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The Female Reproductive System

The female reproductive system consists of two ovaries, two oviducts (uterine tubes), the uterus, the vagina, and the external genitalia. Its functions are to produce female gametes (**oocytes**) and to hold a fertilized oocyte during its complete development through embryonic and fetal stages until birth. The system also produces sexual hormones that control organs of the reproductive system and influence other organs of the body. Beginning at **menarche,** when the first menses occurs, the reproductive system undergoes cyclic changes in structure and functional activity. These modifications are controlled by neurohumoral mechanisms. **Menopause** is a variable period during which the cyclic changes become irregular and eventually disappear. In the postmenopausal period there is a slow involution of the reproductive system. Although the mammary glands do not belong to the genital system, they are studied here because they undergo changes directly connected to the functional state of the reproductive system.

Ovaries

Ovaries are almond-shaped bodies approximately 3 cm long, 1.5 cm wide, and 1 cm thick. Their surface is covered by a simple squamous or cuboidal epithelium, the **germinal epithelium.** Under the germinal epithelium is a layer of dense connective tissue, the **tunica albuginea,** which is responsible for the whitish color of the ovary. Underneath the tunica albuginea is the **cortical region,** where ovarian follicles structures that contain the oocytes predominate. The follicles are embedded in the connective tissue (**stroma**) of the cortical region. This stroma is composed of characteristic spindle-shaped fibroblasts that respond to hormonal stimuli in a different way than do fibroblasts of other organs. The most internal part of the ovary is the **medullary region,** containing a rich vascular bed within a loose connective tissue. There are no sharp limits between the cortical and medullary regions.

Development of the Ovary & Its Function

Around the end of the first month of embryonic life, a small population of **primordial germ cells** migrates from the yolk sac to the gonadal primordia. In the gonads these cells divide and transform into **oogonia.** Division is so intense that in the second month of intrauterine life there are around 600,000 oogonia, and around the fifth month more than 7 million. Beginning in the third month, oogonia begin to enter the prophase of the first meiotic division but stop at the diplotene stage and do not progress to other stages of meiosis. These cells are the **primary oocytes** , and they become surrounded by flattened cells called **follicular cells.** By the seventh month of pregnancy, most oogonia have been transformed into primary oocytes. Many primary oocytes,

however, are lost through a degenerative process called **atresia.** As a result, around puberty the ovaries contain about 300,000 oocytes. Atresia continues over the entire span of the woman's reproductive life so that by 40–45 years of age about 8000 oocytes are left. Because generally only one oocyte is liberated by the ovaries in each menstrual cycle (average duration, 28 days) and the reproductive life of a woman lasts about 30–40 years, only about 450 oocytes are liberated. All others degenerate through atresia.

Ovarian Follicles

An ovarian follicle consists of an oocyte surrounded by one or more layers of **follicular** cells, or **granulosa cells.** A basal lamina underlies the follicular cells and marks the boundary between the follicle and the surrounding stroma. The follicles that are formed during fetal life **primordial follicles** consist of a primary oocyte enveloped by a single layer of flattened follicular cells. These follicles are found in the superficial layer of the cortical region. The oocyte in the primordial follicle is a spherical cell about 25 μm in diameter. Its nucleus is large and has a large nucleolus. These cells are in the first prophase of meiosis. The chromosomes are mostly uncoiled and do not stain intensely. The organelles in the cytoplasm tend to form a clump adjacent to the nucleus. There are numerous mitochondria, several Golgi complexes, and cisternae of endoplasmic reticulum.

Follicular Growth

Beginning in puberty, each day a small group of primordial follicles begins a process called follicular growth. This consists of modifications of the oocyte, of the granulosa cells, and of the stromal fibroblasts that surround these follicles. It is not known how the particular follicles that enter the growth stage are selected from the large population of primordial follicles.

