CHAPTER 39

Fertilization, Pregnancy, and Fetal Development

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CHAPTER OUTLINE

KEY CONCEPTS

1. Fertilization of the ovum occurs in the oviduct. Progesterone and estrogen released from the ovary prepare the oviduct and uterus for receiving the developing embryo.
2. The blastocyst enters the uterus, leaves the surrounding zona pellucida, and implants into the uterine wall on day 7 of gestation.
3. Human chorionic gonadotropin (hCG), produced by trophoblast cells of the developing embryo, activates the corpus luteum to continue producing progesterone and estradiol beyond its normal life span to maintain pregnancy.
4. Shortly after the embryo implants into the uterine wall, a placenta develops from embryonic and maternal cells and becomes the major steroid-secreting organ during pregnancy.
5. Major hormones produced by the fetoplacental unit are progesterone, estradiol, estriol, hCG, and human placental lactogen. Elevated estriol levels indicate fetal well-being, whereas low levels might indicate fetal stress. Human placental lactogen has a role in preparing the breasts for milk production.
6. The pregnant woman becomes insulin-resistant during the latter half of pregnancy in order to conserve maternal glucose consumption and make glucose available for the developing fetus.
7. The termination of pregnancy is initiated by strong uterine contractions induced by oxytocin. Estrogens, relaxin, and prostaglandins are involved in softening and dilating the uterine cervix so that the fetus may exit.
8. Lactogenesis is milk production, which requires prolactin (PRL), insulin, and glucocorticoids. Galactopoiesis is the maintenance of an established lactation and requires PRL and numerous other hormones. Milk ejection is the process by which stored milk is released; "milk letdown" is regulated by oxytocin, which contracts the myoepithelial cells surrounding the alveoli and ejects milk into the ducts.
9. Lactation is associated with the suppression of menstrual cycles and anovulation due to the inhibitory actions of PRL on GnRH release and the hypothalamic-pituitary-ovarian axis.
10. The hypothalamic-pituitary axis becomes activated during the late prepubertal period, resulting in increased frequency and amplitude of GnRH pulses, increased LH and FSH secretion, and increased steroid output by the gonads.
11. Most disorders of sexual development are caused by chromosomal or hormonal alterations, which may result in infertility, sexual dysfunction, or various degrees of intersexuality (hermaphroditism).

A mother is considered pregnant at the moment of fertilization—the successful union of a sperm and an egg. The life span of the sperm and an ovum is less than 2 days, so their rapid transport to the oviduct is required for fertilization to occur. Immediately after fertilization, the zygote or fertilized egg begins to divide and a new life begins. The cell division produces a morula, a solid ball of cells, which then forms a blastocyst. Because the early embryo contains a limited energy supply, the embryo enters the uterus within a short time and attaches to the uterine endometrium, a process that initiates the implantation phase. Implantation occurs only in a uterus that has been primed by gonadal steroids and is, therefore, receptive to accepting the blastocyst. At the time of implantation, the trophoblast cells of the early embryonic placenta begin to produce a hormone, human chorionic gonadotropin (hCG), which signals the ovary to continue to produce progesterone, the major hormone required for the maintenance of pregnancy. As a signal from the embryo to the mother to extend the life of the corpus luteum (and progesterone production), hCG prevents the onset of the next menstruation and ovulatory cycle. The placenta, an organ produced by the mother and fetus, exists only during pregnancy; it regulates the supply of oxygen and the removal of wastes and serves as an en-

ergy supply for the fetus. It also produces protein and steroid hormones, which duplicate, in part, the functions of the pituitary gland and gonads. Some of the fetal endocrine glands have important functions before birth, including sexual differentiation.

Parturition, the expulsion of the fully formed fetus from the uterus, is the final stage of gestation. The onset of parturition is triggered by signals from both the fetus and the mother and involves biochemical and mechanical changes in the uterine myometrium and cervix. After delivery, the mother's mammary glands must be fully developed and secrete milk in order to provide nutrition to the newborn baby. Milk is produced and secreted in response to suckling. The act of suckling, through neurohormonal signals, prevents new ovulatory cycles. Suckling acts as a natural contraceptive until the baby stops suckling. Thereafter, the mother regains metabolic balance, which has been reduced by the nutritional demands of pregnancy and lactation, and ovulatory cycles return. Sexual maturity of the offspring is attained during puberty, at approximately 12 years of age. The onset of puberty requires changes in the sensitivity, activity, and function of several endocrine organs, including those of the hypothalamic-pituitary-gonadal axis.

OVUM AND SPERM TRANSPORT, FERTILIZATION, AND IMPLANTATION

Sperm deposited in the female reproductive tract swim up the uterus and enter the oviduct where fertilization of the ovum occurs. The developing embryo transits the oviduct, enters the uterus, and implants into the endometrium.

The Egg and Sperm Enter the Oviduct

A meiotically active egg is released from the ovary in a cyclical manner in response to the LH surge. For a successful fertilization, fresh sperm must be present at the time the ovum enters the oviduct. To increase the probability that the sperm and egg will meet at an optimal time, the female reproductive tract facilitates sperm transport during the follicular phase of the menstrual cycle, prior to ovulation (see Chapter 38). However, during the luteal phase, after ovulation, sperm survival and access to the oviduct are decreased. If fertilization does not occur, the egg and sperm begin to exhibit signs of degeneration within 24 hours after release.

The volume of **semen** (ejaculatory fluids and sperm) in fertile men is 2 to 6 mL, and it contains some 20 to 30 million sperm per milliliter, which are deposited in the vagina. The liquid component of the semen, called **seminal plasma**, coagulates after ejaculation but liquefies within 20 to 30 minutes from the action of proteolytic enzymes secreted by the prostate gland. The coagulum forms a temporary reservoir of sperm, minimizing the expulsion of semen from the vagina. During intercourse, some sperm cells are immediately propelled into the cervical canal. Those remaining in the vagina do not survive long because of the acidic environment (pH 5.7), although some protection is provided by the alkalinity of the seminal plasma. The cervical canal constitutes a more favorable environment, enabling sperm survival for several hours. Under estrogen dominance, mucin molecules in the **cervical mucus** become oriented in parallel and facilitate sperm migration. Sperm stored in the cervical crypts constitute a pool for slow release into the uterus.

Sperm survival in the uterine lumen is short because of phagocytosis by leukocytes. The **uterotubal junction** also presents an anatomic barrier that limits the passage of sperm into the oviducts. Abnormal or dead spermatozoa may be prevented from entry to the oviduct. Of the millions of sperm deposited in the vagina, only 50 to 100, usually spaced in time, will reach the oviduct. Major losses of sperm occur in the vagina, uterus, and at the uterotubal junction. Spermatozoa that survive can reach the ampulla within 5 to 10 minutes after coitus. The motility of sperm largely accounts for this rapid transit. However, transport is assisted by muscular contractions of the vagina, cervix, and uterus; ciliary movement; peristaltic activity; and fluid flow in the oviducts. Semen samples with low sperm motility can be associated with male infertility.

There is no evidence for chemotactic interactions between the egg and sperm, although evidence exists for specific ligand-receptor binding between egg and sperm. Sperm arrive in the vicinity of the egg at random, and some exit into the abdominal cavity. Although sperm remain motile for up to 4 days, their fertilizing capacity is limited to 1 to 2 days in the female reproductive tract. Sperm can be cryopreserved for years, if agents such as glycerol are used to prevent ice crystal formation during freezing.

Freshly ejaculated sperm cannot immediately penetrate an egg. During maturation in the epididymis, the sperm acquire surface glycoproteins that act as stabilizing factors but also prevent sperm-egg interactions. To bind to and penetrate the zona pellucida, the sperm must undergo **capacitation**, an irreversible process that involves an increase in sperm motility, the removal of surface proteins, a loss of lipids, and merging of the acrosomal and plasma membranes of the sperm head. The uniting of these sperm membranes and change in acrosomal structure is called the **acrosome reaction**. The reaction occurs when the sperm cell binds to the zona pellucida of the egg. It involves a redistribution of membrane constituents, increased membrane fluidity, and a rise in calcium permeability. Capacitation takes place along the female genital tract and lasts 1 hour to several hours. Sperm can be capacitated in a chemically defined medium, a fact that has enabled *in vitro* fertilization (see Clinical Focus Box 39.1). *In vitro* fertilization may be used in female infertility as well.

Because the ovary is not entirely engulfed by the oviduct, an active "pickup" of the released ovum is required. The ovum is grasped by the **fimbria**, ciliated finger-like projects of the oviducts. The grasping of the egg is facilitated by ciliary movement and muscle contractions, under the influence of estrogen secreted during the periovulatory period. Because the oviduct opens into the peritoneal cavity, eggs that are not picked up by the oviducts can enter the abdominal cavity. An **ectopic pregnancy** may result if an abdominal ovum is fertilized. Egg transport from the fimbria to the **ampulla**, the swollen end of the oviduct, is accomplished by coordinated ciliary activity and depends on the presence of granulosa cells surrounding the egg.

CLINICAL FOCUS BOX 39.1

In Vitro Fertilization

Candidates for *in vitro* fertilization (IVF) are women with disease of the oviducts, unexplained infertility, or endometriosis (occurrence of endometrial tissue outside the endometrial cavity, a condition that reduces fertility), and those whose male partners are infertile (e.g., low sperm count). Follicular development is induced with one or a combination of GnRH analogs, clomiphene, recombinant FSH, and menopausal gonadotropins (a combination of LH and FSH). Follicular growth is monitored by measuring serum estradiol concentration and by ultrasound imaging of the developing follicles. When the leading follicle is 16 to 17 mm in diameter and/or the estradiol level is greater than 300 pg/mL, hCG is injected to mimic an LH surge and induce final follicular maturation, including maturation of the oocyte. Approximately, 34 to 36 hours later, oocytes are retrieved from the larger follicles by aspiration using laparoscopy or a transvaginal approach. Oocyte maturity is judged from the morphology of the cumulus (granulosa) cells and the presence of the germinal vesicle and first polar body. The mature oocytes are then placed in culture media.

The donor's sperm are prepared by washing, centrifuging, and collecting those that are most motile. About 100,000 spermatozoa are added for each oocyte. After 24 hours, the eggs are examined for the presence of two pronuclei (male and female). Embryos are grown to the four- to eight-cell stage, about 60 to 70 hours after their retrieval from the follicles. Approximately three embryos are often deposited in the uterine lumen in order to increase the chance for a successful pregnancy. To ensure a receptive endometrium, daily progesterone administrations begin on the day of retrieval. A successful pregnancy rate of 15 to 25% has been reported by many groups, which compares favorably with that of natural human pregnancy.

The fertilizable life of the human ovum is about 24 hours, and fertilization occurs usually by 2 days after ovulation. The fertilized ovum remains in the oviduct for 2 to 3 days, develops into a solid ball of cells called a **morula**, and by day 3 or 4 enters the uterus. While in the uterus, the morula further develops into a **blastocyst**, the **zona pellucida** is shed, and the blastocyst implants into the wall of the uterus on day 7. The movement of the developing embryo from the oviduct to the uterus is largely regulated by progesterone and estrogen.

Fertilization Is Accompanied by a Multitude of Cellular Events

The initial stage of **fertilization** is the attachment of the sperm head to the zona pellucida of the egg. A successful fertilization restores the full complement of 46 chromosomes and subsequently initiates the development of an embryo. Fertilization involves several steps. Recognition of the egg by the sperm occurs first. The next step is the regulation of sperm entry into the egg. A series of key molecular events, collectively called **polyspermy block**, prevent multiple sperm from entering the egg. Coupled with fertilization is the completion of the **second meiotic division** of the egg, which extrudes the second polar body. At this point, the male and female pronuclei unite, followed by initiation of the **first mitotic cell division** (Fig. 39.1).

The zona pellucida contains specific glycoproteins that serve as sperm receptors. They selectively prevent the fusion of inappropriate sperm cells (e.g., from a different species) with the egg. Contact between the sperm and egg triggers the acrosome reaction, which is required for sperm penetration. Sperm proteolytic enzymes are released that dissolve the matrices of the cumulus (granulosa) cells surrounding the egg, enabling the sperm to move through this densely packed group of cells. The sperm penetrates the zona pellucida, aided by proteolytic enzymes and the propulsive force of the tail; this process may take up to 30 minutes. After entering the **perivitelline space**, the sperm head becomes anchored to the membrane surface of the egg, and microvilli protruding from the **oolemma** (plasma membrane of the egg) extend and clasp the sperm. The oolemma engulfs the sperm, and eventually, the whole head and then the tail are incorporated into the **ooplasm**.

Shortly after the sperm enters the egg, **cortical granules**, which are lysosome-like organelles located underneath the oolemma, are released. The cortical granules fuse with the oolemma. Fusion starts at the point of sperm attachment and propagates over the entire egg surface. The content of the granules is released into the perivitelline space and diffuses into the zona pellucida, inducing the **zona reaction**, which is characterized by sperm receptor inactivation and a hardening of the zona. Consequently, once the first spermatozoon triggers the zona reaction, other sperm cannot penetrate the zona, and therefore, polyspermia is prevented.

