovulation
- Distinguish among primary follicle, Graafian follicle, and corpus luteum
- Describe the main function of the corpus luteum

### SEXUAL REPRODUCTION COSTS A LOT BUT IT IS WORTH THE PRICE

Most animal and plant species on this planet engage in sexual reproduction. The whole process is quite an elaborate dance of biochemistry, physiology, and ecology, and in many cases entails risk to both parents and offspring. In humans, especially, death by childbirth historically has been a major cause of death of women in their childbearing years. Similarly, early childhood death historically has been one of the more potent selection processes driving our biological and cultural evolution. One is naturally tempted to ask the question: Why do we reproduce in this way? The short answer is that it confers a benefit on the species. The benefit derives from the scrambling of genes from one generation to the next. Certain gene combinations are deleterious to the survival of the species under specific ecological conditions, whereas other combinations are advantageous. If the environment changes in some way, recombination of already existing genes can produce

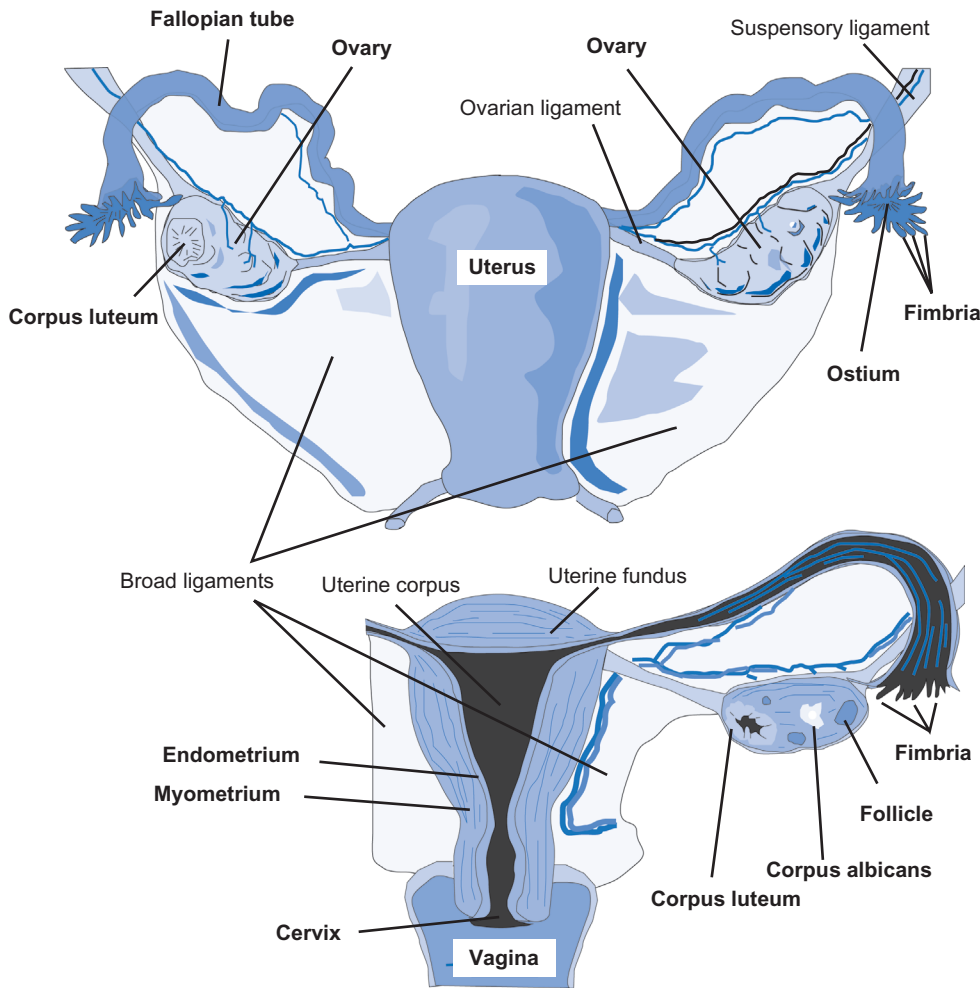
successful offspring much faster than mutation of an already existing but relatively static genome. In a similar vein, isolated but small breeding populations may not have enough genetic diversity to get them through difficult times. The population as a whole becomes more vulnerable to extinction. This scrambling of the genes occurs not only by mixing the genes from two separate organisms but also by scrambling the genes provided by each of those organisms. The resulting potential diversity of the offspring is staggering. The proof of this is the differences between siblings in a single family. Such sibling groups often share enough genetic material that they can be identified as siblings, yet it is clear that each is a unique individual. The source of this variation—the cell divisions that give rise to the reproductive cells, or **gametes**—is discussed in Chapter 9.10.

### THE ANATOMY OF THE FEMALE REPRODUCTIVE TRACT

The internal components of the female reproductive tract consist of the **ovaries**, **fallopian tubes**, **uterus**, and **vagina**. The external genitalia consist of the **labia majora**, **labia minora**, **clitoris**, and **vaginal opening**. The labia are folds of skin that cover fat and smooth muscle and meet along the midline above the vaginal opening. They cover and protect the urinary and vaginal openings as well as the clitoris. The clitoris is invested with numerous nerve endings so that it is highly sensitive to touch, pressure, and temperature. It has an exclusively sexual function to encourage the woman to engage in sexual intercourse and have babies as a consequence. The internal components of the female reproductive system are shown in [Figure 9.9.1](#).

### OVERVIEW OF FEMALE REPRODUCTIVE FUNCTION

Each of the anatomical features of the female reproductive track has defined functions that are sometimes analogous to the functions of their counterparts in the male reproductive system. They differ markedly from the male in their periodicity. Males produce gametes and are normally fertile continuously. Females produce gametes periodically and have a relatively short-lasting window of fertility. The approximately 28-day cycle of female reproductive function is called the **menstrual cycle**. It is outwardly apparent from **menstruation**, the



**FIGURE 9.9.1** The female reproductive apparatus. See text for an explanation of the structures.

shedding of the uterine lining when fertilization has not occurred and there is no baby on board.