Follicular growth is stimulated by follicle-stimulating hormone, secreted by the hypophysis. Oocyte growth is most rapid during the first part of follicular growth, with the oocyte reaching a maximum diameter of about 120μm. The nucleus enlarges, the mitochondria increase in number and become uniformly distributed throughout the cytoplasm, the endoplasmic reticulum hypertrophies, and the Golgi complexes migrate to just beneath the cell surface. Follicular cells divide by mitosis and form a single layer of cuboidal cells; the follicle is then called a **unilaminar primary follicle**. The follicular cells continue to proliferate and form a stratified follicular epithelium, or **granulosa layer,** whose cells communicate through gap junctions. The follicle is then called a **multilaminar primary** or **preantral follicle**. A thick amorphous layer, the **zona pellucida,** composed of several glycoproteins, is secreted and surrounds the oocyte. Both the oocyte and follicular cells are believed to contribute to the synthesis of the zona pellucida. Filopodia of follicular cells and microvilli of the oocyte penetrate the zona pellucida and make contact with one another via gap junctions.

As the follicles grow due mainly to the increase in size and number of granulosa cells they move to deeper areas of the cortical region. Liquid (**liquor folliculi**) begins to accumulate between the follicular cells. The small spaces that contain this fluid coalesce, and the granulosa cells reorganize themselves to form a larger cavity, the **antrum**. The follicles are then called **secondary** or **antral follicles.** Follicular fluid contains components of the plasma and products secreted by follicular cells. Glycosaminoglycans, several proteins (including steroid-binding proteins), and high concentrations of steroids (progesterone, androgens, and estrogens) are present.

While modifications are taking place in the oocyte and granulosa layer, the fibroblasts of the stroma immediately around the follicle differentiate to form the **theca folliculi** (theca from Greek, meaning box). This layer subsequently differentiates into the **theca interna** and the **theca externa**. The cells of the theca interna, when completely differentiated, acquire the ultrastructural characteristics of cells that produce steroids. These characteristics include abundant profiles of smooth endoplasmic reticulum, mitochondria with tubular cristae, and numerous lipid droplets. These cells are known to synthesize a steroid hormone—**androstenedione** that is transported to the granulosa layer. The cells of the granulosa, under the influence of follicle-stimulating hormone, synthesize an enzyme, aromatase, that transforms androstenedione into estrogen. Estrogen returns to the stroma, enters the blood vessels, and is distributed throughout the body. The theca externa, on the other hand, consists mainly of organized layers of fibroblasts that surround the theca interna. The boundary between the two thecas is not sharp; neither is there a clear boundary between the theca externa and the ovarian stroma. On the other hand, the boundary between the theca interna and the granulosa layer is well defined, since their cells are morphologically different and there is a thick basement membrane between them. Small blood vessels penetrate the theca interna and supply a rich capillary plexus around the secretory cells of this region, which, like all organs of endocrine function, is richly vascularized. There are no blood vessels in the granulosa cell layer during the stage of follicular growth.

During each menstrual cycle, usually one follicle grows much more than the others and becomes the dominant follicle. The other follicles of the group that is growing enter atresia. The dominant follicle may reach the most developed stage of follicular growth—the **mature, preovulatory,** or **graafian follicle**—and may ovulate. At the peak of its development, this follicle is so large (about 2.5 cm in diameter) that it protrudes from the surface of the ovary and can be detected with ultrasound. As a result of the accumulation of liquid, the follicular cavity increases in size, and the oocyte adheres to the wall of the follicle through the cumulus oophorus formed by granulosa cells. Because the granulosa cells of the follicle wall do not multiply in proportion to the growth of the follicle, the granulosa layer becomes thinner. These follicles have a very thick theca layer.

Follicular Atresia

Most ovarian follicles undergo atresia, in which follicular cells and oocytes die and are disposed of by phagocytic cells. Follicles at any stage of development (primordial, primary, preantral, and antral) may undergo atresia. This process is characterized by cessation of mitosis in the granulosa cells, detachment of granulosa cells from the basal lamina, and death of the oocyte and granulosa cells. After a certain point macrophages invade the follicle to phagocytose the debris. At a later stage, fibroblasts occupy the follicle and produce a scar of collagen that may persist for a long time. Although follicular atresia takes place from before birth until a few years after menopause, there are times at which it is particularly intense. Atresia is greatly accentuated just after birth, when the effect of maternal hormones ceases, and during puberty and pregnancy, when marked qualitative and quantitative hormonal modifications take place.