An increase in intracellular calcium initiated by sperm incorporation into the egg triggers the next event, which is the activation of the egg for completion of the second meiotic division. The chromosomes of the egg separate and half of the chromatin is extruded with the small **second polar body**. The remaining haploid nucleus with its 23 chromosomes is transformed into a **female pronucleus**. Soon after being incorporated into the ooplasm, the nuclear envelope of the sperm disintegrates; the **male pronucleus** is formed and increases 4 to 5 times in size. The two pronuclei, which are visible 2 to 3 hours after the entry of the sperm into the egg, are moved to the center of the cell by contractions of microtubules and microfilaments. Replication of the haploid chromosomes begins in both pronuclei. Pores are formed in their nuclear membranes, and the pronuclei fuse. The **zygote** (fertilized egg) then enters the first mitotic division (cleavage) producing two unequal sized cells called **blastomeres** within 24 to 36 hours after fertilization. Development proceeds with four-cell and eight-cell embryos and a morula, still in the oviduct, forming at approximately 48, 72, and 96 hours, respectively. The morula enters the uterine cavity at around 4 days after fertilization, and subsequently, a blastocyst develops at approximately 6 days after fertiliza-

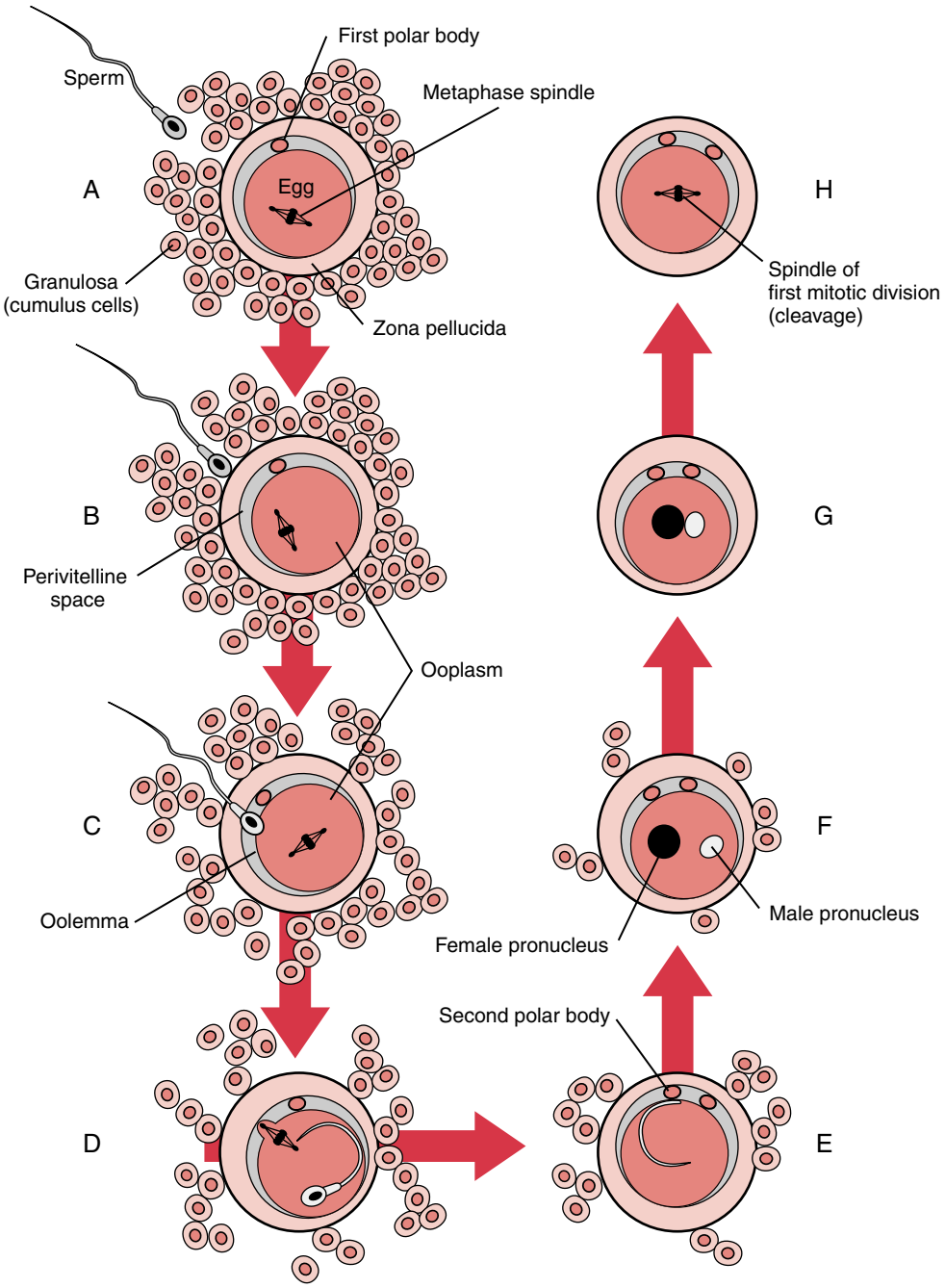

FIGURE 39.1 The process of fertilization. A, A sperm cell approaches an egg. B, Contact between the sperm and the zona pellucida. C, The entry of the sperm and contact with the oolemma. D, The resumption of the second meiotic division. E, The completion of meiosis. F, The formation of male and female pronuclei. G, The migration of the pronuclei to center of cell. H, The zygote is ready for the first mitotic division.

tion. The blastocyst implants into the uterine wall on approximately day 7 after fertilization.

Implantation Requires the Interaction of the Uterine Endometrium and the Embryo

Cell division of the fertilized egg occurs without growth. The cells of the early embryo become progressively smaller, reaching the dimension of somatic cells after several cell divisions. The embryonic cells continue to cleave as the embryo moves from the ampulla toward the uterus (Fig. 39.2). Until implantation, the embryo is enclosed in the zona pellucida. Retention of an intact zona is necessary for embryo transport, protection against mechanical damage or adhesion to the oviduct wall, and prevention of immunological rejection by the mother.

At the 20- to 30-cell stage, a fluid-filled cavity (blastocoele) appears and enlarges until the embryo becomes a hollow sphere, the blastocyst. The cells of the blastocyst have undergone significant differentiation. A single outer layer of the blastocyst consists of extraembryonic ectodermal cells called the **trophoblast**, which will participate in implantation, form the embryonic contribution to the placenta and embryonic membranes, produce hCG, and provide nutrition to the embryo. A cluster of smaller centrally located cells comprises the **embryoblast** or **inner cell mass** and will give rise to the fetus.

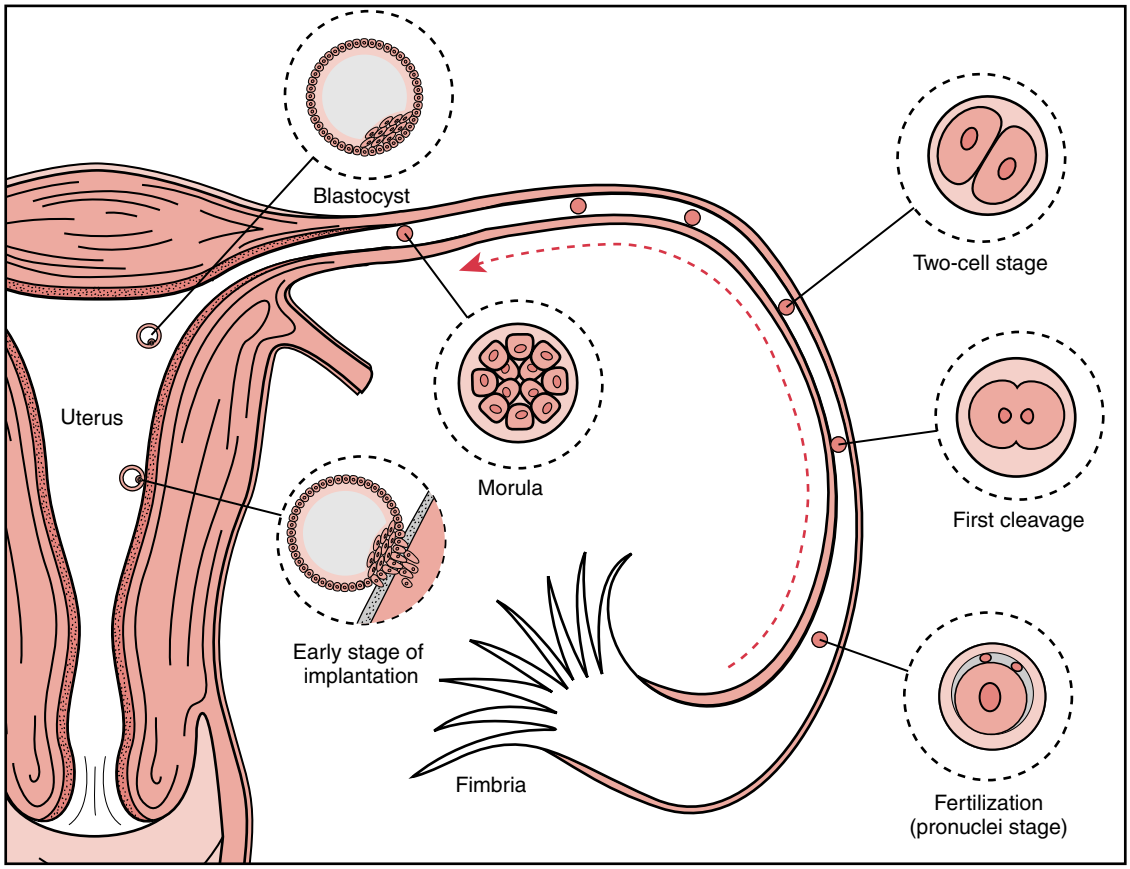

FIGURE 39.2 **Transport of the developing embryo from the oviduct, the site of fertilization, to the uterus, the site of implantation.**

The morula reaches the uterus about 4 days after fertilization. It remains suspended in the uterine cavity for 2 to 3 days while developing into a blastocyst and is nourished by constituents of the uterine fluid during that time. **Implantation** of the blastocyst, which is attachment to the surface endometrial cells of the uterine wall, begins on days 7 to 8 after fertilization and requires proper priming of the uterus by estrogen and progesterone. In preparing for implantation, the blastocyst escapes from the zona pellucida. The zona is ruptured by expansion of the blastocyst and lysed by enzymes. The denuded trophoblast cells become negatively charged and adhere to the endometrium via surface glycoproteins. Microvilli from the trophoblast cells interdigitate with and form junctional complexes with the uterine endometrial cells.

In the presence of progesterone emanating from the corpus luteum, the endometrium undergoes **decidualization**, which involves the hypertrophy of endometrial cells that contain large amounts of glycogen and lipid. In some cases, the cells are multinucleated. This group of decidualized cells is called the **decidua**, which is the site of implantation and the maternal contribution to the placenta. In the absence of progesterone, decidualization does not occur and implantation would fail. As the blastocyst implants into the decidualizing uterus, a **decidual reaction** occurs involving the dilation of blood vessels, increased capillary permeability, edema formation, and increased proliferation of endometrial glandular and epithelial cells (Fig. 39.3). The exact embryonic signals that trigger this reaction are unclear, but histamine, catechol estrogens, steroids, prostaglandins, leukemia inhibitory factor, epidermal growth factor, transforming growth factor α, platelet-derived growth factor, placental growth factor, and several other pregnancy-associated proteins have been proposed.

Invasion of the endometrium is mediated by the release of proteases produced by trophoblast cells adjacent to the uterine epithelium. By 8 to 12 days after ovulation, the human conceptus has penetrated the uterine epithelium and is embedded in the uterine stroma (see Fig. 39.3). The trophoblast cells have differentiated into large polyhedral **cytotrophoblasts**, surrounded by peripheral **syncytiotrophoblasts** lacking distinct cell boundaries. Maternal blood vessels in the endometrium dilate and spaces appear and fuse, forming blood-filled **lacunae**. Between weeks 2 and 3, villi, originating from the embryo, are formed that protrude into the lacunae, establishing a functional communication between the developing embryonic vascular system and the maternal blood (see Fig. 17.6). At this time, the embryoblast has differentiated into three layers:

- Ectoderm, destined to form the epidermis, its appendages (nails and hair), and the entire nervous system
- Endoderm, which will give rise to the epithelial lining of the digestive tract and associated structures
- Mesoderm, which will form the bulk of the body, in-

cluding connective tissue, muscle, bone, blood, and lymph.

PREGNANCY

Pregnancy is maintained by protein and steroid hormones from the mother's ovary and the placenta. The maternal endocrine system adapts to allow optimum growth of the fetus.

The Mother and Fetus Contribute to the Placenta

In the human **placenta**, the maternal and fetal components are interdigitated. The functional units of the placenta, the **chorionic villi** (see Fig. 17.6), form on days 11 to 12 and extend tissue projections into the maternal lacunae that form from endometrial blood vessels immediately after implantation. By week 4, the villi are spread over the entire surface of the chorionic sac. As the placenta matures, it becomes discoid in shape. During the third month, the chorionic villi are confined to the area of the **decidua basalis**. The decidua basalis and **chorionic plate** together form the placenta proper (Fig. 39.4).

The **decidua capsularis** around the conceptus and the **decidua parietalis** on the uterine wall fuse and occlude the uterine cavity. The **yolk sac** becomes vestigial and the **amniotic sac** expands, pushing the chorion against the uterine wall. From the fourth month onward, the fetus is enclosed within the **amnion** and **chorion** and is connected to the placenta by the **umbilical cord**. Fetal blood flows through two umbilical arteries to capillaries in the villi, is brought into juxtaposition with maternal blood in the sinuses, and returns to the fetus through a single umbilical vein. The fetal and maternal circulations do not mix. The human placenta is a **hemochorial type**, in which the fetal endothelium and fetal connective tissues are surrounded by maternal blood. The chorionic villi aggregate into groups known as **cotyledons** and are surrounded by blood from the maternal **spiral arteries** that course through the decidua.

Major functions of the placenta are the delivery of nutrients to the fetus and the removal of its waste products. Oxygen diffuses from maternal blood to the fetal blood down an initial gradient of 60 to 70 mm Hg. The oxygen-transporting capacity of fetal blood is enhanced by **fetal hemoglobin**, which has a high affinity for oxygen. The P_{CO_2} of fetal arterial blood is 2 to 3 mm Hg higher than that of maternal blood, allowing the diffusion of carbon dioxide toward the maternal compartment. Other compounds, such as glucose, amino acids, free fatty acids, electrolytes, vitamins, and some hormones, are transported by diffusion, facilitated diffusion, or pinocytosis. Waste products, such as urea and creatinine, diffuse away from the fetus down their concentration gradients. Large proteins, including most polypeptide hormones, do not readily cross the placenta, whereas the lipid-soluble steroids pass through quite easily. The **blood-placental barrier** allows the transfer of some immunoglobulins, viruses, and drugs from the mother to the fetus (Fig. 39.5).