The gonad in the female is the ovary. The two ovaries are arranged bilaterally, one on each side of the pelvic abdomen. Each ovary in the adult weighs about 15 g and is attached to the pelvic wall and to the side of the uterus by the ovarian ligament. The ovarian artery, vein, lymphatics, and nerve supply run along the ovarian ligament. As in the male, these gonads produce gametes and reproductive hormones and are sensitive to the gonadotropins, LH (luteinizing hormone) and FSH (follicle stimulating hormone). In fact, these hormones derive their names from their effects in the female in whom their roles were first discovered and clarified. Each month the ovaries generally produce one ovum or at most a few **ova**, large haploid germ cells (containing half of the genetic information of the mother) that can be fertilized by the male's spermatozoa and subsequently begin development into a baby. This release of the ovum from the ovary is called **ovulation**. The ovum is released from an ovarian **follicle**. It is actually released into an open space in the abdominal cavity but immediately adjacent to a funnel-shaped portion of the **fallopian tube** called the **infundibulum**. The fallopian tube is also called the **oviduct**. Little finger-like processes called **fimbriae** extend from the infundibulum to

closely appose the lateral portions of the ovary. The fimbriae undulate so as to draw the ovum into a fallopian tube, which projects about 10 cm from the uterus toward the ovary on each side of the body. The fallopian tube consists of an epithelial lining with secretory and ciliated cells, and a smooth muscular layer capable of peristaltic-like contractions. The number and activity of the cilia and secretory cells change throughout the female's period. Their actions and the peristaltic contractions of the smooth muscle layers of the fallopian tubes propel the ovum from the ovary, where it is released, toward the uterus. The fallopian tubes also provide a conduit for the movement of the sperm toward the ovum.

The **uterus** is colloquially known as the womb. A thick smooth muscle wall encloses a cavity that is lined with a mucous epithelium called the **endometrium**. The composition and thickness of the endometrium varies cyclically with the periodic variation in reproductive hormones that accompanies ovulation. The shedding of the lining when fertilization does not occur makes up the monthly menstrual flow in adult females. It is accompanied by contraction of the uterus which is generally referred to as "cramping" and which can sometimes be very painful. The function of the uterus is to protect and nourish the developing fetus from its time

of conception to birth, and to provide the motive force for delivery of the baby during **parturition**, or birth.

Once captured by the fallopian tubes, the ova secrete chemoattractant compounds that attract the sperm. An ovum is viable for 12–24 h. Sperm deposited in the female remain viable for about 48 h. Thus, timing of sexual intercourse surrounding ovulation is crucial for fertilization of the ovum. Fertilization of the ovum typically occurs in the fallopian tube but may occur in rare cases in the abdominal cavity. Implantation of the fertilized ovum outside of the uterus is called **ectopic pregnancy** and is a medical emergency. Normally, the fertilized ovum begins to divide at once and gradually moves down the fallopian tubes to reach the uterus and completes the trip in about 2 or 3 days. After another 2 or 3 days in the uterus, the developing zygote, now typically in the blastocyst stage, initiates implantation. This is the process by which the developing zygote attaches itself to the uterine lining and invades it to eventually form the **placenta**. The placenta has two main functions: to exchange materials for the developing fetus with the mother and to secrete hormones that affect both mother and fetus. The placenta derives nutrients and oxygen from the mother and gives back to her waste products and carbon dioxide.

The cervix is the most inferior part of the uterus that projects out into the vagina. The mucus secreted by the cervix also varies with the cycle to form channels for the sperm to travel into the uterus. The geometry of the cervix and its relatively narrow opening help protect the uterus from foreign objects and thereby protects against injury and infection.

The vagina is essentially a tube leading from its external opening at the surface of the body to its end at the uterus. It is invested with smooth muscle that can contract or expand and a stratified epithelium that secretes a lubricating mucus during sexual arousal that aids in sexual intercourse. The vagina itself has few sensory nerves and is relatively insensitive to touch and pressure.

## OOGENESIS BEGINS IN THE FETUS

**Oogenesis is the formation of the ova.** It begins in the early fetus when primordial germ cells migrate from the yolk sac of the embryo to the genital ridge at 5–6 weeks of gestation. In the developing ovary, these germ cells divide by mitosis to form a population of primary **oogonia**, which are analogous to the male's primary spermatogonia. By 20–24 weeks of gestation, the number of oogonia has peaked at about 7 million. Beginning at 8 or 9 weeks of gestation, some of these oogonia enter into the prophase of meiosis I to become primary oocytes and they arrest at this stage due to inhibitory hormones. Eventually all of the oogonia convert to primary oocytes or degenerate. At birth, the female ovaries contain in excess of 2 million primary oocytes which enlarge gradually to become the single largest uninuclear cell in the body at 100–120  $\mu\text{m}$  in diameter. After birth, the number of primary oocytes decreases because there is no

further mitosis and some of the primary oocytes are lost by **apoptosis**, or programmed cell death. At the time of puberty, there are typically 400,000 primary oocytes remaining. Over the reproductive span, typically a woman will ovulate only 400–500 of these oocytes. The remaining oocytes disappear by a process called **atresia**.

## PUBERTY INITIATES OVULATION AND DEVELOPMENT OF SECONDARY SEX CHARACTERISTICS

Puberty is the transition from the childhood, nonreproductive state to the adult reproductive state. It requires maturation of the entire hypothalamic–pituitary–gonadal axis. Prior to puberty, LH and FSH secretions are low despite the fact that both gonadal steroids and **inhibin**, which both negatively regulate LH and FSH secretion in adults, are low. This points to other mechanisms, most likely the neuronal circuits that give rise to GnRH release by neurons in the hypothalamus, as the cause of puberty. The process by which puberty begins remains unclear, partly because there is no single precipitating event. Instead, there are gradual changes in a variety of signals each of which, by themselves, does not constitute puberty.