Ovulation

Ovulation consists of the rupture of part of the wall of the mature follicle and liberation of the oocyte, which is caught by the dilated extremity of the oviduct. It takes place in approximately the middle of the menstrual cycle, ie, around the fourteenth day of a 28-day cycle. In the human, usually only one oocyte is liberated by the ovary during each cycle, but sometimes no oocyte is ovulated (anovulatory cycle). Sometimes two or more oocytes can be expelled at the same time, and if they are fertilized, there may be two or more fetuses.

The stimulus for ovulation is a surge of luteinizing hormone (LH) secreted by the anterior pituitary gland in response to high levels of circulating estrogen produced by the growing follicles. Within minutes after the increase in blood LH, there is an increase in blood flow through the ovary, and plasma proteins leak through capillaries and postcapillary venules, resulting in edema. There is a local release of prostaglandins, histamine, vasopressin, and collagenase. The granulosa cells produce more hyaluronic acid and become loose. A small area of the wall of the follicle becomes weak because of collagen degradation of the tunica albuginea, ischemia, and the death of some cells. This weakness, combined with an increased pressure of the follicular fluid and possibly the contraction of contractile cells that surround the follicle, leads to the rupture of the outer follicular wall and ovulation. An indication of impending ovulation is the appearance on the surface of the follicle of the **stigma,** in which the flow of blood ceases, resulting in a local change in color and translucence of the follicular wall.

The first meiotic division is completed just before ovulation. The chromosomes are equally divided between the daughter cells, but one of the secondary oocytes retains almost all of the cytoplasm. The other becomes the **first polar body,** a very small cell containing a small nucleus and a minimal amount of cytoplasm. Immediately after

expulsion of the first polar body, the nucleus of the oocyte starts the second meiotic division, which stops in metaphase.

Because of the rupture of the follicular wall, the oocyte and the first polar body, both enclosed by the zona pellucida, the corona radiata, and some follicular fluid, leave the ovary and enter the open extremity of the uterine tube where the oocyte may be fertilized. If this does not happen within the first 24 h after ovulation, it degenerates.

Corpus Luteum

After ovulation, the granulosa cells and the cells of the theca interna of the ovulated follicle reorganize to form a temporary endocrine gland called the **corpus luteum,** which becomes embedded within the cortical region.

Release of the follicular fluid during ovulation results in collapse of the follicle's wall so that it becomes folded. Some blood flows into the follicular cavity, where it coagulates and is later invaded by connective tissue. This connective tissue, with remnants of blood clots that are gradually removed, remains as the most central part of the corpus luteum.

Although the granulosa cells do not divide after ovulation, they increase greatly in size (20–35 μm in diameter). They make up about 80% of the parenchyma of the corpus luteum and are then called **granulosa lutein cells**, with the characteristics of steroid-secreting cells. This is in contrast to their structure in the preovulatory follicle, where they appear to be protein-secreting cells.

Cells of the theca interna also contribute to the formation of the corpus luteum by giving rise to **theca lutein cells**. These cells are similar in structure to granulosa lutein cells but are smaller (about 15 μm in diameter) and stain more intensely. They are located in the folds of the wall of the corpus luteum.

The blood capillaries and lymphatics that were restricted to the theca interna now grow into the interior of the corpus luteum and form the rich vascular network of this structure.

The reorganization of the ovulated follicle and the development of the corpus luteum result from the LH released before ovulation. Also under stimulus by LH, the cells of the corpus luteum change their sets of enzymes and begin secreting progesterone and estrogens.