The Recognition and Maintenance of Pregnancy Depend on Maternal and Fetal Hormones

The placenta is an endocrine organ that produces **progesterone** and **estrogens**, hormones essential for the continuance of pregnancy. The placenta also produces protein hormones unique to pregnancy, such as **human placental**

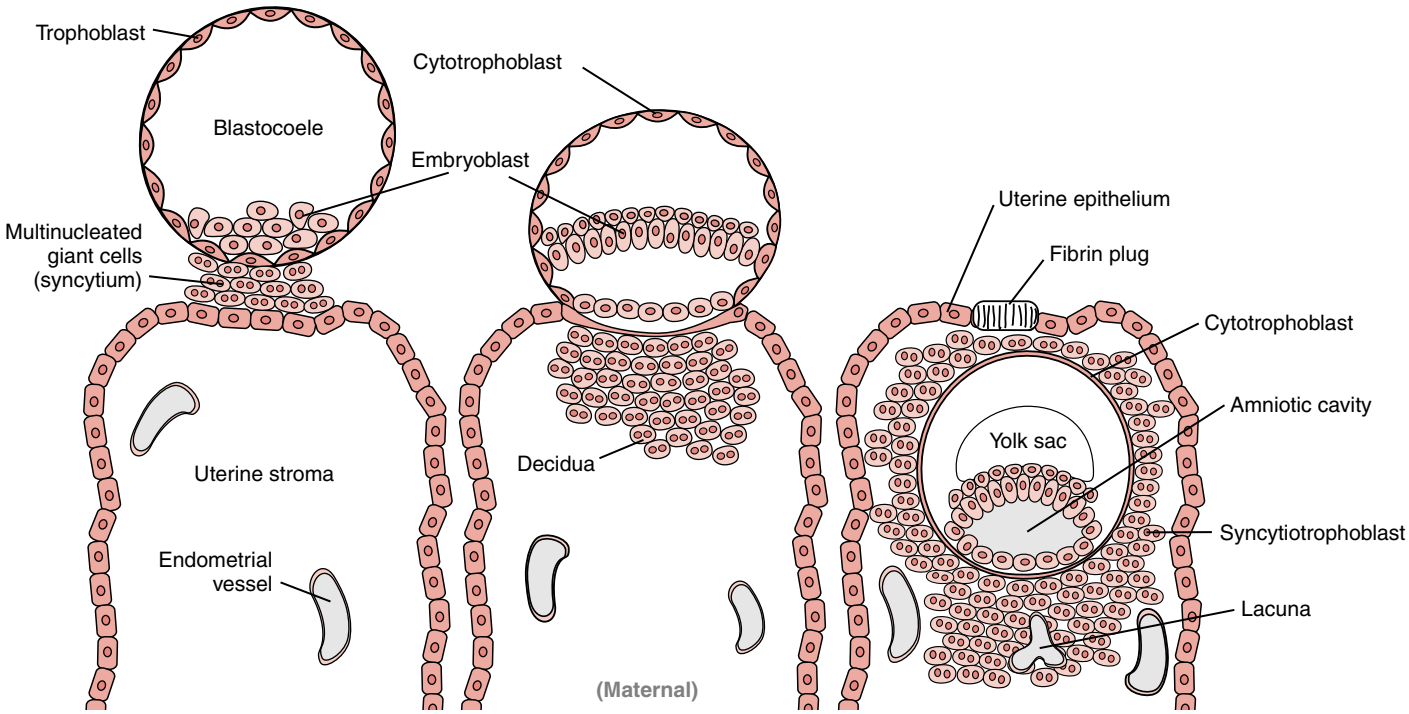

FIGURE 39.3 The process of embryo implantation and the decidual reaction.

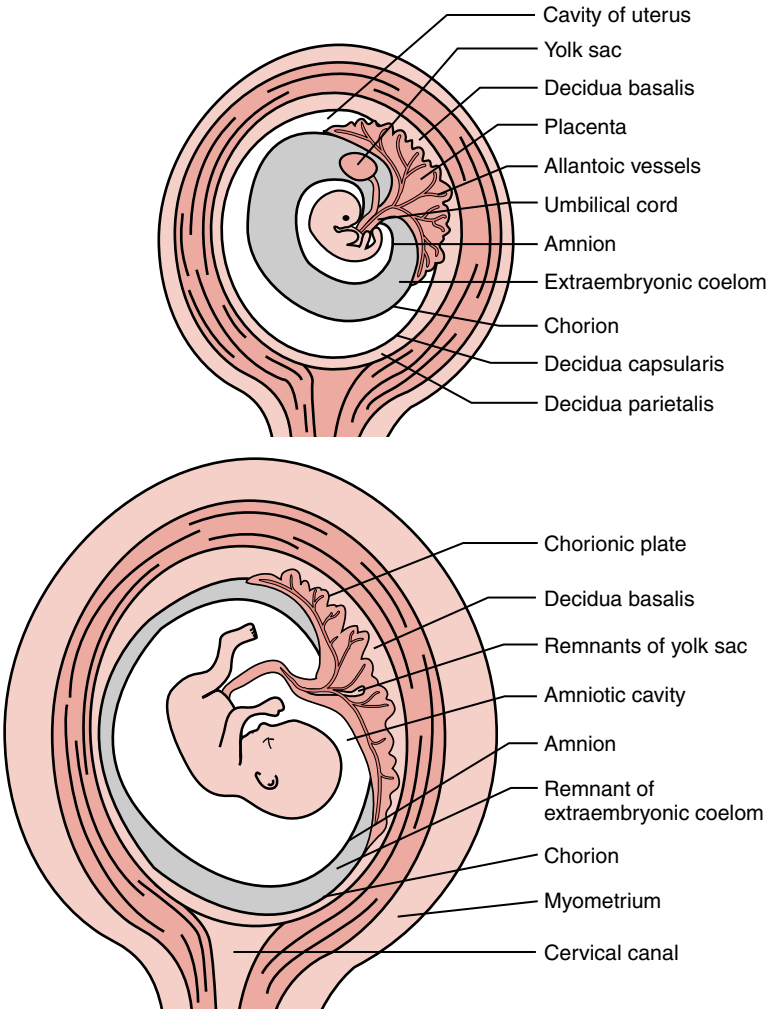

FIGURE 39.4 **Two stages in the development of the placenta, showing the origin of the membranes around the fetus.**

lactogen (hPL) and **human chorionic gonadotropin** (hCG). Several peptides and polypeptides, including corticotropin-releasing hormone (CRH), GnRH, and insulin-like growth factors, are also synthesized by the placenta and function as paracrine factors.

During the menstrual cycle, the corpus luteum forms shortly after ovulation and produces significant amounts of progesterone and estrogen to prepare the uterus for receiving a fertilized ovum. If the egg is not fertilized, the corpus luteum regresses at the end of the luteal phase, as indicated by declining levels of progesterone and estrogen in the circulation. After losing ovarian steroidal support, the superficial endometrial layer of the uterus is expelled, resulting in menstruation. If the egg is fertilized, the developing embryo signals its presence by producing hCG, which extends the life of the corpus luteum. This signaling process is called the maternal recognition of pregnancy. Syncytiotrophoblast cells produce hCG 6 to 8 days after ovulation (fertilization), and hCG enters the maternal and fetal circulations. Very similar to LH, hCG has a molecular weight of approximately 38 kDa, binds LH receptors on the corpus luteum, stimulates luteal progesterone production, and prevents menses at the end of the anticipated cycle. It can be detected in the pregnant woman's urine using commercial colorimetric kits.

Human chorionic gonadotropin is a glycoprotein made of two dissimilar subunits, α and β. It belongs to the same hormone family as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). The α subunit is made of the same 92 amino acids as the other glycoprotein hormones. The β subunit is made of 145 amino acids, with six N- and O-linked oligosaccharide units. It resembles the LH β subunit but has a 24-amino acid extension at the C-terminal end. Because of extensive glycosylation, the half-life of hCG in the circulation is longer than that of LH. Like LH, the major function of hCG in early pregnancy is the stimulation of luteal steroidogenesis. Both bind to the same or similar membrane receptors and increase the formation of pregnenolone from cholesterol by a cAMP-dependent mechanism.

The hCG level in plasma doubles about every 2 to 3 days in early pregnancy and reaches peak levels at about 10 to 15 weeks of gestation. It is reduced by about 75% by 25 weeks and remains at that level until term (Fig. 39.6). Fetal concentrations of hCG follow a similar pattern. The hCG levels are higher in pregnancies with multiple fetuses. During the first trimester, GnRH locally produced by cytotrophoblasts appears to regulate hCG production by a paracrine mechanism. The suppression of hCG release during the second half of pregnancy is attributed to negative

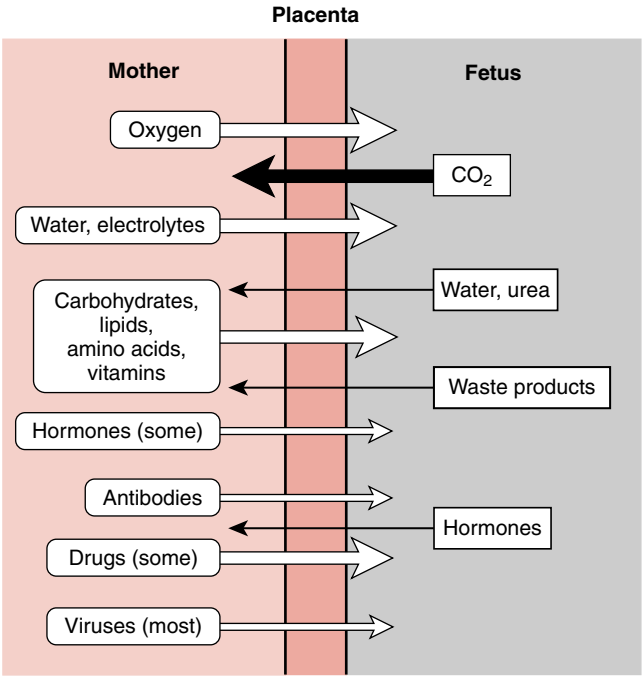

FIGURE 39.5 **Role of the placenta in exchanges between the fetal and maternal compartments.** The size of the arrows indicates the amount of exchange between the compartments.

feedback by placental progesterone or other steroids produced by the fetus. Progesterone secretion by the corpus luteum is maximal 4 to 5 weeks after conception and declines, although hCG levels are still rising. Corpus luteum refractoriness to hCG results from receptor desensitization and the rising levels of placental estrogens. From week 7 to 10 of gestation, steroid production by the corpus luteum is gradually replaced by steroid production by the placenta. Removal of the corpus luteum after week 10 does not terminate the pregnancy. Other placental-derived growth regulators affecting hCG production are activin, inhibin, and transforming growth factors α and β.

Human chorionic gonadotropin has been shown to increase progesterone production by the trophoblast. Therefore, hCG may have a critical role in maintaining placental steroidogenesis throughout pregnancy and replacing luteal progesterone secretion after week 10 when the ovaries are no longer needed to maintain pregnancy. Another important function of hCG is in sexual differentiation of the male fetus, which depends on testosterone production by the fetal testes. Peak production of testosterone occurs 11 to 17 weeks after conception. This timing coincides with peak hCG production and predates the functional maturity of the fetal hypothalamic-pituitary axis (fetal LH levels are low). Human chorionic gonadotropin appears to regulate fetal Leydig cell proliferation as well as testosterone biosynthesis, especially because LH/hCG receptors are present in the early fetal testes. The role of hCG in fetal ovarian development is less clear since LH/hCG receptors are not present on fetal ovaries. There are some indications that increased levels of hCG and thyroxine accompany maternal morning sickness, but a cause-and-effect relationship is not established.

Human placental lactogen (hPL) has lactogenic and growth hormone-like actions. As a result, it is also called human chorionic somatomammotropin and chorionic growth hormone. This hormone is synthesized by syncytiotrophoblasts and secreted into the maternal circulation, where its levels gradually rise from the third week of pregnancy until term. Although hPL is produced by the same cells as hCG, its pattern of secretion is different, indicating the possibility of control by different regulatory mechanisms. The hormone is composed of a single chain of 191 amino acids with two disulfide bridges and has a molecular weight of about 22 kDa. Its structure and function resemble those of prolactin (PRL) and growth hormone (GH).

Human placental lactogen promotes cell specialization in the mammary gland but is less potent than PRL in stimulating milk production and is much less potent than GH in stimulating growth. Its main function is to alter fuel availability by antagonizing maternal glucose consumption and enhancing fat mobilization. This ensures adequate fuel supplies for the fetus. Its effects on carbohydrate, protein, and fat metabolism are similar to those of GH. The amniotic fluid also contains large amounts of PRL produced mainly by the decidual compartments. Decidual PRL is indistinguishable from pituitary PRL, but its function and regulation are unclear.

Steroid Production During Pregnancy Involves the Ovary and Fetoplacental Unit

Progesterone is required to maintain normal human pregnancy. During the early stages of pregnancy (approximately the first 8 weeks), the ovaries produce most of the sex steroids; the corpus luteum produces primarily progesterone and estrogen. As the placenta develops, trophoblast cells gradually take over a major role in the production of progesterone and estrogen. Although the corpus luteum continues to secrete progesterone, the placenta secretes most of the progesterone. Progesterone levels gradually rise during early pregnancy and plateau during the transition period from corpus luteal to placental production (see Fig. 39.6). Thereafter, plasma progesterone levels continue

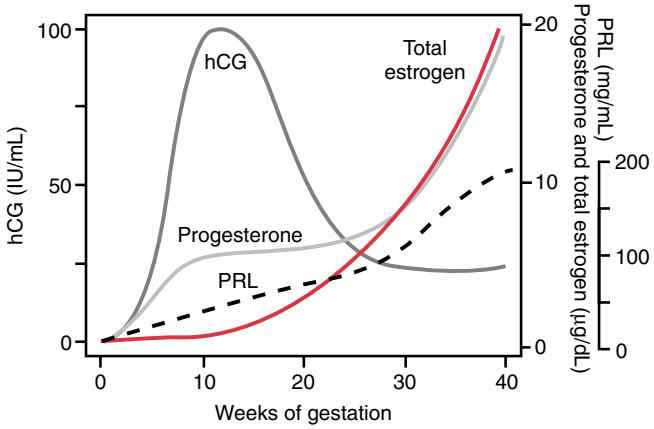

FIGURE 39.6 **Profiles of hCG, progesterone, total estrogens, and PRL in the maternal blood throughout gestation.**

to rise and reach about 150 ng/mL near the end of pregnancy. Two major estrogens, estradiol and estriol, gradually rise during the first half of pregnancy and steeply increase in the latter half of pregnancy to more than 25 ng/mL near term.

Progesterone and estrogen have numerous functions throughout gestation. Estrogens increase the size of the uterus and uterine blood flow, are critical in the timing of implantation of the embryo into the uterine wall, induce the formation of uterine receptors for progesterone and oxytocin, enhance fetal organ development, stimulate maternal hepatic protein production, and increase the mass of breast and adipose tissues. Progesterone is essential for maintaining the uterus and early embryo, inhibits myometrial contractions, and suppresses maternal immunological responses to fetal antigens. Progesterone also serves as a precursor for steroid production by the fetal adrenal glands and plays a role in the onset of parturition.

Beginning at approximately week 8 of gestation, progesterone production is carried out by the placenta, but its synthesis requires cholesterol, which is contributed from the mother. The placenta cannot make significant amounts of cholesterol from acetate and obtains it from the maternal blood via LDL cholesterol. Trophoblast cells have **LDL receptors**, which bind the LDL cholesterol and internalize it. Free cholesterol is released and used by cholesterol side-chain cleavage enzyme to synthesize pregnenolone. Pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase.

The placenta lacks the 17α-hydroxylase for converting pregnenolone or progesterone to androgens (the precursors of the estrogens). Maternal 17α-hydroxyprogesterone can be measured during the first trimester and serves as a marker of corpus luteum function, since the placenta cannot make this steroid. The production of estrogens (estradiol, estrone, and estriol) during gestation requires cooperation between the maternal compartment and the placental and fetal compartments, referred to as the fetoplacental unit (Fig. 39.7). To produce estrogens, the placenta uses androgenic substrates derived from both the fetus and the mother. The primary androgenic precursor is **dehydroepiandrosterone sulfate** (DHEAS), which is produced by the fetal zone of the fetal adrenal gland. The fetal adrenal gland is extremely active in the production of steroid hormones, but because it lacks 3β-hydroxysteroid dehydrogenase, it cannot make progesterone. Therefore, the fetal adrenals use progesterone from the placenta to produce androgens, which are ultimately sulfated in the adrenal glands. The conjugation of androgenic precursors to sulfates ensures greater water solubility, aids in their transport, and reduces their biological activity while in the fetal circulation. DHEAS diffuses into the placenta and is cleaved by a **sulfatase** to yield a nonconjugated androgenic precursor. The placenta has an active aromatase that converts androgenic precursors to estradiol and estrone.