The beginning of menses, or the monthly blood flow representing the sloughing of the uterine lining, is called **menarche**. This is accompanied by full reproductive capacity in the female. However, changes in secondary sex characteristics precede menarche. These include the following:

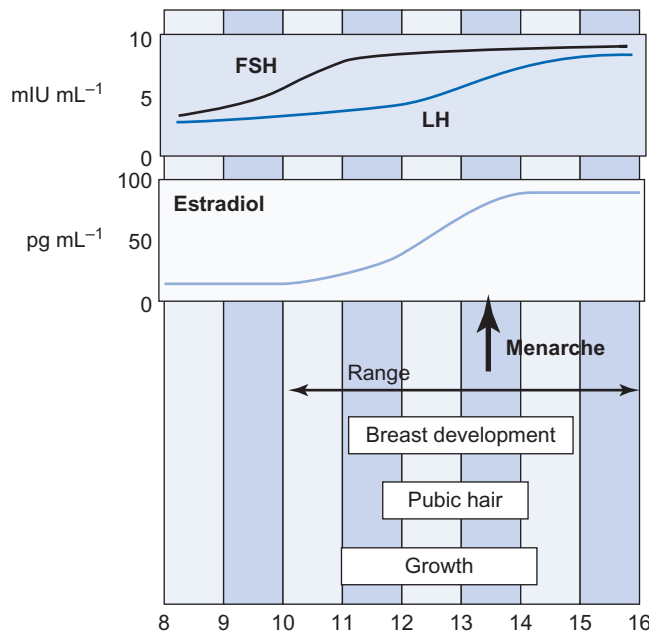
- Accelerated linear growth associated with the puberty growth spurt
- Development of breasts
- Maturation of the genitalia
- Appearance of pubic and axillary hair
- Widening of the hips
- Enlargement of the uterus, fallopian tubes, and vagina.

Testosterone and estradiol levels in the blood rise during puberty, and these increase the amplitude of the GH pulses in response to GHRH. Although GH is as high or higher in girls than in boys, the estradiol interferes with the effect of GH on the long bones, whereas testosterone, and lack of estradiol, increases the effect in boys. The result is that the boys grow larger. Since girls typically enter puberty earlier, there is a period in which the girls are briefly taller than the boys, but the boys rapidly catch up and surpass the girls. Most of the effects listed above are mediated by estrogen.

The time course of events in puberty is illustrated in [Figure 9.9.2](#).

## LH AND FSH DRIVE THE MENSTRUAL CYCLE

The menstrual cycle refers to all of the events that occur during the approximately month-long reproductive cycle of the adult female. The menstrual period is the



**FIGURE 9.9.2** Chronology of events in female puberty. Although the average age of menarche is about 12 years in the United States, regular cycles do not begin until about age 14. There is great variability in the age of menarche. Menstruation can begin as early as 10 years or as late as 16 years of age.

time of the cycle in which the uterine lining sloughs off and is discarded. A summary of some of the events that occur during the cycle is shown in [Figure 9.9.3](#). The entire cycle typically lasts 28 days, but it can last from 25 to 30 days. It consists of three phases:

### THE FOLLICULAR PHASE

The follicular phase begins at the first day of menstrual bleeding and lasts until ovulation. It is more variable and accounts for the fluctuations in cycle length. It averages 15 days.

### THE OVULATORY PHASE

The ovulatory phase lasts 1–3 days and ends with ovulation. It is characterized by a sharp spike in LH and FSH levels, with LH increasing much more than FSH.

### THE LUTEAL PHASE

After ovulation, the dominate follicle becomes the **corpus luteum**, or “yellow body,” and its secretions dominate the rest of the cycle.

## OVERVIEW OF FOLLICULAR DEVELOPMENT

The development of ovarian follicles can be divided into three stages as shown in [Figure 9.9.4](#).

- A. **Stage 1:** Development of the follicle prior to ovulation. This stage is usually not less than 13 years long but may be as long as 50 years. The follicle develops in this stage to a primordial follicle

([Figure 9.9.4](#)) and then falls quiescent until puberty.

- B. **Stage 2:** Activation of the follicle to compete for ovulation. This stage lasts 70–85 days. A small group of the many primary follicles is recruited for the next phase. The primary, secondary, and tertiary follicles can grow in the absence of the pituitary, whereas full development of the **Graafian follicle** requires FSH from the anterior pituitary. Details of the structures of the follicles are shown in [Figure 9.9.5](#).
- C. **Stage 3:** Some 5–7 days after the beginning of the menstrual flow, one of the 20 or so sister Graafian follicles becomes the **dominant follicle** of that cycle. This is the one that will ovulate. The ones that will not ovulate, involute and undergo **atresia** through apoptosis, or programmed cell death. After the LH and FSH surges, the follicle ruptures and releases a single ovum into the peritoneal cavity. The first meiotic division is complete at this time. The second meiotic division does not occur until after the sperm penetrates the ovum. Thus, the released ovum is a secondary oocyte.
- D. The remnants of the ruptured follicle form a new structure, the **corpus luteum**. This structure produces hormones that optimize the conditions for implantation of the fertilized ovum and maintain the zygote until the placenta can assume this role. The normal life of the corpus luteum is about 14 days. If there is no pregnancy, the corpus luteum spontaneously regresses, forming an avascular scar called the **corpus albicans**, or “white body.”

It is important to emphasize that the stages in follicular development described here and shown in [Figure 9.9.4](#) do not happen in a single ovarian cycle. Rather, the stages leading up to ovulation take approximately 85 days, beginning its growth in the late luteal phase of the third cycle preceding ovulation. This point is made clear in [Figure 9.9.6](#), in which the size of the follicle and the time line over several cycles are shown.