The fate of the corpus luteum depends on whether pregnancy is established. Following the stimulus by LH, the corpus luteum is programmed to secrete for 10–12 days. If pregnancy does not occur, no further hormonal stimulation takes place and the cells of the corpus luteum degenerate by apoptosis. One of the consequences of the

decreasing secretion of progesterone is menstruation, which constitutes the shedding of part of the uterine mucosa. Estrogen produced by the active corpus luteum inhibits the liberation of follicle-stimulating hormone from the hypophysis. However, after the corpus luteum degenerates, the concentration of blood steroids decreases and follicle-stimulating hormone is liberated, stimulating the growth of another group of follicles, beginning the next menstrual cycle. The corpus luteum that lasts for only part of a menstrual cycle is called the **corpus luteum of menstruation.** Its cellular remnants are phagocytosed by macrophages. Neighboring fibroblasts invade the area and produce a scar of dense connective tissue called the **corpus albicans** ("white body," because of the large amount of collagen).

If pregnancy occurs, the uterine mucosa cannot be allowed to shed. If it does, the implanting embryo dies and the pregnancy is aborted. Instead, a signal to the corpus luteum is given by a hormone called **human chorionic gonadotropin** (**HCG**) secreted by the trophoblastic cells of the implanting embryo. The action of HCG is similar to that of LH. Thus, HCG rescues the corpus luteum from degeneration, causes further growth of this endocrine gland, and stimulates secretion of progesterone (which will maintain the uterine mucosa throughout pregnancy). In addition to maintaining the uterine mucosa, progesterone also stimulates secretion of the uterine glands, which is thought to be important for the nutrition of the embryo before the placenta is functional. This is the **corpus luteum of pregnancy.** It persists for 4–5 months and then degenerates and is replaced by a corpus albicans that is much larger than the corpus albicans of menstruation.

Interstitial Cells

Although granulosa cells and the oocytes undergo degeneration during follicular atresia, the theca interna cells frequently persist in isolation or in small groups throughout the cortical stroma and are called **interstitial cells.** Present from childhood through menopause, interstitial cells are active steroid secretors, stimulated by LH.

Oviducts

The oviducts are two muscular tubes of great mobility, each measuring about 12 cm in length. One of its extremities, the infundibulum, opens into the peritoneal cavity next to the ovary and has a fringe of fingerlike extensions called **fimbriae;** the other extremity, the intramural portion, passes through the wall of the uterus and opens into the interior of this organ.

The wall of the oviduct is composed of three layers: (1) a mucosa, (2) a thick muscularis composed of smooth muscle disposed as an inner circular or spiral layer and

an outer longitudinal layer, (3) and a serosa composed of visceral peritoneum.

The mucosa has longitudinal folds that are most numerous in the ampulla. In cross sections, the lumen of the ampulla resembles a labyrinth. These folds become smaller in the segments of the tube that are closer to the uterus. In the intramural portion, the folds are reduced to small bulges in the lumen, so its internal surface is almost smooth.

The mucosa is composed of a simple columnar epithelium and a lamina propria composed of loose connective tissue. The epithelium contains two types of cells: one has cilia and the other is secretory. The cilia beat toward the uterus, causing movement of the viscous liquid film that covers its surface. This liquid consists mainly of products of the secretory cells interspersed between ciliated cells. At the moment of ovulation, the oviduct exhibits active movement. The funnel-shaped extremity (fringed with numerous fimbriae) comes very close to the surface of the ovary. This favors the transport of the ovulated oocyte into the tube. Promoted by muscle contraction and the activity of ciliated cells, the oocyte enters the infundibulum of the oviduct. The secretion of the tube epithelium contains nutrients for the oocyte. Unless it is fertilized, the oocyte remains viable for a maximum of about 24 h. The secretion also promotes activation (**capacitation**) of spermatozoa.

Fertilization usually occurs in the ampulla and reconstitutes the diploid number of chromosomes typical of the species. It also serves as a stimulus for the oocyte to complete the second meiotic division. Only at this moment does the primary oocyte transform into a secondary oocyte. The corona radiata is usually still present when the spermatozoon fertilizes the oocyte; it is retained for some time during the passage of the oocyte through the oviduct.