The major estrogen produced during human pregnancy is estriol, which has relatively weak estrogenic activity. **Estriol** is produced by a unique biosynthetic pathway (see Fig. 39.7). DHEAS from the fetal adrenal is converted to **16-hydroxydehydroepiandrosterone sulfate** by **16-hy-**

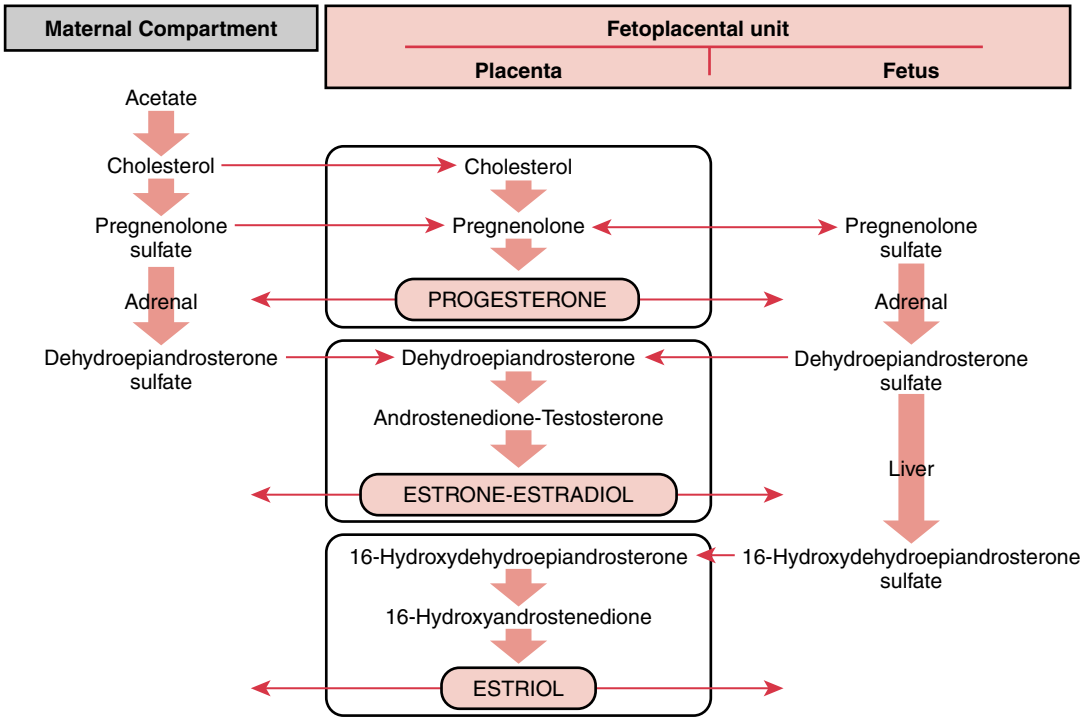

FIGURE 39.7 The fetoplacental unit and steroidogenesis. Note that estriol is the product of reactions occurring in the fetal adrenal, fetal liver, and placenta. (Modified from Goodman HM. Basic Medical Endocrinology. New York: Raven, 1988.)

droxylation in the fetal liver and, to a lesser extent, the fetal adrenal gland. This step is followed by desulfation using a placental sulfatase and conversion by 3β-hydroxysteroid dehydrogenase to 16-hydroxyandrostenedione, which is subsequently aromatized in the placenta to estriol. Although 16-OH-DHEAS can be made in the maternal adrenal from maternal DHEAS, the levels are low. It has been estimated that 90% of the estriol is derived from the fetal 16-OH-DHEAS. Therefore, the levels of estriol in plasma, amniotic fluid, or urine are used as an index of fetal well-being. Low levels of estriol would indicate potential fetal distress, although rare inherited sulfatase deficiencies can also lead to low estriol.

Maternal Physiology Changes Throughout Gestation

The pregnant woman provides nutrients for her growing fetus, is the sole source of fetal oxygen, and removes fetal waste products. These functions necessitate significant adjustments in her pulmonary, cardiovascular, renal, metabolic, and endocrine systems. Among the most notable changes during pregnancy are hyperventilation, reduced arterial blood P_{CO_2} and osmolality, increased blood volume and cardiac output, increased renal blood flow and glomerular filtration rate, and substantial weight gain. These are brought about by the rising levels of estrogens, progesterone, hPL, and other placental hormones and by mechanical factors, such as the expanding size of the uterus and the development of uterine and placental circulations.

The maternal endocrine system undergoes significant adaptations. The hypothalamic-pituitary-ovarian axis is suppressed by the high levels of sex steroids. Consequently, circulating gonadotropins are low, and ovulation does not occur during pregnancy. In contrast, the rising levels of estrogens stimulate PRL release. PRL levels begin to rise during the first trimester, increasing gradually to reach a level 10 times higher near term (see Fig. 39.6). Pituitary lactotrophs undergo hyperplasia and hypertrophy and mostly account for the enlargement of the pregnant woman's pituitary gland. However, somatotrophs that produce growth hormone are reduced, and GH levels are low throughout pregnancy.

The thyroid gland enlarges, but TSH levels are in the normal nonpregnant range. T_3 and T_4 increase, but thyroxine-binding globulin (TBG) also increases in response to the rising levels of estrogen, which are known to stimulate TBG synthesis. Therefore, the pregnant woman stays in an euthyroid state. The parathyroid glands and their hormone, PTH, increase mostly during the third trimester. PTH enhances calcium mobilization from maternal bone stores in response to the fetus's growing demands for calcium. The rate of adrenal secretion of mineralocorticoids and glucocorticoids increases, and plasma free cortisol is higher because of its displacement from transcortin, the cortisol-binding globulin, by progesterone, but hypercortisolism is not apparent during pregnancy.

Changes in maternal ACTH levels throughout pregnancy are variable, although there is a significant increase at the time of parturition. Current reports indicate that maternal pituitary secretion of ACTH may be suppressed by the high levels of steroids during pregnancy. However, the placenta can produce ACTH, so plasma levels tend to rise throughout pregnancy because placental secretion (unlike pituitary hormone secretion) is not regulated by the high level of steroids.

Maternal metabolism responds in several ways to the increasing nutritional demands of the fetus. The major net weight gain of the mother occurs during the first half of gestation, mostly resulting from fat deposition. This response is attributed to progesterone, which increases appetite and diverts glucose into fat synthesis. The extra fat stores are used as an energy source later in pregnancy, when the metabolic requirements of the fetus are at their peak, and also during periods of starvation. Several maternal and placental hormones act together to provide a constant supply of metabolic fuels to the fetus. Toward the second half of gestation, the mother develops a resistance to insulin. This is brought about by combined effects of hormones antagonistic to insulin action, such as GH, PRL, hPL, glucagon, and cortisol. As a result, maternal glucose use declines and gluconeogenesis increases, maximizing the availability of glucose to the fetus.

FETAL DEVELOPMENT AND PARTURITION

At fertilization, genetic sex is determined; subsequently, sexual differentiation is controlled by gonadal hormones. The fetal endocrine system participates in growth and development of the fetus, and parturition is regulated by interactions of fetal and maternal factors.

The Fetal Endocrine System Gradually Matures

The protective intrauterine environment postpones the initiation of some physiological functions that are essential for life after birth. For example, the fetal lungs and kidneys do not act as organs of gas exchange and excretion because their functions are carried out by the placenta. Constant isothermal surroundings alleviate the need to expend calories to maintain body temperature. The gastrointestinal tract does not carry out digestive activities, and fetal bones and muscles do not support weight or locomotion. Being exposed to low levels of external stimuli and environmental insults, the fetal nervous and immune systems develop slowly. Homeostasis in the fetus is regulated by hormones. The fetal endocrine system plays a vital role in fetal growth and development.

Given that most protein and polypeptide hormones are excluded from the fetus by the blood-placental barrier, the maternal endocrine system has little direct influence on the fetus. Instead, the fetus is almost self-sufficient in its hormonal requirements. Notable exceptions are some of the steroid hormones, which are produced by the fetoplacental unit; they cross easily between the different compartments and carry out integrated functions in both the fetus and the mother. By and large, fetal hormones perform the same functions as in the adult, but they also subserve unique processes, such as sexual differentiation and the initiation of labor.

The fetal hypothalamic nuclei, including their releasing hormones such as TRH, GnRH, and several of the neuro-

transmitters, are well developed by 12 weeks of gestation. At about week 4, the anterior pituitary begins its development from Rathke's pouch, an ectodermal evagination from the roof of the fetal mouth (stomodeum), and by week 8, most anterior pituitary hormones can be identified. The posterior pituitary or neurohypophysis is an evagination from the floor of the primitive hypothalamus, and its nuclei, supraoptic and paraventricular with AVP and oxytocin, can be detected around week 14. The hypothalamic-pituitary axis is well developed by midgestation, and well-differentiated hormone-producing cells in the anterior pituitary are also apparent at this time. Whether the fetal pituitary is tightly regulated by hypothalamic hormones or possesses some autonomy is unclear. However, the release of pituitary hormones can occur prior to the establishment of the portal system, indicating that the hypothalamic-releasing hormones may diffuse down to the pituitary from the hypothalamic sites.

Experiments with long-term catheterization of monkey fetuses indicate that by the last trimester, both LH and testosterone increase in response to GnRH administration. In the adult, GH largely regulates the secretion of the insulin-like growth factors (IGF-I and IGF-II) from the liver. In the fetus, this may not be the case, since newborns with low GH have normal birth size; therefore, other mechanisms may control the secretion of IGFs in the fetus. GH levels increase in the fetus until midgestation and decline thereafter when fetal weight is increasing significantly, representing another dichotomy in GH and IGF in the fetus versus postnatal life. PRL levels increase in the fetus throughout gestation and can be inhibited by an exogenous dopamine agonist. Although the role of PRL in fetal growth is unclear, it has been implicated in adrenal and lung function, as well as in the regulation of amniotic fluid volume.

The fetal adrenal glands are unique in both structure and function. At month 4 of gestation, they are larger than the kidneys, as a result of the development of a fetal zone that constitutes 75 to 80% of the whole gland. The outer definitive zone will form the adult adrenal cortex, whereas the deeper fetal zone involutes after birth; the reason for the involution is unknown, but it is not caused by the withdrawal of ACTH support. The fetal zone produces large amounts of DHEAS and provides androgenic precursors for estrogen synthesis by the placenta (see Fig. 39.7). The definitive zone produces cortisol, which has multiple functions during fetal life, including the promotion of pancreas and lung maturation, the induction of liver enzymes, the promotion of intestinal tract cytodifferentiation and, possibly, the initiation of labor. ACTH is the main regulator of fetal adrenal steroidogenesis, partly evidenced by the observation that anencephalic fetuses have low ACTH and the fetal zone is small. The adrenal medulla develops by about week 10 and is capable of producing epinephrine and norepinephrine.

The rate of fetal growth increases significantly during the last trimester. Surprisingly, growth hormone of maternal, placental, or fetal origin has little effect on fetal growth, as judged by the normal weight of hypopituitary dwarfs or anencephalic fetuses. Fetal insulin is the most important hormone in regulating fetal growth. Glucose is the main metabolic fuel for the fetus. Fetal insulin, produced by the pancreas by week 12 of gestation, regulates tissue glucose use, controls liver glycogen storage, and facilitates fat deposition. It does not control the supply of glucose, however; this is determined by maternal gluconeogenesis and placental glucose transport. The release of insulin in the fetus is relatively constant, increasing only slightly in response to a rapid rise in blood glucose levels. When blood glucose levels are chronically elevated, as in diabetic women, the fetal pancreas becomes enlarged and circulating insulin levels increase. Consequently, fetal growth is accelerated, and infants of uncontrolled diabetic women are overweight (Fig. 39.8).

Calcium is in large demand because of the fetus's rapid growth and large amount of bone formation during pregnancy. Maternal calcium is highly important for meeting this fetal requirement. During pregnancy, maternal calcium intake increases, and 1,25 dihydroxyvitamin D_3 and PTH increase to meet the increased calcium demands of the fetus. In the mother, total plasma calcium and phosphate decline without affecting free calcium. The placenta has a specialized calcium pump that transfers calcium to the fetus, resulting in sustained increases in calcium and phosphate throughout pregnancy. Although PTH and calcitonin are evident in the fetus near week 12 of gestation, their role in regulating fetal calcium is unclear. In addition, the placenta has 1α-hydroxylase and can convert 25-hydroxyvitamin D_3 to 1,25 dihydroxyvitamin D_3. At the end of gestation, calcium and phosphate levels in the fetus are higher than in the mother. However, after delivery, neonatal calcium levels decrease and PTH levels rise to raise the levels of serum calcium.

The Sex Chromosomes Dictate the Development of the Fetal Gonads

Sexual differentiation begins at the time of fertilization by a random unification of an X-bearing egg with either an X- or Y-bearing spermatozoon and continues during early em-

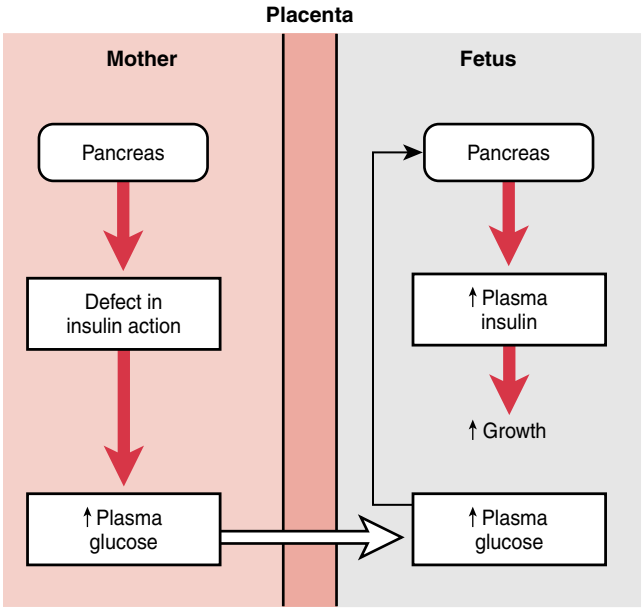

FIGURE 39.8 **Effects of maternal diabetes on fetal growth.**

bryonic life with the development of male or female gonads. Therefore, at the time of fertilization, **chromosomal sex** or **genetic sex** is determined. Sexual differentiation is controlled by gonadal hormones that act at critical times during organogenesis. Testicular hormones induce masculinization, whereas feminization does not require (female) hormonal intervention. The process of sexual development is incomplete at birth; the secondary sex characteristics and a functional reproductive system are not fully developed until puberty.