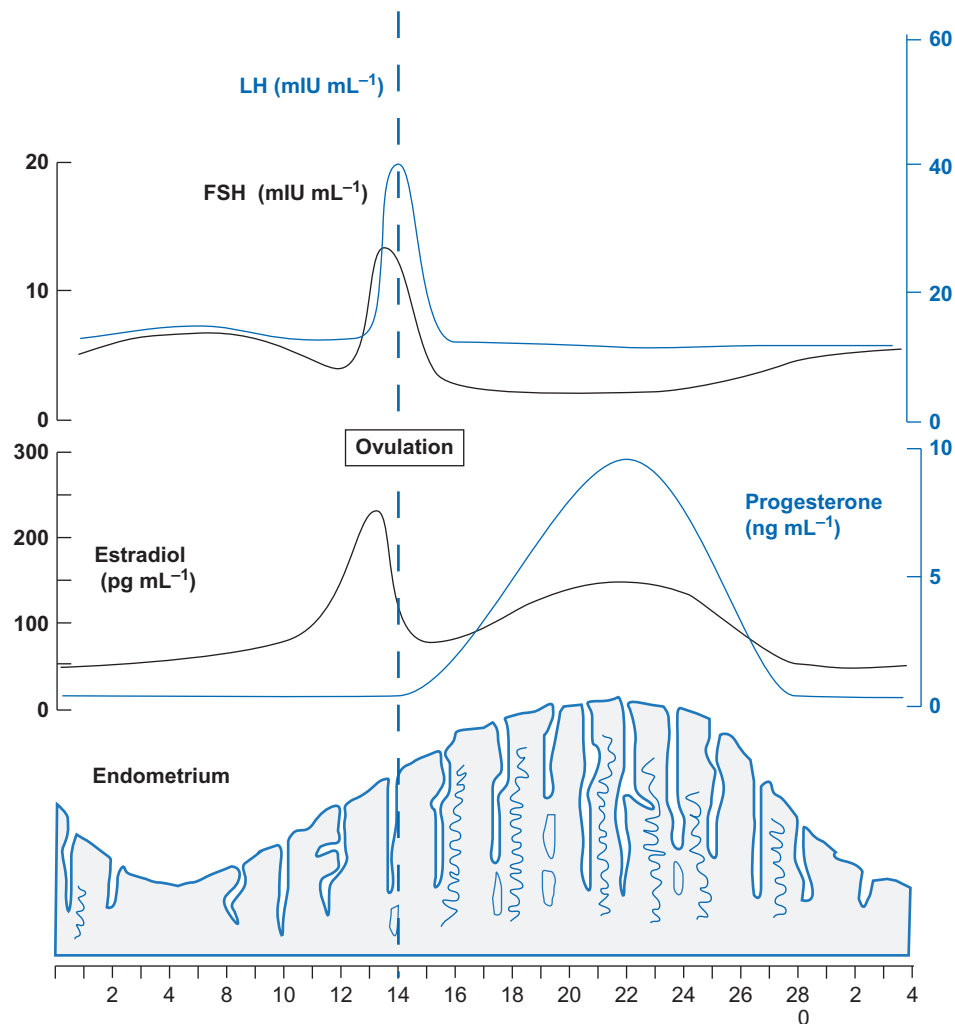
## CELLULAR ASPECTS OF FOLLICULAR DEVELOPMENT

### THE PRIMORDIAL FOLLICLE IS NOT GROWING

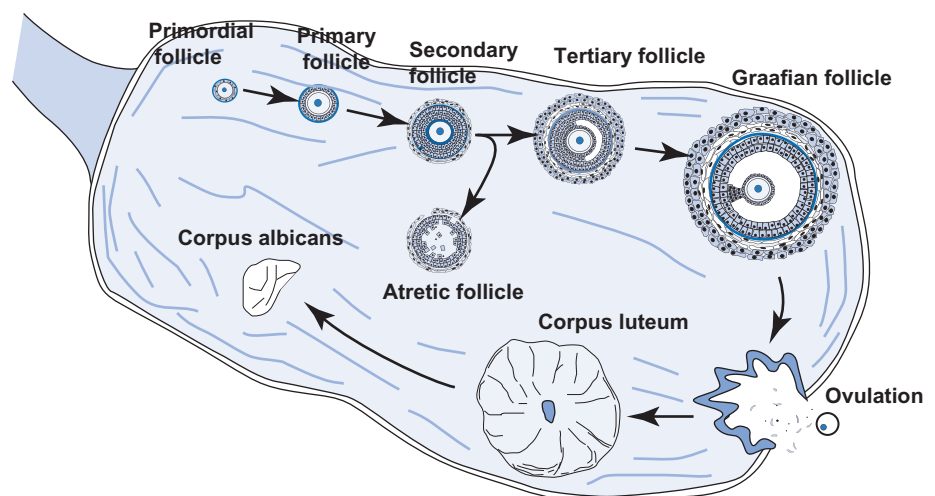
Primordial follicles consist of the ovum and a number of spindle-shaped granulosa cells that surround the ovum but lie within the basement membrane (see [Figure 9.9.5](#)). Because of this arrangement, the granulosa cells are avascular and do not have ready access to the circulation. These follicles constitute the majority of follicles, making up 90–95% of all follicles, and they do not grow.

### THE PRIMARY FOLLICLE HAS BEEN RECRUITED

In the late luteal phase of a cycle, several primordial follicles begin to grow. The granulosa cells form a