Once fertilized, the oocyte, now called a zygote (Gr. *zygotos*, yolked), begins cell division and is transported to the uterus, a process that lasts about 5 days. Movement of the film that covers the mucosa of the tube, in conjunction with contractions of the muscle layer, helps to transport the oocyte or the conceptus toward the uterus. This movement also hampers the passage of microorganisms from the uterus to the peritoneal cavity. Transport of the oocyte or conceptus to the uterus, however, is normal in females with **immotile cilia syndrome,** showing that ciliary activity is not essential for transport.

Uterus

The uterus is a pear-shaped organ that consists of a **body** (**corpus**), which lies above a narrowing of the uterine cavity (**the internal os**), and a lower cylindrical structure, the **cervix,** which lies below the internal os. The dome-shaped part of the body of the uterus is called the **fundus**.

The wall of the uterus is relatively thick and is composed of three layers. Depending on the part of the uterus, there is either an outer **serosa** (connective tissue and mesothelium) or **adventitia** (connective tissue). The other uterine layers are the **myometrium,** a thick tunic of smooth muscle, and the **endometrium,** or mucosa of the uterus.

Myometrium

The myometrium (Gr. *mys,* muscle, + *metra,* uterus), the thickest tunic of the uterus, is composed of bundles of smooth muscle fibers separated by connective tissue. The bundles of smooth muscle form four poorly defined layers. The first and fourth layers are composed mainly of fibers disposed longitudinally, ie, parallel to the long axis of the organ. The middle layers contain the larger blood vessels.

During pregnancy, the myometrium goes through a period of great growth as a result of both **hyperplasia** (an increase in the number of smooth muscle cells) and **hypertrophy** (an increase in cell size). During pregnancy, many smooth muscle cells actively synthesize collagen, promoting a significant increase in uterine collagen content.

After pregnancy, there is destruction of some smooth muscle cells, reduction in the size of others, and enzymatic degradation of the collagen. The uterus is reduced in size almost to its prepregnancy dimensions.

Endometrium

The endometrium consists of epithelium and a lamina propria containing simple tubular glands that sometimes branch in their deeper portions (near the myometrium). Its covering epithelial cells are a mixture of ciliated and secretory simple columnar cells. The epithelium of the uterine glands is similar to the superficial epithelium, but ciliated cells are rare within the glands.

The connective tissue of the lamina propria is rich in fibroblasts and contains abundant ground substance. Connective tissue fibers are mostly made of collagen type III.

The endometrial layer can be subdivided into two zones: (1) The **basalis** is the deepest one, adjacent to the myometrium; it contains lamina propria and the closed tips of the uterine glands. (2) The **functionalis** contains the remainder of the lamina propria and the glands, as well as the surface epithelium. Whereas the functionalis undergoes profound changes during the menstrual cycles, the basalis remains mostly unchanged.

The blood vessels supplying the endometrium are of special significance in the periodic sloughing of most of this layer. **Arcuate arteries** are circumferentially oriented in the middle layers of the myometrium. From these vessels, two sets of arteries arise to supply blood to the endometrium: **straight arteries,** which supply the basalis, and **spiral arteries,** which bring blood to the functionalis.

The Menstrual Cycle

Estrogens and progesterone control the organs of the female reproductive system. The proliferation and the differentiation of epithelial cells and the associated connective tissues depend on these hormones. Even before birth, these organs are influenced by estrogen and progesterone that circulate in the maternal blood and reach the fetus through the placenta. After menopause, the diminished synthesis of these hormones causes a general involution of the reproductive organs.

After puberty, the ovarian hormones, under the stimulus of the anterior lobe of the pituitary, cause the endometrium to undergo cyclic structural modifications during the menstrual cycle. The duration of the menstrual cycle is variable but averages 28 days.