Human somatic cells have 44 autosomes and 2 sex chromosomes. The female is **homogametic** (having two X chromosomes) and produces similar X-bearing ova. The male is **heterogametic** (having one X and one Y chromosome) and generates two populations of spermatozoa, one with X chromosomes and the other with Y chromosomes. The X chromosome is large, containing 80 to 90 genes responsible for many vital functions. The Y chromosome is much smaller, carrying only few genes responsible for testicular development and normal spermatogenesis. Gene mutation of genes on an X chromosome results in the transmission of X-linked traits, such as hemophilia and color-blindness, to male offspring, which, unlike females, cannot compensate with an unaffected allele.

Theoretically, by having two X chromosomes, the female has an advantage over the male, who has only one. However, because one of the X chromosomes is inactivated at the morula stage, the advantage is lost. Each cell randomly inactivates either the paternally or the maternally derived X chromosome, and this continues throughout the cell's progeny. The inactivated X chromosome is recognized cytologically as the sex chromatin or **Barr body**. In males, with more than one X chromosome, or in females, with more than two extra X chromosomes are inactivated and only one remains functional. This does not apply to the germ cells. The single active X chromosome of the spermatogonium becomes inactivated during meiosis, and a functional X chromosome is not necessary for the formation of fertile sperm. The oogonium, however, reactivates its second X chromosome, and both are functional in oocytes and important for normal oocyte development.

Testicular differentiation requires a Y chromosome and occurs even in the presence of two or more X chromosomes. **Gonadal sex** determination is regulated by a testis-determining gene designated **SRY** (sex-determining region, Y chromosome). Located on the short arm of the Y chromosome, *SRY* encodes a DNA-binding protein, which binds to the target DNA in a sequence-specific manner. The presence or absence of *SRY* in the genome determines whether male or female gonadal differentiation takes place. Thus, in normal XX (female) fetuses, which lack a Y chromosome, ovaries, rather than testes, develop.

Whether possessing the XX or the XY karyotype, every embryo goes initially through an **ambisexual stage** and has the potential to acquire either masculine or feminine characteristics. A 4- to 6-week-old human embryo possesses indifferent gonads, and undifferentiated pituitary, hypothalamus, and higher brain centers.

The indifferent gonad consists of a **genital ridge**, derived from coelomic epithelium and underlying mesenchyme, and primordial germ cells, which migrate from the yolk sac to the genital ridges. Depending on genetic programming, the inner **medullary tissue** will become the testicular components, and the outer **cortical tissue** will develop into an ovary. The primordial germ cells will become oogonia or spermatogonia. In an XY fetus, the testes differentiate first. Between weeks 6 and 8 of gestation, the cortex regresses, the medulla enlarges, and the seminiferous tubules become distinguishable. Sertoli cells line the basement membrane of the tubules, and Leydig cells undergo rapid proliferation. Development of the ovary begins at weeks 9 to 10. Primordial follicles, composed of oocytes surrounded by a single layer of granulosa cells, are discernible in the cortex between weeks 11 and 12 and reach maximal development by weeks 20 to 25.

Differentiation of the Genital Ducts Is Determined by Hormones

During the indifferent stage, the primordial genital ducts are the paired **mesonephric (wolffian) ducts** and the paired **paramesonephric (müllerian) ducts**. In the normal male fetus, the wolffian ducts give rise to the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, while the müllerian ducts become vestigial. In the normal female fetus, the müllerian ducts fuse at the midline and develop into the oviducts, uterus, cervix, and upper portion of the vagina, while the wolffian ducts regress (Fig. 39.9). The mesonephros is the embryonic kidney.

The fetal testes differentiate between weeks 6 and 8 of gestation. Leydig cells, either autonomously or under regulation by hCG, start producing testosterone. Sertoli cells produce two nonsteroidal compounds. One is the **antimüllerian hormone** (AMH), also known as **müllerian inhibiting substance**, a large glycoprotein with a sequence homologous to inhibin and transforming growth factor β, which inhibits cell division of the müllerian ducts. The second is **androgen-binding protein** (ABP), which binds testosterone. Peak production of these compounds occurs between weeks 9 and 12, coinciding with the time of differentiation of the internal genitalia along the male line. The ovary, which differentiates later, does not produce hormones and has a passive role.

The primordial external genitalia include the genital tubercle, genital swellings, urethral folds, and urogenital sinus. Differentiation of the external genitalia also occurs between weeks 8 and 12 and is determined by the presence or absence of male sex hormones. Differentiation along the male line requires active **5α-reductase**, the enzyme that converts testosterone to DHT. Without DHT, regardless of the genetic, gonadal, or hormonal sex, the external genitalia develop along the female pattern. The structures that develop from the primordial structures are illustrated in Figure 39.10, and a summary of sexual differentiation during fetal life is shown in Figure 39.11. Androgen-dependent differentiation occurs only during fetal life and is thereafter irreversible. However, the exposure of females to high androgens either before or after birth can cause clitoral hypertrophy. Testicular descent into the scrotum, which occurs during the third trimester, is also controlled by androgens.

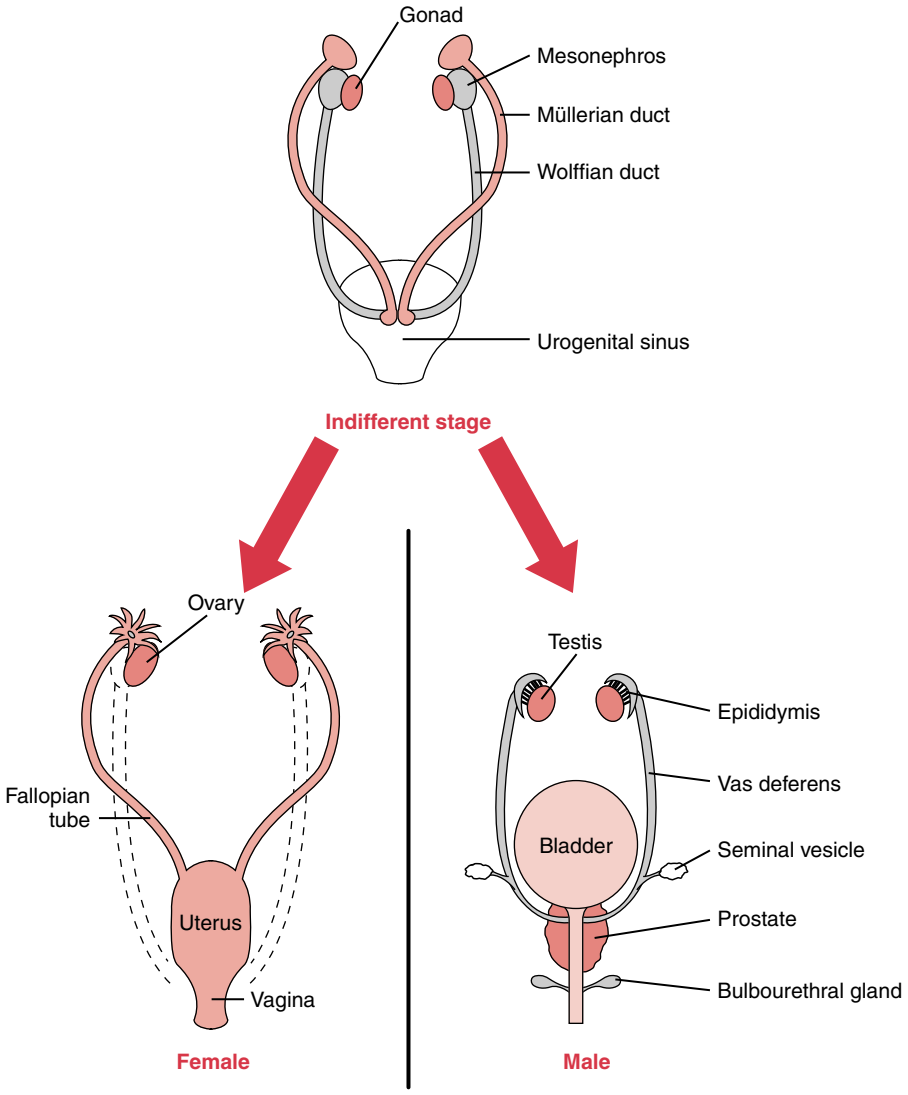

FIGURE 39.9 Differentiation of the internal genitalia and the primordial ducts. (Modified from George FW, Wilson JD. Embryology of the urinary tract. In: Walsh PC, Retik AB, Stamey TA, et al., eds. Campbell's Urology. 6th Ed. Philadelphia: WB Saunders, 1992;1496.)

A Complex Interplay Between Maternal and Fetal Factors Induces Parturition

The duration of pregnancy in women averages 270 ± 14 days from the time of fertilization. **Parturition** or the onset of birth is regulated by the interactions of fetal and maternal factors. Uncoordinated uterine contractions start about 1 month before the end of gestation. The termination of pregnancy is initiated by strong rhythmic contractions that may last several hours and eventually generate enough force to expel the conceptus. The contraction of the uterine muscle is regulated by hormones and by mechanical factors. The hormones include progesterone, estrogen, prostaglandins, oxytocin, and relaxin. The mechanical factors include distension of the uterine muscle and stretching or irritation of the cervix.

Progesterone hyperpolarizes myometrial cells, lowers their excitability, and suppresses uterine contractions. It also prevents the release of phospholipase A_2, the rate-limiting enzyme in prostaglandin synthesis. Estrogen, in general, has the opposite effects. The maintenance of uterine quiescence throughout gestation, preventing premature delivery, is called the **progesterone block**. In many species, a sharp decline in the circulating levels of progesterone and a concomitant rise in estrogen precede birth. In humans, progesterone does not fall significantly before delivery. However, its effective concentration may be altered by a rise in placental progesterone-binding protein or by a decline in the number of myometrial progesterone receptors.

Prostaglandins F_{2A} and E_2 are potent stimulators of uterine contractions and also cause significant ripening of the cervix and its dilation. They increase intracellular calcium concentrations of myometrial cells and activate the actin-myosin contractile apparatus. Shortly before the onset of parturition, the concentration of prostaglandins in amniotic fluid rises abruptly. Prostaglandins are produced by the myometrium, decidua, and chorion. Aspirin and indomethacin, inhibitors of prostaglandin synthesis, delay or prolong parturition.

Oxytocin is also a potent stimulator of uterine contractions, and its release from both maternal and fetal pituitaries increases during labor. Oxytocin is used clinically to

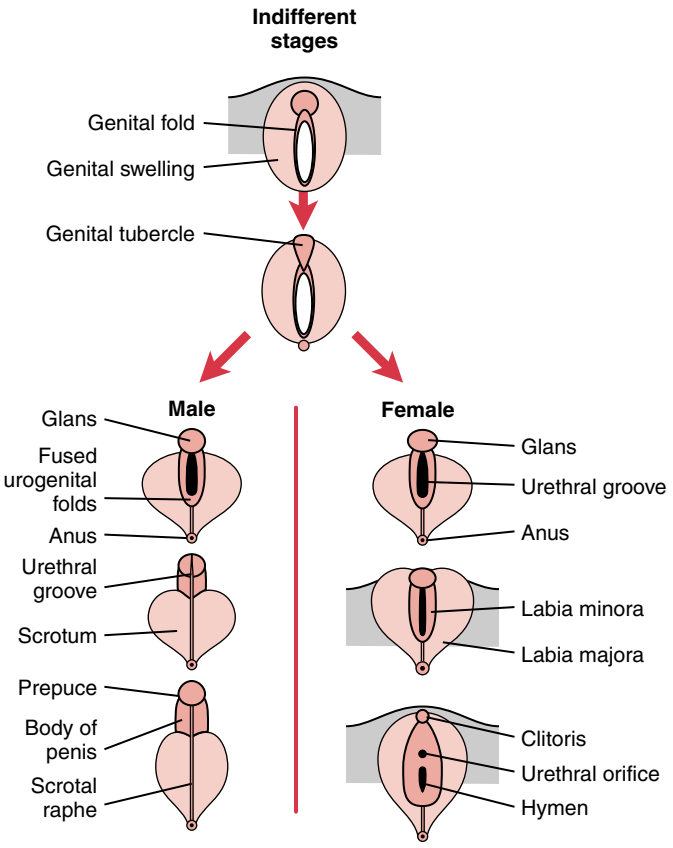

FIGURE 39.10 **Differentiation of the external genitalia from bipotential primordial structures.**

induce labor (see Clinical Focus Box 39.2). The functional significance of oxytocin is that it helps expel the fetus from the uterus, and by contracting uterine muscles, it reduces uterine bleeding when bleeding may be significant after delivery. Interestingly, oxytocin levels do not rise at the time of parturition.

Relaxin, a large polypeptide hormone produced by the corpus luteum and the decidua, assists parturition by softening the cervix, permitting the eventual passage of the fetus, and by increasing oxytocin receptors. However, the relative role of relaxin in parturition in humans is unclear, as its levels do not rise toward the end of gestation. Relaxin reaches its peak during the first trimester, declines to about half, and remains unchanged throughout the remainder of pregnancy.

The fetus may play a role in initiating labor. In sheep, the concentration of ACTH and cortisol in the fetal plasma rise during the last 2 to 3 days of gestation. Ablation of the fetal lamb pituitary or removal of the adrenals prolongs gestation, while administration of ACTH or cortisol leads to premature delivery. Cortisol enhances the conversion of progesterone to estradiol, changing the progesterone-to-estrogen ratio, and increases the production of prostaglandins. The role of cortisol and ACTH, however, has not been established in humans. Anencephalic or adrenal-deficient fetuses, which lack a pituitary and have atrophied adrenal glands, have an unpredictable length of gestation. Those pregnancies also exhibit low estrogen levels because of the lack of adrenal androgen precursors. Injections of ACTH and cortisol in late pregnancy do not induce labor. Interestingly, the administration of estrogens to the cervix causes ripening, probably by increasing the secretion of prostaglandins.

POSTPARTUM AND PREPUBERTAL PERIODS

Lactation is controlled by pituitary and ovarian hormones, requires suckling for continued milk production, and is the major source of nutrition for the newborn. As the child grows, puberty will occur around age 10 to 11 because the hypothalamus activates secretion of pituitary hormones that cause secretion of estrogens and androgens from the gonads and adrenals during that time. Alterations in hormone secretion lead to abnormal onset of puberty and gonadal development.

Mammogenesis and Lactogenesis Are Regulated by Multiple Hormones

Lactation (the secretion of milk) occurs at the final phase of the reproductive process. Several hormones participate in **mammogenesis**, the differentiation and growth of the mammary glands, and in the production and delivery of milk. **Lactogenesis** is milk production by alveolar cells. **Galactopoiesis**, the maintenance of lactation, is regulated by PRL. **Milk ejection** is the process by which stored milk is released from the mammary glands by the action of oxytocin.