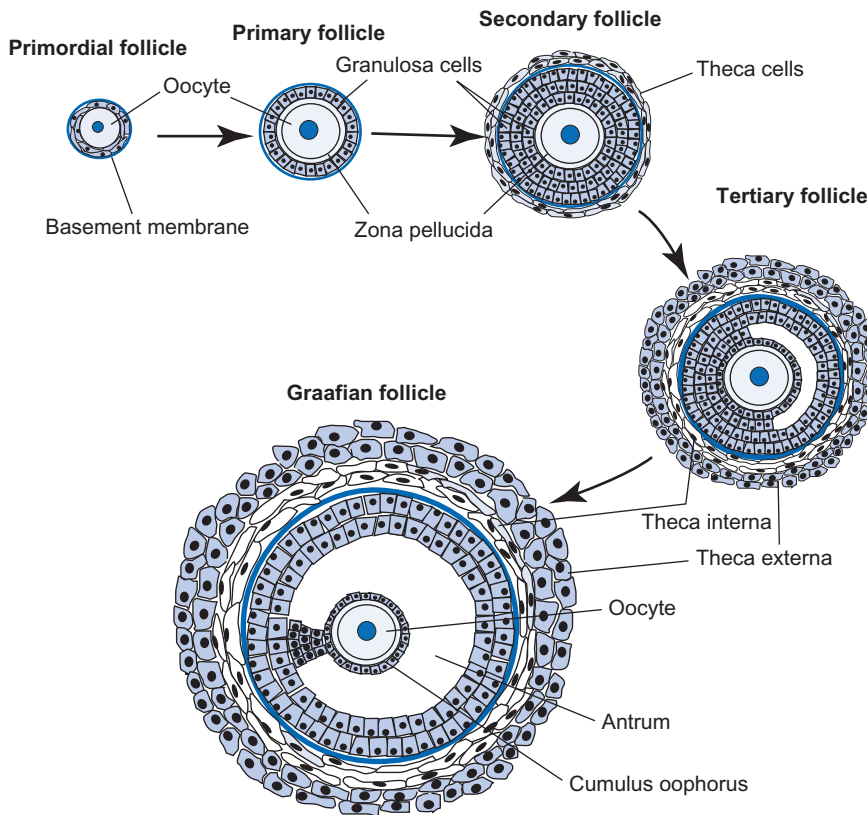


**FIGURE 9.9.3** Summary of some of the events in the adult human female menstrual cycle. Estradiol secretion by a maturing follicle gradually increases and exerts a positive feedback on LH and FSH release by gonadotrophs in the anterior pituitary. The surge in LH and FSH causes ovulation or release of the ovum from the dominant follicle. Increasing estradiol levels in the follicular phase of the cycle increase the thickness and vascularity of the uterine lining. After ovulation, progesterone levels rise and alter the vascular tortuosity of the uterine lining and promote glycogen storage within it. The abrupt loss of estradiol and progesterone, if pregnancy does not occur, causes spasmodic contractions of the uterine blood vessels and uterine muscles. The resulting ischemia produces necrosis (cell death) and the lining condenses and degenerates.

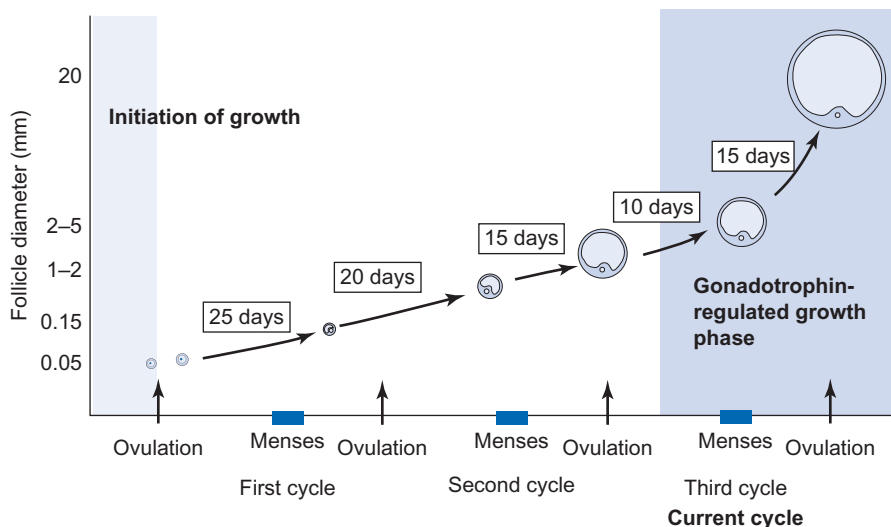


**FIGURE 9.9.4** Stages in follicular development. During gestation, some follicles are advanced to secondary follicles where they arrest until puberty. During adult reproductive years, some secondary follicles become Graafian follicles with the appearance of the antrum. One of these in one ovary is promoted to the dominant follicle, which ruptures at the time of ovulation, releasing its ovum into the peritoneal cavity.





**FIGURE 9.9.5** Progression of follicles. Primordial follicles reside in the ovaries and do not grow. After recruitment in the late luteal phase, their spindle-shaped granulosa cells become cuboidal and the oocyte enlarges, forming the primary follicle. This grows progressively into the secondary and tertiary follicle without gonadotropins. The Graafian follicle forms upon selection during the early days of the current cycle and matures into a preovulatory follicle.



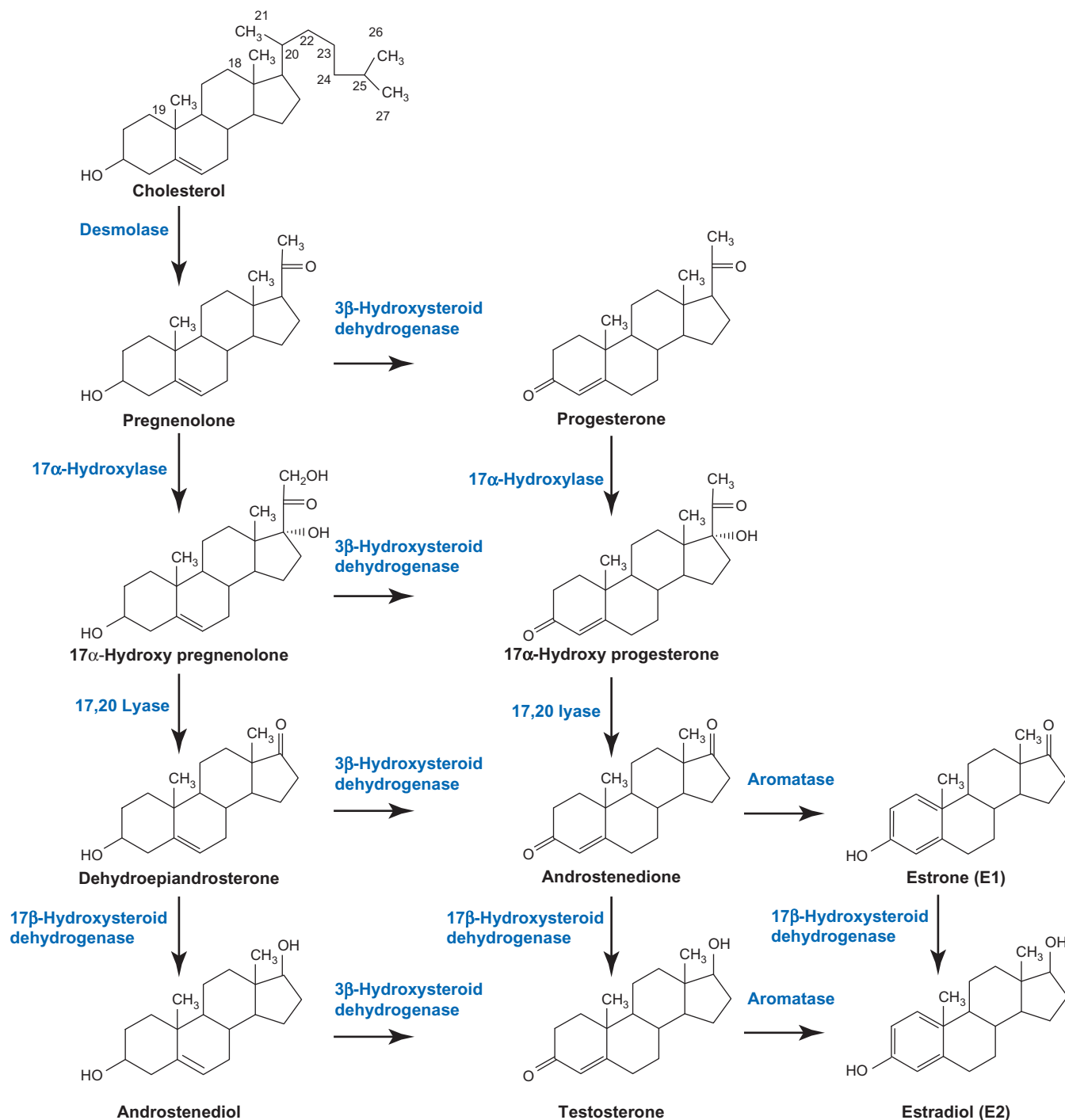
**FIGURE 9.9.6** Time course of follicular development from primordial follicle to Graafian follicle. The entire development takes approximately 85 days, which spans several menstrual cycles.