Menstrual cycles usually start between 12 and 15 years of age and continue until about age 45–50 years. Because menstrual cycles are a consequence of ovarian modifications related to the production of oocytes, the female is fertile only during the years when she is having menstrual cycles. This does not mean that sexual activity is terminated by menopause only that fertility ceases.

For practical purposes, the beginning of the menstrual cycle is taken as the day when menstrual bleeding appears. The menstrual discharge consists of degenerating endometrium mixed with blood from the ruptured blood vessels. The **menstrual phase** lasts 3–4 days on average. The next phases of the menstrual cycle are called the **proliferative** and **secretory** (or **luteal**) phases. The secretory phase begins at ovulation and lasts about 14 days. The duration of the proliferative phase is variable, 10 days on average. The structural changes that occur during the cycle are gradual, and the clear division of the phases implied here is mainly for teaching value.

The Proliferative, Follicular, or Estrogenic Phase

After the menstrual phase, the uterine mucosa is relatively thin (about 0.5 mm). The beginning of the proliferative phase coincides with the rapid growth of a small group of ovarian follicles that, when the cycle began, was probably at the transition from preantral to antral follicles. When their theca interna develops, these follicles begin to actively secrete estrogens, whose plasma concentrations increase gradually.

Estrogens act on the endometrium, inducing cell proliferation and reconstituting the endometrium lost during menstruation. (Estrogen also acts on other parts of the reproductive system, eg, inducing the production of cilia by epithelial cells of the oviduct.)

During the proliferative phase, the endometrium is covered by a simple columnar epithelium. The glands, formed by simple columnar epithelial cells, are straight tubules with narrow lumens. These cells gradually accumulate more cisternae of rough endoplasmic reticulum, and the Golgi complex increases in size in preparation for secretory activity. At the end of the proliferative phase, the endometrium is 2–3 mm thick.

The Secretory, or Luteal, Phase

The secretory phase starts after ovulation and results from the action of progesterone secreted by the corpus luteum. Acting on glands already developed by the action of estrogen, progesterone further stimulates the gland cells. The epithelial cells begin to accumulate glycogen below their nuclei. Later, the amount of glycogen diminishes, and glycoprotein secretory products dilate the lumens of the glands. One important feature of this phase is that the glands become highly coiled. In this phase, the endometrium reaches its maximum thickness (5 mm) as a result of the accumulation of secretions and of edema in the stroma. Mitoses are rare during the secretory phase.

If fertilization has taken place, the embryo has been transported to the uterus and attaches to the uterine epithelium during the secretory stage, around 7 or 8 days after ovulation. It is thought that the secretion of the glands is the major source of embryonic nutrition before embryo implantation.

Progesterone inhibits the contractions of smooth muscle cells of the myometrium that might otherwise interfere with the implantation of the embryo.

The Menstrual Phase

When fertilization of the oocyte and embryo implantation do not occur and the corpus luteum ceases functioning, the consequent rapid decrease of blood levels of progesterone and estrogens causes menstruation. Menstruation is a complex phenomenon and its exact mechanisms are still not completely understood. Several factors are involved in the shedding of the endometrium, such as cycles of contraction and relaxation of the spiral arteries, activation (by lack of progesterone) of locally produced matrix metalloproteinases, and local release of prostaglandins, cytokines, and nitric oxide. These factors lead to breakdown of blood vessel walls and basement membranes as well as collagen of the endometrial lamina propria. Blood vessels rupture above the constrictions, and bleeding begins. Consequently, part of the functional layer

of the endometrium becomes detached. The amount of endometrium and blood lost varies between women and even in the same woman at different times.

At the end of the menstrual phase, the endometrium is usually reduced to a thin layer of lamina propria, the blind ends of uterine glands (both of which present in the basalis layer), and some covering epithelium. The endometrium is thus ready to begin a new cycle as its epithelial, connective tissue, and vascular cells begin dividing to reconstitute the mucosa.