Mammogenesis occurs at three distinct periods: embryonic, pubertal, and gestational. The **mammary glands** begin to differentiate in the pectoral region as an ectodermal thickening on the epidermal ridge during weeks 7 to 8 of fetal life. The prospective mammary glands lie along bilateral mammary ridges or milk lines extending from axilla to groin on the ventral side of the fetus. Most of the ridge disintegrates except in the axillary region. However, in mammals with serially repeated nipples, a distinct milk line with several nipples persists, accounting for the accessory nipples that can occur in both sexes, although rarely. Mammary buds are derived from surface epithelium, which invades the underlying mesenchyme. During the fifth month, the buds elongate, branch, and sprout, eventually forming the **lactiferous ducts**, the primary milk ducts. They continue to branch and grow throughout life. The ducts unite, grow, and extend to the site of the future nipple. The primary buds give rise to secondary buds, which are separated into lobules by connective tissue. These become surrounded by **myoepithelial cells** derived from epithelial progenitors. In response to oxytocin, myoepithelial cells will contract, and expel milk from the duct. The **nipple** and **areola**, which are first recognized as circular areas, are formed during the eighth month of gestation. The development of the mammary glands in utero appears to be independent of hormones but is influenced by paracrine interactions between the mesenchyme and epithelium.

The mammary glands of male and female infants are identical. Although underdeveloped, they have the capacity to respond to hormones, revealed by the secretion of small amounts of milk (witch's milk) in many newborns. Witch's milk results from the responsiveness of the fetal mammary

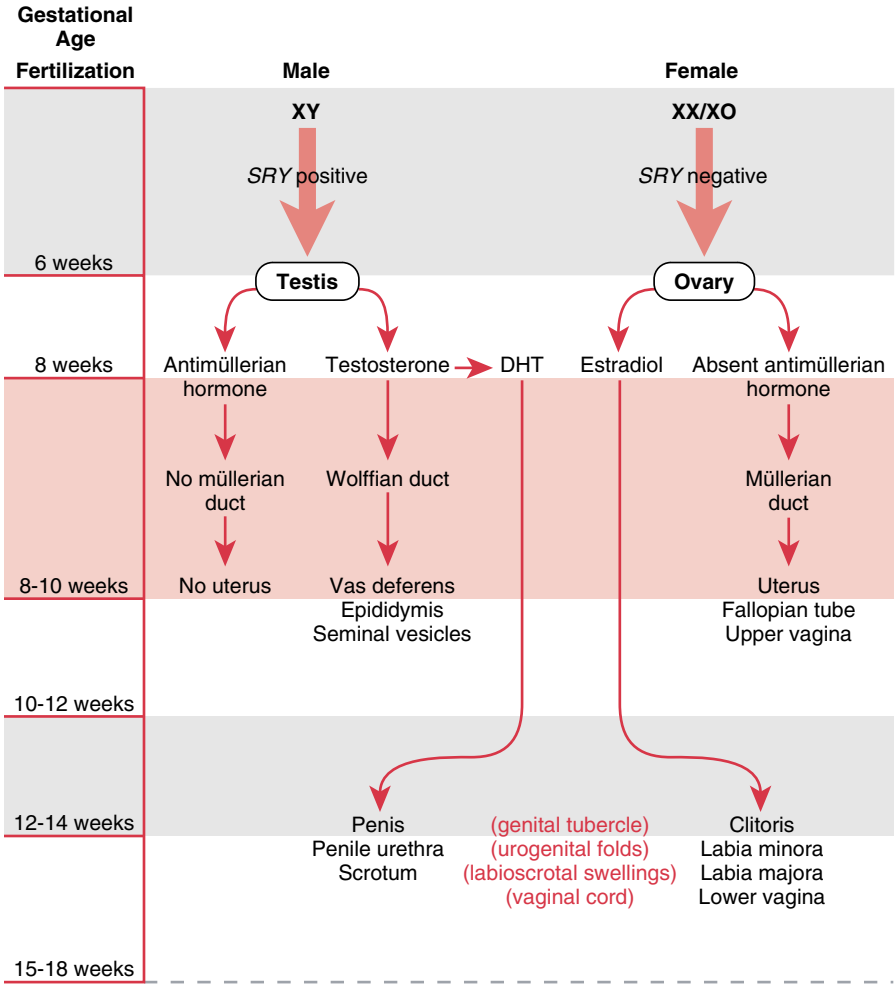

FIGURE 39.11 The process of sexual differentiation and its time course.

tissue to lactogenic hormones of pregnancy and the withdrawal of placental steroids at birth. Sexual dimorphism in breast development begins at the onset of puberty. The male breast is fully developed at about age 20 and is similar to the female breast at an early stage of puberty.

In females, estrogen exerts a major influence on breast growth at puberty. The first response to estrogen is an increase in size and pigmentation of the areola and accelerated deposition of adipose and connective tissues. In association with menstrual cycles, estrogen stimulates the growth and branching of the ducts, whereas progesterone acts primarily on the alveolar components. The action of both hormones, however, requires synergism with PRL, GH, insulin, cortisol, and thyroxine.

The mammary glands undergo significant changes during pregnancy. The ducts become elaborate during the first trimester, and new lobules and alveoli are formed in the second trimester. The terminal alveolar cells differentiate into

CLINICAL FOCUS BOX 39.2

Pharmacological Induction and Augmentation of Labor

Several drugs are currently used to assist in the therapeutic induction and augmentation of labor. Therapeutic induction implies that labor is initiated by the use of a drug. Augmentation indicates that labor has started and that the process is further stimulated by a therapeutic agent.

Oxytocin, the natural hormone produced from the posterior pituitary, is widely used to induce and augment labor. Several synthetic forms of oxytocin can be used by intravenous routes. Recently, the prostaglandins ($F_{2\alpha}$ and E_2) have also been used to induce and augment labor and cervical ripening. Prostaglandins promote dilatation and effacement of the cervix and can be used for various reasons intravaginally, intravenously, or intra-amniotically. Another therapeutic agent being tested for efficacy in labor induction and augmentation is mifepristone (RU-486), a progesterone receptor blocker. It is used to induce labor and to increase the sensitivity of the uterus to oxytocin and prostaglandins. An additional and interesting feature of these drugs is that they reduce postpartum hemorrhage by causing muscle contractions.

secretory cells, replacing most of the connective tissue. The development of the secretory capability requires estrogen, progesterone, PRL, and placental lactogen. Their action is supported by insulin, cortisol, and several growth factors. Lactogenesis begins during the fifth month of gestation, but only **colostrum** (initial milk) is produced. Full lactation during pregnancy is prevented by elevated progesterone levels, which antagonize the action of PRL. The ovarian steroids synergize with PRL in stimulating mammary growth but antagonize its actions in promoting milk secretion.

Lactogenesis is fully expressed only after parturition, on the withdrawal of placental steroids. Lactating women produce up to 600 mL of milk each day, increasing to 800 to 1,100 mL/day by the sixth postpartum month. Milk is isosmotic with plasma, and its main constituents include proteins, such as casein and lactalbumin, lipids, and lactose. The composition of milk changes with the stage of lactation. Colostrum, produced in small quantities during the first postpartum days, is higher in protein, sodium, and chloride content and lower in lactose and potassium than normal milk. Colostrum also contains immunoglobulin A, macrophages, and lymphocytes, which provide passive immunity to the infant by acting on its GI tract. During the first 2 to 3 weeks, the protein content of milk decreases, whereas that of lipids, lactose, and water-soluble vitamins increases.

The milk-secreting **alveolar cells** form a single layer of epithelial cells, joined by junctional complexes (Fig. 39.12). The bases of the cells abut on the contractile myoepithelial cells, and their luminal surface is enriched with microvilli. They have a well-developed endoplasmic reticulum and Golgi apparatus and numerous mitochondria and lipid droplets. Alveolar cells contain plasma membrane receptors for PRL, which can be internalized after binding to the hormone. In synergism with insulin and glucocorticoids, PRL is critical for lactogenesis, promotes mammary cell division and differentiation, and increases the synthesis of milk constituents. This hormone also stimulates the synthesis of casein by increasing its transcription rate and stabilizing its mRNA, and stimulates enzymes that regulate the production of lactose.

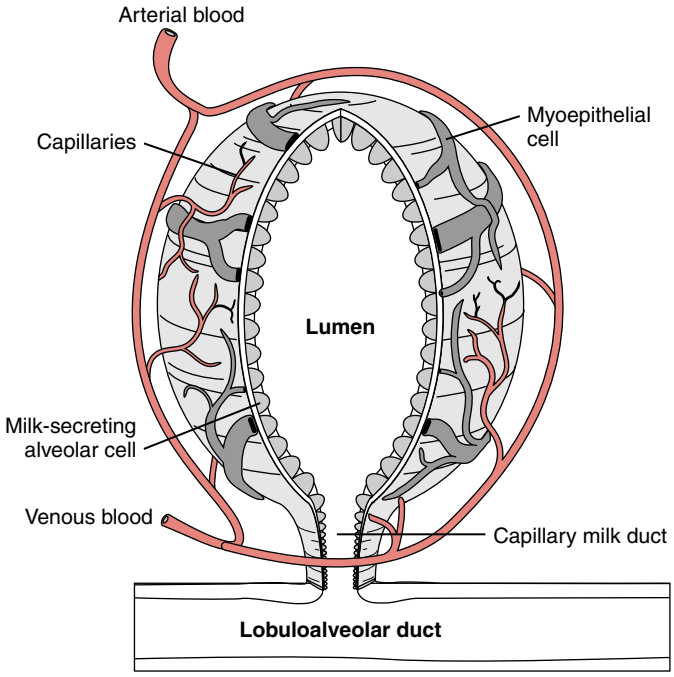

FIGURE 39.12 **The structure of a mammary alveolus.** Milk-producing cells are surrounded by a meshwork of contractile myoepithelial cells.

The Suckling Reflex Maintains Lactation and Inhibits Ovulation

The suckling reflex is central to the maintenance of lactation in that it coordinates the release of PRL and oxytocin and delays the onset of ovulation. Lactation involves two components, **milk secretion** (synthesis and release) and **milk removal**, which are regulated independently. Milk secretion is a continuous process, whereas milk removal is intermittent. Milk secretion involves the synthesis of milk constituents by the alveolar cells, their intracellular transport, and the subsequent release of formed milk into the alveolar lumen (see Fig. 39.12). PRL is the major regulator of milk secretion in women and most other mammals. Oxytocin is responsible for milk removal by activating **milk ejection** or **letdown**.

The stimulation of sensory nerves in the breast by the infant initiates the **suckling reflex**. Unlike ordinary reflexes with only neural components, the afferent arc of the suckling reflex is neural and the efferent arc is hormonal. The suckling reflex increases the release of PRL, oxytocin, and ACTH and inhibits the secretion of gonadotropins (Fig. 39.13). The neuronal component is composed of sensory receptors in the nipple that initiate nerve impulses in response to breast stimulation. These impulses reach the hypothalamus via ascending fibers in the spinal cord and then via the mesencephalon. Eventually, fibers terminating in the supraoptic and paraventricular nuclei trigger the release of oxytocin from the posterior pituitary into the general circulation (see Chapter 32). On reaching the mammary glands, oxytocin induces the contraction of myoepithelial cells, increasing intramammary pressure and forcing the milk into the main collecting ducts. The milk ejection reflex can be conditioned; milk ejection can occur because of anticipation or in response to a baby's cry.

PRL levels, which are elevated by the end of gestation, decline by 50% within the first postpartum week and decrease to near pregestation levels by 6 months. Suckling elicits a rapid and significant rise in plasma PRL. The amount released is determined by the intensity and duration of nipple stimulation. The exact mechanism by which suckling triggers PRL release is unclear, but the suppression of dopamine, the major inhibitor of PRL release, and the stimulation of prolactin-releasing factor(s) have been considered. Lactation can be terminated by dopaminergic agonists that reduce PRL or by the discontinuation of suckling. Swollen alveoli can depress milk production by exerting local pressure, resulting in vascular stasis and alveolar regression.

Lactation is associated with the suppression of cyclicity and **anovulation**. The contraceptive effect of lactation

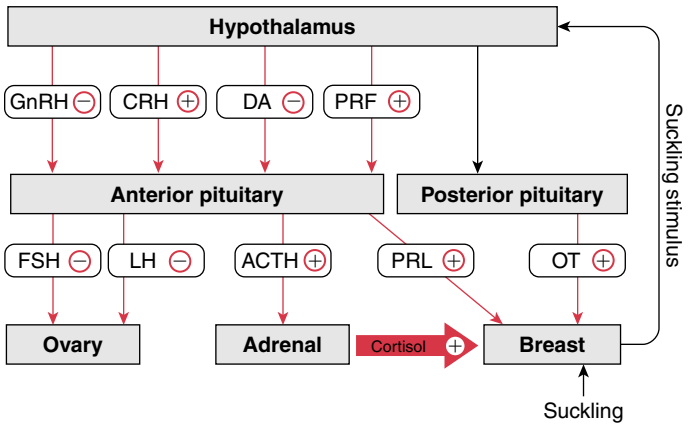

FIGURE 39.13 Effect of suckling on hypothalamic, pituitary, and adrenal hormones. GnRH, gonadotropin-releasing hormone; CRH, corticotropin-releasing hormone; DA, dopamine; PRF, prolactin-releasing factor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; OT, oxytocin. Plus and minus signs indicate positive and negative effects.

CLINICAL FOCUS BOX 39.3

Contraceptive Methods

Fertility can be controlled by interfering with the association between the sperm and ovum, by preventing ovulation or implantation, or by terminating an early pregnancy. Contraceptive methods may also be categorized as reversible and irreversible. Most current methods regulate fertility in women, with only a few contraceptives available for men (Table 39.A).

Methods based on preventing contact between the germ cells include coitus interruptus (withdrawal before ejaculation), the rhythm method (no intercourse at times of the menstrual cycle, especially when an ovum is present in the oviduct), and barriers. Barrier methods include condoms, diaphragms, and cervical caps. When combined with spermicidal agents, barrier methods approach the high success rate of oral contraceptives. Condoms are the most widely used reversible contraceptives for men. Because they also provide protection against the transmission of venereal diseases and AIDS, their use has increased in recent years. Diaphragms and cervical caps seal off the opening of the cervix. Spermicides are inserted into the vagina. Postcoital douching is not an effective contraceptive because some sperm enter the uterus and oviduct very rapidly.

Vasectomy is cutting of the two vasa deferentia, and it prevents sperm from passing into the ejaculate. An increased incidence of sperm antibodies occurs following vasectomy, but its consequences are unknown. Tubal ligation is the closure or ligation of the oviducts. Restorative surgery for the reversal of a tubal ligation and a vasectomy can be performed; its success is limited.