single layer of cuboidal cells, and the oocyte enlarges. The oocyte forms the **zona pellucida**, a clear region surrounding the oocyte and separating it from the granulosa cells. The zona pellucida is a glycoprotein, mucoid substance.

### THE SECONDARY FOLLICLE HAS THE BEGINNINGS OF THE THECAL LAYER

The secondary follicle has several layers of cuboidal granulosa cells by attainment of full oocyte size of

about  $120\ \mu\text{m}$  ( $=0.12\ \text{mm}$ ); it is just visible to the naked eye. The secondary follicle recruits a population of cells that reside immediately adjacent to the basement membrane on the side opposite the granulosa cells. These constitute the **theca**. The secondary follicle acquires its own blood supply, with one or two arterioles breaking up into a capillary network immediately outside the basement membrane. The granulosa cells and oocyte remain avascular. The thecal cells have receptors for LH and make androgens during the preovulatory phases. The granulosa cells have FSH



**FIGURE 9.9.7** Synthetic pathway for estrogens and progesterone. Both estradiol and progesterone synthesis begins with cholesterol and require specific enzymes. Only some cells have each of the required enzymes, so that synthesis of estradiol requires two cell types, thecal cells and granulosa cells.

receptors and make estrogens from the androgens supplied by the thecal cells (see Figure 9.9.5).

### THE TERTIARY FOLLICLE HAS AN ANTRUM

The tertiary follicle is marked by the appearance of a fluid-filled cavity, the **antrum**, adjacent to the oocyte and further development of the theca into **theca interna**—the cells adjacent to the basement membrane and circumferentially organized; and the **theca externa**—less

well-organized cells that merge with the stroma of the ovary. The fluid in the antrum is a plasma transudate.

### GRAAFIAN FOLLICLE GROWS UNDER THE INFLUENCE OF GONADOTROPINS

The Graafian follicle grows under the influence of gonadotropins. The antrum enlarges and the oocyte, surrounded by a layer of granulosa cells, forms the **cumulus oophorus**, which occupies a polar and eccentric position

within the follicle. One of the Graafian follicles becomes dominant and all others undergo atresia. The granulosa cells acquire LH receptors as well as FSH receptors. The follicle becomes preovulatory.

## OVARIAN STEROIDOGENESIS REQUIRES TWO CELL TYPES AND TWO HORMONES

The principal biologically active ovarian steroids are estrogen and progesterone, but the ovary also secretes dihydroepiandrosterone (DHEA), androstenedione, and testosterone. The preovulatory follicle secretes estrogen during the follicular phase of the menstrual cycle, whereas the corpus luteum produces both estrogen and progesterone during the luteal phase. The production of these steroids is controlled in a cell-specific manner by LH and FSH.

The pathways for estrogen and progesterone synthesis are shown in Figure 9.9.7. Thecal cells have the enzymes necessary for production of androstenedione, but **thecal cells lack aromatase that is necessary for making estradiol**. Granulosa cells have the aromatase, but **granulosa cells lack 17 $\alpha$  hydroxylase and 17,20 lyase** (also called desmolase) necessary for the syntheses of the androstenedione precursor of estradiol. Also, granulosa cells are not near a source of cholesterol for synthesis of steroids, namely LDL cholesterol, whereas the thecal

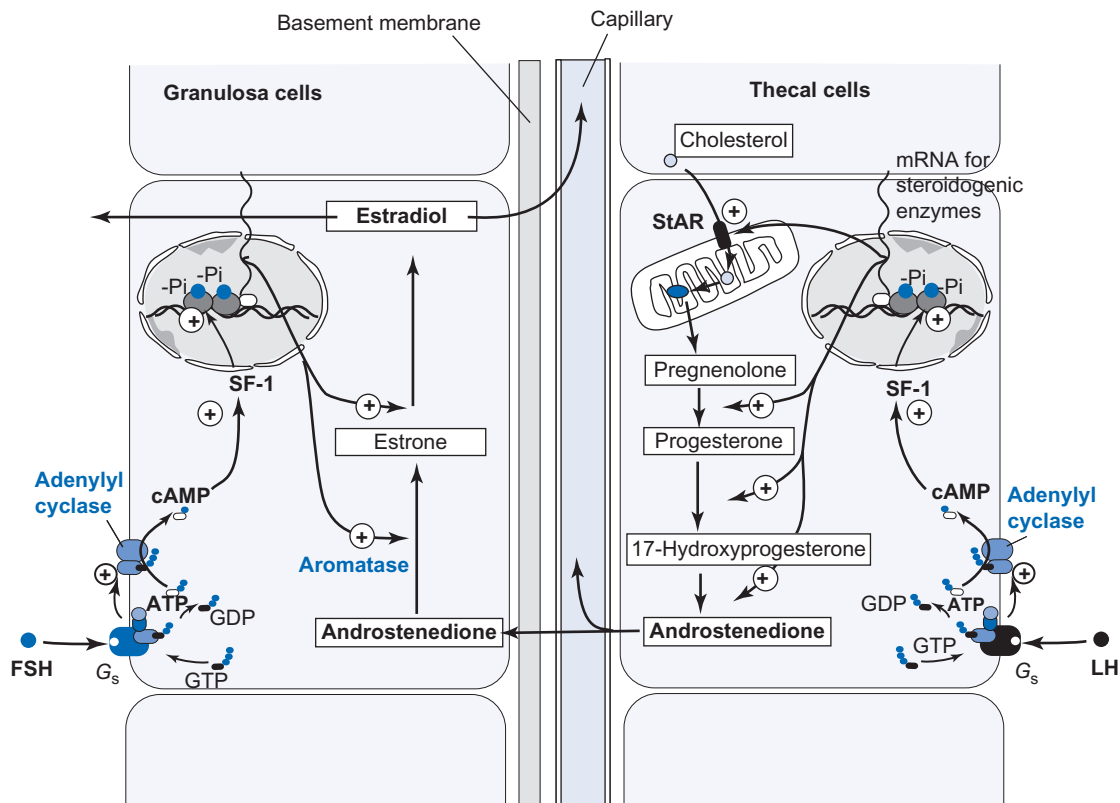
cells have access to LDL cholesterol. In the preovulatory follicle, thecal cells synthesize androstenedione under the influence of LH, and granulosa cells use the androstenedione to make estradiol, under the influence of FSH. The arrangement in the preovulatory follicle is shown in Figure 9.9.8.

After ovulation, granulosa cells become vascularized and gain access to cholesterol through low-density lipoprotein (LDL) uptake. These granulosa cells also acquire LH receptors, which stimulates them to take up LDL cholesterol as they do in thecal cells. As a result, the corpus luteum produces progesterone and estradiol. These are the most active steroidogenic cells in the body, producing up to 40 mg of progesterone per day.

In these cells, LH and FSH both activate SF-1, a transcription factor called steroidogenesis factor-1, which regulates the expression of the genes that code for StAR, desmolase, 17 $\alpha$  dehydrogenase, 17,20 lyase, 3 $\beta$  hydroxysteroid dehydrogenase, and aromatase.

## CENTRAL HORMONAL CONTROL OF THE MENSTRUAL CYCLE

Hormonal control of the menstrual cycle is complicated by the fact that at any one time there are several types of follicles in various stages of development. The follicle that becomes dominant and ovulates in any one cycle,



**FIGURE 9.9.8** Steroidogenesis by thecal and granulosa cells in the preovulatory follicle. The basement membrane separates the thecal cells from the granulosa cells and granulosa cells have no direct access to the circulation. Thecal cells respond to LH through a G<sub>s</sub> mechanism that activates SF-1, the steroidogenesis factor transcription factor that turns on the synthesis of several steroidogenic enzymes. These cells produce androstenedione but cannot produce estrone because they lack aromatase. The androstenedione is transferred to granulosa cells that convert it to estradiol under the control of FSH, also working through a G<sub>s</sub> mechanism in the granulosa cells.



for example, typically begins its run 2.5 cycles previously. In the early luteal phase of a cycle, a small group of primary follicles begins further development. Their development depends on the relatively lower concentrations of FSH and LH during the luteal phase. The cohort develops over the next 60–70 days. During this time, FSH increases the growth of the **granulosa cells** that surround the ovum and line the **antrum** (see Figure 9.9.5). FSH increases the enzyme **aromatase** that converts androstenedione to estrone and testosterone to estradiol (see Figure 9.9.7). The increase in granulosa cell mass and increase in aromatase increases estrogen synthesis during the follicular phase of the cycle. The increased estradiol also has a local effect on the granulosa cells to increase their receptors for FSH, which further boost estrogen levels. These effects are illustrated in Figure 9.9.9.

Simultaneously, FSH along with estradiol induces LH receptors on the granulosa cells. Both FSH and LH work through a  $G_s$  mechanism. As the follicle approaches ovulation, the increased estrogen production becomes more influenced by LH than by FSH, and this prepares the follicle for its later function as an LH-regulated corpus luteum following ovulation.

The continuously rising estrogen levels also sensitize the anterior pituitary gonadotrophs to GnRH, so that similar amounts of GnRH now cause greater LH and FSH release, which then further stimulate estrogen release from the follicle. This positive feedback requires a critical estrogen level of at least  $200 \text{ pg mL}^{-1}$  for at least 2 days and relatively low progesterone levels, conditions that pertain

only during the late follicular phase of the cycle. This results in the LH and FSH surge that induces ovulation.

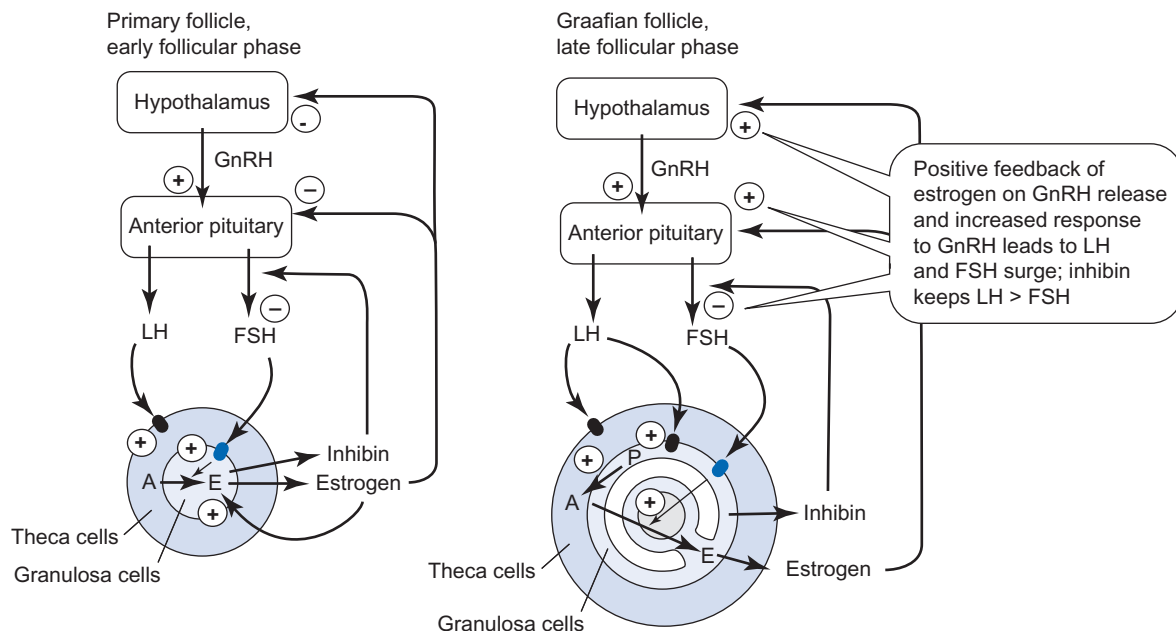
Estradiol also increases the number of LH receptors on theca cells, the cells that surround the entire follicle on its outer borders. These theca cells synthesize androstenedione and testosterone, which then diffuse to the granulosa cells that possess aromatase activity to convert these androgens to estrogens.