Oral contraceptive steroids prevent ovulation by reducing LH and FSH secretion through negative feedback. Reduced secretion of LH and FSH retard follicular development. The pill's effectiveness is also increased by adversely affecting the environment within the reproductive tract, making it unlikely for pregnancy to result even if fertilization were to occur. Exogenous estrogen and progesterone are likely to alter normal endometrial development and may contribute to their detrimental effects in the early establishment of pregnancy. Progesterone thickens cervical mucus and reduces oviductal peristalsis, impeding gamete transport.

Noncontraceptive benefits of the pill include a reduction in excessive menstrual bleeding, alleviation of premenstrual syndrome, and some protection against pelvic inflammatory disease. Adverse effects include nausea, headache, breast tenderness, water retention, and weight gain, some of which disappear after prolonged use. There is no evidence that fertility is reduced after discontinuation of the pill.

Several contraceptives act by interfering with zygote transport or implantation and cause early pregnancy termination. Among these are long-acting progesterone preparations, high doses of estrogen, and progesterone receptor antagonists, such as RU-486 (also called mifepristone). RU-486 blocks the action of the progesterone required for early pregnancy. Prostaglandins are given in combination with RU-486 to assist in the expulsion of the products of conception. The intrauterine device (IUD) also prevents implantation by provoking sterile inflammation of the endometrium and prostaglandin production. The contraceptive efficacy of IUDs, especially those impregnated with progestins, copper, or zinc, is high. The drawbacks include a high rate of expulsion, uterine cramps, excessive bleeding, perforation of the uterus, and increased incidence of ectopic pregnancy. Established pregnancy can be interrupted by surgical means (dilatation and curettage).

TABLE 39.A Contraceptive Use and Efficacy Rates in the United States

Method	Estimated Use (%)	Accidental Pregnancy in Year 1 (%)
Pill	32	3
Female sterilization	19	0.4
Condom	17	12
Male sterilization	14	0.15
Diaphragm	4–6	2–23
Spermicides	5	20
Rhythm	4	20
Intrauterine device	3	6

From Developing New Contraceptives: Obstacles and Opportunities. Washington, DC: National Academy Press, 1990.

is moderate in humans. In non-breast-feeding women, the menstrual cycle may return within 1 month after delivery, whereas *fully* lactating women have a period of several months of **lactational amenorrhea**, with the first few menstrual cycles being anovulatory. The cessation of cyclicity results from the combined effects of the act of suckling and elevated PRL levels. PRL suppresses ovulation by inhibiting pulsatile GnRH release, suppressing pituitary responsiveness to GnRH, reducing LH and FSH, and decreasing ovarian activity. It is also possible that PRL may inhibit the action of the low circulating levels of gonadotropins on ovarian cells. Thus, follicular development would be suppressed by a direct inhibitory action of PRL on the ovary. Although fertility is reduced by lactation, there are numerous other methods of contraception (see Clinical Focus Box 39.3).

The Onset of Puberty Depends on Maturation of the Hypothalamic GnRH Pulse Generator

The onset of puberty depends on a sequence of maturational processes that begin during fetal life. The hypothalamic-pituitary-gonadal axis undergoes a prolonged and multiphasic activation-inactivation process. By midgestation, LH and FSH levels in fetal blood are elevated, reaching near adult values. Experimental evidence suggests that the hypothalamic GnRH pulse generator is operative at this time, and gonadotropins are released in a pulsatile manner. The levels of FSH are lower in males than in females, probably because of suppression by fetal testosterone at midgestation. As the levels of placental steroids increase, they exert negative feedback on GnRH release, lowering LH and FSH to very low levels toward the end of gestation.

After birth, the newborn is deprived of maternal and placental steroids. The reduction in steroidal negative feedback stimulates gonadotropin secretion, which stimulates the gonads, resulting in transient increases in serum testosterone in male infants and estradiol in females. FSH levels in females are usually higher than those in males. At approximately 3 months of age, the levels of both gonadotropins and gonadal steroids are in the low-normal adult range. Circulating gonadotropins decline to low levels by 6 to 7 months in males and 1 to 2 years in females and remain suppressed until the onset of puberty.

Throughout childhood, the gonads are quiescent and plasma steroid levels are low. Gonadotropin release is also suppressed. The prepubertal restraint of gonadotropin secretion is explained by two mechanisms, both of which affect the hypothalamic GnRH pulse generator. One is a sex steroid-dependent mechanism that renders the pulse generator extremely sensitive to negative feedback by steroids. The other is an intrinsic central nervous system (CNS) inhibition of the GnRH pulse generator. Together, they suppress the amplitude, and probably the frequency, of GnRH pulses, resulting in diminished secretion of LH, FSH, and gonadal steroids. Throughout this period of quiescence, the pituitary and the gonads can respond to exogenous GnRH and gonadotropins, but at a relatively low sensitivity.

The hypothalamic-pituitary axis becomes reactivated during the late prepubertal period. This response involves a decrease in hypothalamic sensitivity to sex steroids and a reduction in the effectiveness of intrinsic CNS inhibition over the GnRH pulse generator. The mechanisms underlying these changes are unclear but might involve endogenous opioids. As a result of disinhibition, the frequency and amplitude of GnRH pulses increase. Initially, pulsatility is most prominent at night, entrained by deep sleep; later it becomes established throughout the 24-hour period. GnRH acts on the gonadotrophs of the anterior pituitary as a self-primer. It increases the number of GnRH receptors (up-regulation) and augments the synthesis, storage, and secretion of the gonadotropins. The increased responsiveness of FSH to GnRH in females occurs earlier than that of LH, accounting for a higher FSH/LH ratio at the onset of puberty than during late puberty and adulthood. A reversal of the ratio is seen again after menopause.

The increased pulsatile GnRH release initiates a cascade of events. The sensitivity of gonadotrophs to GnRH is increased, the secretion of LH and FSH is augmented, the gonads become more responsive to the gonadotropins, and the secretion of gonadal hormones is stimulated. The rising circulating levels of gonadal steroids induce progressive development of the secondary sex characteristics and establish an adult pattern of negative feedback on the hypothalamic-pituitary axis. Activation of the positive-feedback mechanism in females and the capacity to exhibit an estrogen-induced LH surge is a late event, expressed in midpuberty to late puberty.

The onset of puberty in humans begins at age 10 to 11. Lasting 3 to 5 years, the process involves the development of secondary sex characteristics, a growth spurt, and the ac-

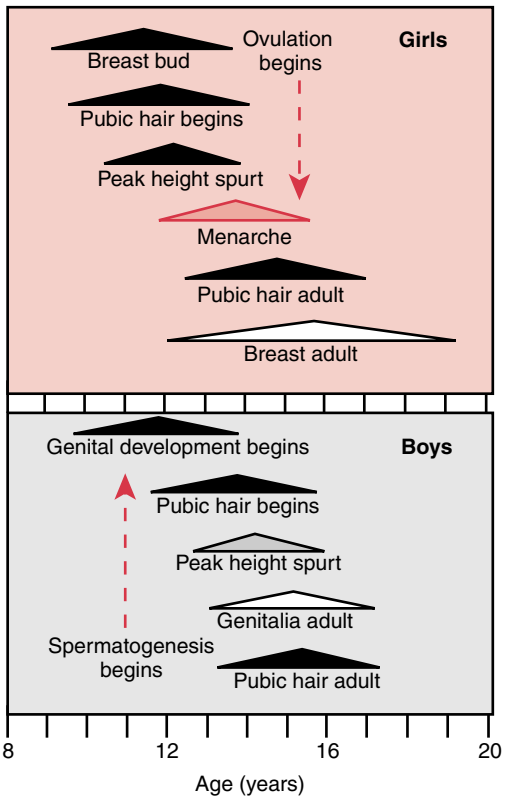

FIGURE 39.14 **Peripubertal maturation of secondary sex characteristics in girls and boys.**

quisition of fertility. The timing of puberty is determined by genetic, nutritional, climatic, and geographic factors. Over the last 150 years, the age of puberty has declined by 2 to 3 months per decade; this pattern appears to correlate with improvements in nutrition and general health in Americans.

The first physical signs of puberty in girls are breast budding, **thelarche**, and the appearance of pubic hair. Axillary hair growth and peak height spurt occur within 1 to 2 years. **Menarche**, the beginning of menstrual cycles, occurs at a median age of 12.8 years in American girls. The first few cycles are usually anovulatory. The first sign of puberty in boys is enlargement of the testes, followed by the appearance of pubic hair and enlargement of the penis. The peak growth spurt and appearance of axillary hair in boys usually occurs 2 years later than in girls. The growth of facial hair, deepening of the voice, and broadening of the shoulders are late events in male pubertal maturation (Fig. 39.14).

Puberty is also regulated by hormones other than gonadal steroids. The adrenal androgens DHEA and DHEAS are primarily responsible for the development of pubic and axillary hair. Adrenal maturation or **adrenarche** precedes gonadal maturation or **gonadarche** by 2 years. The pubertal growth spurt requires a concerted action of sex steroids and growth hormone. The principal mediator of GH is insulin-like growth factor-I (IGF-I). Plasma concentration of IGF-I increases significantly during puberty, with peak levels observed earlier in girls than in boys. IGF-I is essential for accelerated growth. The gonadal steroids appear to act primarily by augmenting pituitary growth hormone release, which stimulates the production of IGF-I in the liver and other tissues.

Disorders of Sexual Development Can Manifest Before or After Birth

Normal sexual development depends on a complex, orderly sequence of events that begins during early fetal life and is completed at puberty. Any deviation can result in infertility, sexual dysfunction, or various degrees of intersexuality or **hermaphroditism**. A true hermaphrodite possesses both ovarian and testicular tissues, either separate or combined as ovotestes. A **pseudohermaphrodite** has one type of gonads but a different degree of sexuality of the opposite sex. Sex is normally assigned according to the type of gonads. Disorders of sexual differentiation can be classified as gonadal dysgenesis, female pseudohermaphroditism, male pseudohermaphroditism, or true hermaphroditism. Se-

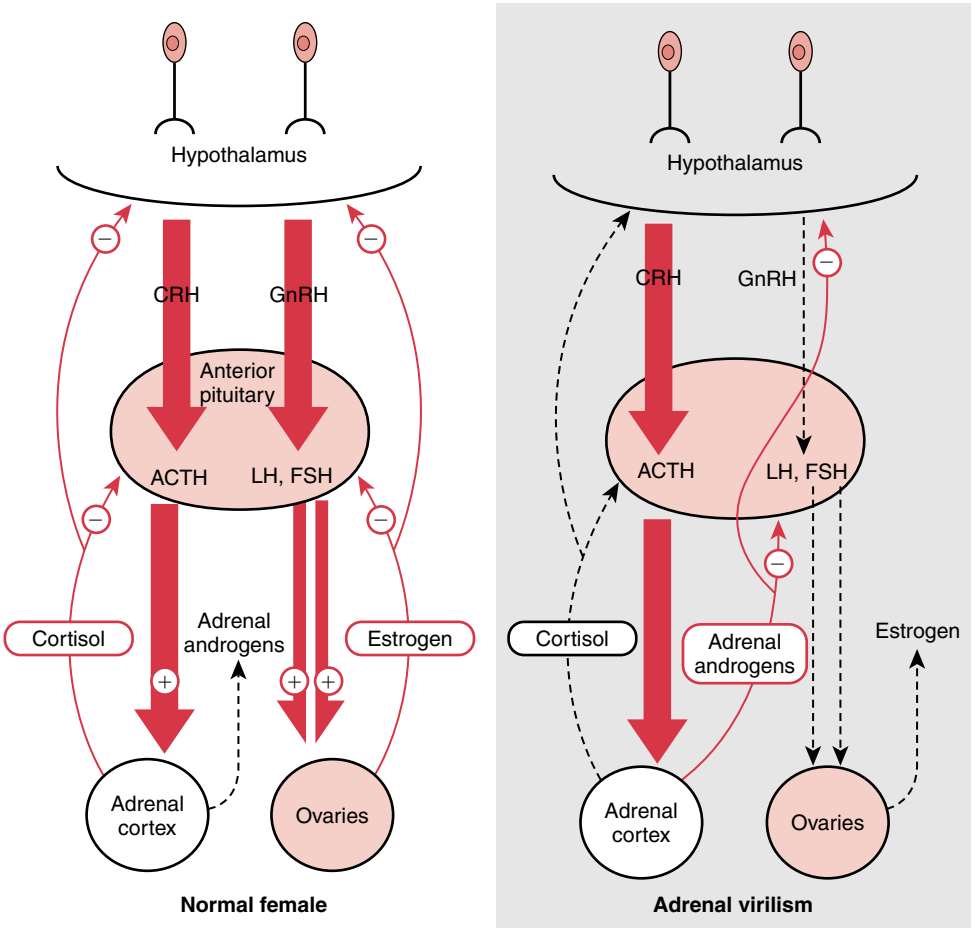

FIGURE 39.15 Hormonal interactions along the ovarian and adrenal axes during normal female development, compared with adrenal virilism. Dashed arrows indicate low production of the hormone. Heavy arrows indicate increased hormone production. Plus and minus signs indicate positive and negative effects.

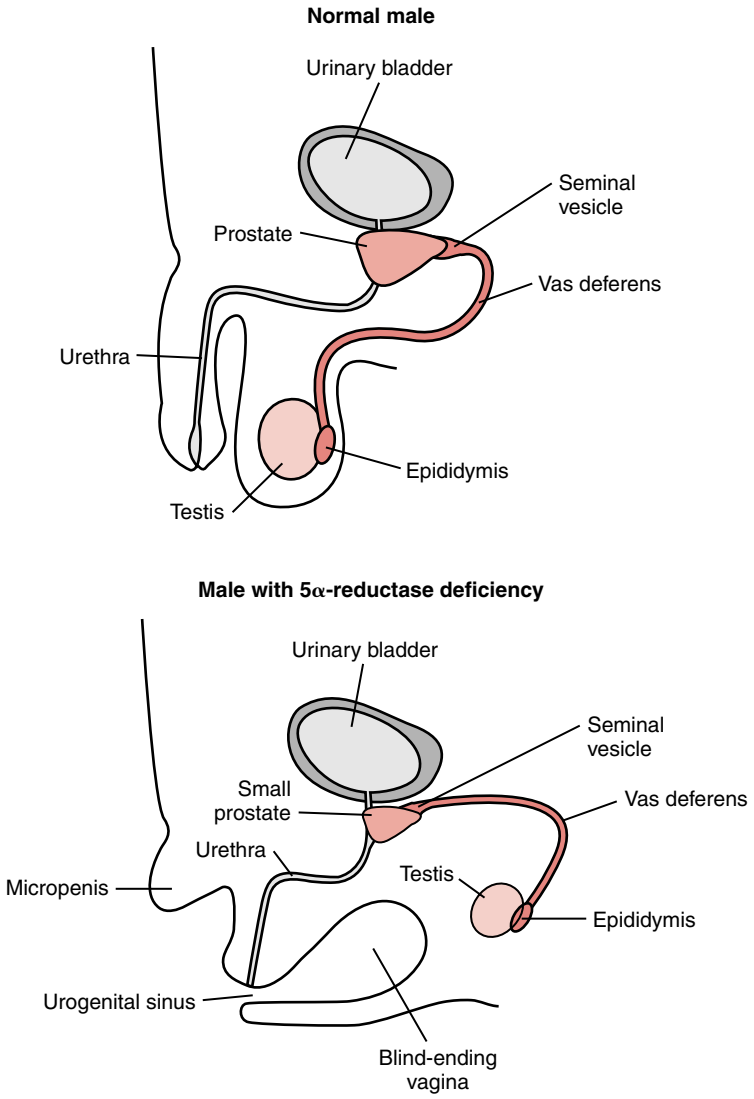

FIGURE 39.16 **Effects of 5α-reductase deficiency** on differentiation of the internal and external genitalia.

lected cases and their manifestations are briefly discussed here, as are disorders of pubertal development (see also Chapters 37 and 38).

Gonadal dysgenesis refers to incomplete differentiation of the gonads and is usually associated with sex chromosome abnormalities. These result from errors in the first or second meiotic division and occur by chromosomal nondisjunction, translocation, rearrangement, or deletion. The two most common disorders are Klinefelter's syndrome (47,XXY) and Turner's syndrome (45,XO). Because of a Y chromosome, an individual with a 47,XXY karyotype has normal testicular function in utero in terms of testosterone and AMH production and no ambiguity of the genitalia at birth. The extra X chromosome, however, interferes with the development of the seminiferous tubules, which show extensive hyalinization and fibrosis, whereas the Leydig cells are hyperplastic. Such males have small testes, are azoospermic, and often exhibit some eunuchoidal features. Because of having only one X chromosome, an individual with a 45,XO karyotype will have no gonadal development during fetal life and is presented at birth as a phenotypic female. Given the absence of ovarian follicles, such patients have very low levels of estrogens, primary amenorrhea, and do not undergo normal pubertal development.

Female pseudohermaphrodites are 46,XX females with normal ovaries and internal genitalia but a different degree of virilization of the external genitalia, resulting from exposure to excessive androgens in utero. The most common cause is **congenital adrenal hyperplasia**, an inherited abnormality in adrenal steroid biosynthesis, with most cases of virilization resulting from 21-hydroxylase or 11β-hydroxylase deficiency (see Chapter 34). In such cases, cortisol production is low, causing increased production of ACTH by activating the hypothalamic-pituitary axis (Fig. 39.15). The elevated ACTH levels induce adrenal hyperplasia and an abnormal production of androgens and corticosteroid precursors. These infants are born with ambiguous external genitalia (i.e., clitoromegaly, labioscrotal fusion, or phallic urethra). The degree of virilization depends on the time of onset of excess fetal androgen production. When aldosterone levels are also affected, a life-threatening salt-wasting disease results. Untreated patients with congenital adrenal virilism develop progressive masculinization, amenorrhea, and infertility.

Male pseudohermaphrodites are 46,XY individuals with differentiated testes but underdeveloped and/or absent wolffian-derived structures and inadequate virilization of the external genitalia. These effects result from defects in testosterone biosynthesis, metabolism, or action. The 5α-reductase deficiency is an autosomal recessive disorder caused by the inability to convert testosterone to DHT. Such infants have ambiguous or female external genitalia and normal male internal genitalia (Fig. 39.16). They are often raised as females but undergo a complete or partial testosterone-dependent puberty, including enlargement of the penis, testicular descent, and the development of male psychosexual behavior. Azoospermia is common.

The **testicular feminization** syndrome is an X-linked recessive disorder caused by end-organ insensitivity to androgens, usually because of absent or defective androgen receptors. These 46,XY males have abdominal testes that secrete normal testosterone levels. Because of androgen insensitivity, the wolffian ducts regress, and the external genitalia develop along the female line. The presence of AMH in utero causes regression of the müllerian ducts. These individuals have neither male nor female internal genitalia and phenotypic female external genitalia, with the vagina ending in a blind pouch. They are reared as females and undergo feminization during puberty because of the peripheral conversion of testosterone to estradiol.

Disorders of puberty are classified as **precocious puberty**, defined as sexual maturation before the age of 8 years, and **delayed puberty**, in which menses does not start by age 17 or testicular development is delayed beyond age 20. True precocious puberty results from premature activation of the hypothalamic-pituitary-gonadal axis, leading to the development of secondary sex characteristics as well as gametogenesis. The most frequent causes are CNS lesions or infections, hypothalamic disease, and hypothyroidism. **Pseudoprecocious puberty** is the early development of secondary sex characteristics without gametogenesis. It can result from the abnormal exposure of immature boys to androgens and of immature girls to estrogens. Augmented steroid production can be of gonadal or adrenal origin.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. The suckling reflex
   (A) Has afferent hormonal and efferent neuronal components
   (B) Increases placental lactogen secretion
   (C) Increases the release of dopamine from the arcuate nucleus
   (D) Triggers the release of oxytocin by stimulating the supraoptic nuclei
   (E) Reduces PRL secretion from the pituitary
2. Implantation occurs
   (A) On day 4 after fertilization
   (B) After the endometrium undergoes a decidual reaction
   (C) When the embryo is at the morula stage
   (D) Only after priming of the uterine endometrium by progesterone and estrogen
   (E) On the first day after entry of the embryo into the uterus
3. Upon contact between the sperm head and the zona pellucida, penetration of the sperm into the egg is allowed because of
   (A) The acrosome reaction
   (B) The zona reaction
   (C) The perivitelline space
   (D) Pronuclei formation
   (E) Cumulus expansion
4. The next ovulatory cycle after implantation is postponed because of
   (A) High levels of PRL
   (B) The production of hCG by trophoblast cells
   (C) The production of prostaglandins by the corpus luteum
   (D) The depletion of oocytes in the ovary
   (E) Low levels of progesterone
5. Polyspermy block occurs as a result of the
   (A) Cortical reaction
   (B) Enzyme reaction
   (C) Acrosome reaction
   (D) Decidual reaction
   (E) Inflammatory reaction
6. Oral steroidal contraceptives are most effective in preventing pregnancy by
   (A) Blocking ovulation
   (B) Altering the uterine environment
   (C) Thickening the cervical mucus
   (D) Reducing sperm motility
   (E) Inducing a premature LH surge
7. The maternal recognition of pregnancy occurs as a result of the
   (A) Prolonged secretion of estrogen by the placenta
   (B) Production of human placental lactogen
   (C) Increased secretion of progesterone by the corpus luteum
   (D) Secretion of hCG by the trophoblast
   (E) Activation of an inflammatory reaction at implantation
8. Estriol production during pregnancy requires
   (A) Androgens produced from cholesterol in the placenta
   (B) Estradiol as a precursor from the mother's ovary
   (C) Androgenic substrates from the fetus
   (D) Androgens from the ovary of the mother
   (E) Estradiol to be produced in the placenta
9. One benefit of insulin resistance in the mother during pregnancy is
   (A) A reduction of her plasma glucose concentrations
   (B) The blockage of the development of diabetes mellitus in later life
   (C) The increased availability of glucose to the fetus
   (D) A reduction of pituitary function
   (E) Increased appetite
10. The primary reason that the female phenotype develops in an XY male is
    (A) The secretion of progesterone
    (B) Adrenal insufficiency
    (C) The lack of testosterone action
    (D) Increased inhibin secretion
    (E) The secretion of antimüllerian hormone (AMH)

SUGGESTED READING

Carr BR. Fertilization, implantation, and endocrinology of pregnancy. In: Griffin JE, Ojeda SR, eds. Textbook of Endocrine Physiology. 4th Ed. New York: Oxford University Press, 2000;265–285.

Hay WW Jr. Metabolic changes in pregnancy. In: Knobil E, Neill JD, eds. The

Encyclopedia of Reproduction. New York: Academic Press, 1999;106–1026.
Johnson MH, Everitt BJ. Essential Reproduction. Oxford, UK: Blackwell Science, 2000.
Parker CR Jr. The endocrinology of pregnancy. In: Carr BR, Blackwell RE, eds. Textbook of Reproductive Medicine. East Norwalk, CT: Appleton & Lange, 1993;17–40.
Regan CL. Overview, pregnancy in humans. In Knobil E, Neill JD, eds. The encyclopedia of reproduction. New York: Academic Press, 1999;986–991.
Spencer TE: Maternal recognition of pregnancy. In: Knobil E, Neill JD, eds. The Encyclopedia of Reproduction. New York: Academic Press, 1999;1006–1015.

CASE STUDIES FOR PART X • • •

Case Study for Chapter 37

Steroid Abuse

A 30-year-old man and his 29-year-old wife have been trying to have a baby. She has been having regular menstrual cycles. They have intercourse 2 to 3 times a week, with no physical problems, and try to time intercourse around the time of her ovulation.

Physical examination and history for the wife are normal. The husband's physical examination reveals a muscular man with an excellent physique who works out regularly to build his body. His testes are small and soft. Laboratory results indicate that his plasma testosterone is 1850 ng/dL (normal, 300 to 100 ng/dL) and LH $<$ 2 μU/mL (normal, 3 to 18 μU/mL). His semen analysis reveals a sperm count of 1.2 $\times$ 10^6/mL (normal, $>$20 $\times$ 10^6/mL)

Questions

1. What is the major reason for the failure of the wife to get pregnant?
2. What is a reasonable explanation for the abnormal hormone levels?

Answers to Case Study Questions for Chapter 37

1. He has an extremely low sperm count.
2. Since he is a body builder with small, soft testes, high testosterone levels, and low LH levels, the physician should suspect androgen abuse or possibly androgen-producing tumor (extremely rare). The high androgen levels would suppress LH secretion and reduce intratesticular testosterone levels. The low LH and intratesticular testosterone would correlate well with small testes and low sperm count, respectively.

Case Study for Chapter 38

Early Spontaneous Pregnancy Termination

A 35-year-old woman visited her obstetrician/gynecologist and complained that she was unable to get pregnant. Upon taking a medical history, the physician notes that the patient had regular 28- to 30-day cycles during the past year, during which time she had regular unprotected intercourse. She does not smoke and does not use caffeine, drugs, or alcohol. She appears to be in good health. Her ovaries and uterus appear normal in size for her age. Laboratory tests indicate that her preovulatory (late follicular phase) estradiol is 40 pg/mL (normal, 200 to 500 pg/mL) and midluteal phase progesterone is 3 ng/mL (normal, 4 to 20 ng/mL). Her husband's sperm count is 30 million/mL.

Questions

1. What are the clinical indications of a fertility problem with this patient?
2. Based on the clinical signs, what basic physiological principles provide insight into the infertility?
3. What are some theoretical treatment options for this patient?

Answers to Case Study Questions for Chapter 38

1. There are two laboratory tests that indicate a problem, the low late follicular phase plasma estradiol concentration and the low midluteal phase plasma progesterone concentration.
2. The low estradiol could be due to the development of a small dominant graafian follicle with insufficient numbers of granulosa cells. The reduced number of granulosa cells would not contain sufficient aromatase to synthesize the high levels of estradiol required during the late follicular phase. In addition, low estradiol could be due to inadequate FSH receptors on the granulosa cells or inadequate FSH secretion. The low estradiol could also be explained by a lack of LH stimulation of thecal androgen production from the small dominant follicle, possibly the result of inadequate LH receptors on theca cells or low LH levels.
   The low progesterone during the luteal phase might be due to the ovulation of a small follicle or premature ovulation of a follicle that was not fully developed. The number of LH receptors on the luteinized granulosa cells in the graafian follicle and developing corpus luteum may be insufficient, or LH secretion may be deficient. LH receptors mediate the action of LH, which stimulates progesterone secretion. An insufficient number of LH receptors could be due to insufficient priming of the developing follicle with FSH. Finally, the LH surge may be insufficient for maximal progesterone secretion.
3. Theoretical treatment options for the patient include exogenous progesterone during the luteal phase, which would raise the overall circulating progesterone to levels compatible with maintaining pregnancy, allowing implantation of the embryo.
   Another option would be to use exogenous FSH to stimulate follicular development to produce larger follicle(s) with sufficient estradiol secretion and LH receptors. Follicles with adequate LH receptors would respond to an LH surge with increased progesterone in the normal range. Another option is the administration of hCG during the periovulatory period for inducing ovulation and full luteinization. The latter would overcome any deficiency in the endogenous LH surge. Finally, the use of clomiphene, an antiestrogen, would increase FSH (and LH) secretion in the follicular phase and, subsequently, induce follicular development with sufficient estradiol to induce a full LH surge. Exogenous hCG could be given during the ovulatory phase to ensure full luteinization of the corpus luteum with sufficient progesterone to maintain pregnancy.

Case Study

Female Infertility

A 25-year-old woman and her 29-year-old husband have been trying to have a baby for one year. She has regular menstrual cycles of 26 to 28 days in length. They have intercourse three times a week, with no physical problems,

and they try to time intercourse around the time of her ovulation.

Physical examination and history for the wife are normal. The husband's physical examination is normal. The husband's semen analysis reveals a semen volume of 4 mL; pH 7.5; sperm count of 30 million/mL; and normal morphology and motility of the sperm. Because of the short cycles (24 to 26 days versus 28 days), the wife's plasma progesterone level during the midluteal phase is assessed and determined to be 10 ng/mL, which is considered normal (4 to 20 ng/mL, see Table 38.3).

Questions

1. What hormones can be measured in the blood to determine why the patient is not able to get pregnant?
2. Based on the hormone measurements, what treatment would likely result in a successful pregnancy?

Answers to Case Study for Chapter 39

1. Estradiol should be measured at the end of the anticipated follicular phase. High serum levels of estradiol would indicate that a dominant follicle has been recruited and is active; low levels would indicate a subnormal dominant follicle or lack of a dominant follicle; this could be verified by ultrasound of the ovaries. Serum LH should be measured during the anticipated preovulatory period. High serum levels of LH would indicate that the dominant follicle is getting the signal to ovulate. Low levels of LH may lead to an unruptured dominant follicle that fails to ovulate but luteinizes, leading to progesterone levels in the normal range for the luteal phase. Plasma concentrations of hCG could be determined during the midluteal to late luteal phase to determine whether she was pregnant.
2. Low estradiol indicates a lack of development of a dominant follicle. Therapies such as gonadotropins and clomiphene (see Chapter 38) would be appropriate to stimulate follicular development, estradiol secretion, and ovulation. If a dominant follicle is present, then hCG can be given to induce follicular rupture. hCG binds to the LH receptor and is preferred over LH and GnRH for ovulation induction because of its longer half-life.