## LH AND FSH SURGE INDUCES OVULATION

As stated above, the positive feedback provided by high estrogen for protracted periods with low progesterone induces ovulation, the rupture of the Graafian follicle, and release of the ovum into the peritoneal cavity. LH receptors on the granulosa cells neutralize factors within the ovum that inhibit the completion of the first meiotic division. Removal of the inhibition allows this first meiotic division to be completed. LH and FSH activate a number of enzymes that induce a pseudo-inflammatory response that leads to follicular rupture.

## AFTER OVULATION, THE FOLLICLE FORMS THE CORPUS LUTEUM

As its name implies, LH is instrumental in inducing changes in the follicle that produce the corpus luteum. LH levels drop following the LH surge immediately prior to ovulation, but partly because the pattern of LH release changes to a low-frequency, high-amplitude



**FIGURE 9.9.9** Control of LH and FSH in the early and late follicular phases of the menstrual cycle. In the early follicular phase, FSH stimulates estrogen (E) production by the granulosa cells and LH stimulates androgen (A) production by theca cells in primary follicles. Estrogen feeds back to both the hypothalamus and anterior pituitary to limit GnRH secretion and LH and FSH secretion. FSH induces growth of the follicle and so does estrogen. The two together induce LH receptors on the granulosa cells. After the follicle has grown, LH induces progesterone secretion which begins to increase prior to ovulation, which can be used to produce androgens in the thecal cells to subsequently produce estrogens in the granulosa cells. The continuous increased estrogen levels now exert a positive feedback on the hypothalamus and anterior pituitary to bring about the LH and FSH surge. The LH surge is much greater than the FSH surge because inhibin selectively inhibits FSH synthesis and release by the anterior pituitary. The resulting LH and FSH surge, with progesterone, induces ovulation of the Graafian follicle.

pulsatile release. This pattern produces the increased progesterone and estradiol levels in the luteal phase of the cycle. Because the corpus luteum also produces **inhibin**, LH levels gradually fall and the corpus luteum will regress and undergo atresia through apoptosis. If the ovum is fertilized, it releases hCG, human chorionic gonadotropin. Recall that hCG, LH, FSH, and TSH are all glycoproteins that share structural similarities with identical  $\alpha$  subunits and different, but similar,  $\beta$  subunits. hCG is the first hormone to increase in pregnancy, and it is responsible for the early increase in progesterone prior to the establishment of the placenta.

## SUMMARY

The female gonads are the ovaries, paired structures that secrete estrogens, androgens, and progestins at various stages in the menstrual cycle, and that release, generally, a single ovum in the middle of the cycle. The ovum is released from a mature Graafian follicle that takes about 85 days to complete its development. The early phases of this development are independent of LH or FSH but maturation depends on both.

The menstrual cycle begins on the first day of menses, or sloughing of the uterine lining when there is no pregnancy. The cycle has three phases: the follicular phase, marked by the growth of the Graafian follicle, and characterized by a peak of estrogen exceeding  $200 \text{ pg mL}^{-1}$  in plasma around day 13, that originates from the granulosa cells of the Graafian follicle. This is followed by the brief (1–3 days) ovulatory phase, marked by peaks in FSH and LH originating from the gonadotroph cells in the anterior pituitary, and controlled by the GnRH-releasing cells of the hypothalamus in response to secretions of the follicle. Ovulation occurs, and the remnant of the Graafian follicle becomes the corpus luteum in the luteal phase of the cycle. It secretes both estrogen and prodigious quantities of progesterone. This sustains the endometrial lining until the fertilized ovum produces hCG.

Production of estrogen by the follicle during the follicular phase is explained by the two-cell, two-gonadotropin hypothesis. Thecal cells have receptors for LH that are

linked to a  $G_s$  mechanism. The increased cAMP activates steroidogenesis factor-1 (SF-1) that acts as a switch to turn on a program of steroidogenic enzymes in the thecal cells, but these cells do not express aromatase to convert androstenedione to estrone, which is then converted to estradiol. The thecal cells make androstenedione which is then supplied to the granulosa cells, which are on the other side of the basement membrane of the follicle. Granulosa cells have receptors for FSH, which also works through a  $G_s$  mechanism, to convert thecal cell androstenedione to estrone and then to estradiol. This is the origin of circulating estradiol during the follicular phase of the cycle. After ovulation, the basement membrane is no longer an impediment to uptake of LDL cholesterol by the granulosa cells, which also acquire receptors for LH and then make large quantities of progesterone and estrogen during the luteal phase of the cycle.

Ovulation itself is a dance between central secretion of LH and FSH and follicular secretion of estradiol and inhibin. The estradiol peak during the follicular phase informs the gonadotroph cells that the follicle is mature and ready for ovulation, and these cells respond with a peak of LH and FSH secretion that induces ovulation.

## REVIEW QUESTIONS

1. What is the fallopian tube? Why does it have a ciliated lining? Why does it have smooth muscle? What do the fimbriae do?
2. What is the start of the menstrual cycle? What hormone increases during the follicular phase? Where is it made? What hormones activate its synthesis?
3. When in the cycle is the LH surge? Where does LH come from? Why does it spike? What happens after the spike?
4. What happens to the ovum after ovulation? What happens to the follicle after ovulation?
5. What hormones are secreted by the corpus luteum? What sustains it? What happens if this sustenance is removed?