Pregnant Endometrium

If implantation occurs, embryonic trophoblast cells produce HCG, which stimulates the corpus luteum to continue secreting progesterone. As pregnancy is established, menstruation does not occur, and the menstrual cycle is deferred during the whole duration of pregnancy. Progesterone makes the uterine glands wider, more tortuous, and able to contain more secretions than during the secretory stage. The endometrium as a whole becomes thicker during the beginning of pregnancy.

Implantation, Decidua, & Placenta

The human oocyte is fertilized in the lateral third of the uterine tube, and the zygote undergoes cell division as it is moved passively toward the uterus. Through successive mitoses, a compact collection of cells, the **morula,** is formed. The morula, covered by the zona pellucida, is about the same size as the fertilized oocyte. The cells that result from segmentation of the zygote are called **blastomeres** (Gr. *blastos,* germ, + *meros,* part). Because the zygote does not grow in size, at each division the blastomeres become smaller.

At the center of the morula a liquid-filled cavity develops and the blastomeres arrange themselves in a peripheral layer (**trophoblast**) while a few blastomeres accumulate inside the cavity (**inner cell mass**). This embryo is now called a **blastocyst,** which is the stage at which it arrives in the uterus. This happens on approximately the fourth or fifth day after ovulation. The blastocyst remains in the lumen of the uterus for 2 or 3 days, immersed in the secretion of the endometrial glands, and comes into contact with the surface of the endometrium. The zona pellucida is then dissolved, allowing cells of the trophoblast to interact directly with cells of the uterine surface epithelium.

Implantation, or nidation, involves the attachment of the embryo to the endometrial epithelial cells and its penetration into the lamina propria. This type of implantation is called **interstitial** and occurs in humans and a few other mammals. The process starts around the seventh day; on about the ninth day after ovulation, the

embryo is totally submerged in the endometrium, from which it will receive protection and nourishment during pregnancy.

During implantation of the embryo, the endometrial connective tissue goes through profound changes. The fibroblasts of the lamina propria become enlarged and round and exhibit the characteristics of protein-synthesizing cells. They are now called decidual cells, and the whole endometrium is called the **decidua.** Based on the endometrial region, the decidua can be classified as the **decidua basalis,** situated between the embryo and the myometrium; the **decidua capsularis,** situated between the embryo and the lumen of the uterus; and the **decidua parietalis,** the remainder of the decidua.

The placenta is a temporary organ and is the site of physiological exchanges between the mother and the fetus. It consists of a fetal part (**chorion**) and a maternal part (decidua basalis). Thus the placenta is composed of cells derived from two genetically distinct individuals. The decidua basalis supplies maternal arterial blood to, and receives venous blood from, spaces that exist inside the placenta.

The placenta is also an endocrine organ, producing hormones such as HCG, a placental prolactin, estrogens, and progesterone.

More detailed information on the developing embryo and on the formation and structure of the placenta should be sought in embryology textbooks.

Uterine Cervix

The **cervix** is the lower, cylindrical part of the uterus, and it differs in histological structure from the rest of the uterus. The lining consists of a mucus-secreting simple columnar epithelium. The cervix has few smooth muscle fibers and consists mainly (85%) of dense connective tissue. The external aspect of the cervix that bulges into the lumen of the vagina is covered with stratified squamous epithelium.

The mucosa of the cervix contains the mucous **cervical glands,** which are extensively branched. This mucosa does not undergo remarkable changes during the menstrual cycle and does not desquamate during menstruation. During pregnancy, the cervical mucous glands proliferate and secrete a more viscous and abundant mucus.

Cervical secretions play a significant role in fertilization of the oocyte. At the time of ovulation, the mucous secretions are watery and allow penetration of the uterus by sperm. In the luteal phase or in pregnancy, the progesterone levels alter the mucous secretions so that they become more viscous and prevent the passage of sperm, as well as microorganisms, into the body of the uterus. The dilation of the cervix that precedes parturition is due to intense collagenolysis, which promotes its softening.

Vagina

The wall of the vagina (from Latin, meaning sheath) is devoid of glands and consists of three layers: a **mucosa,** a **muscular layer,** and an **adventitia.** The mucus found in the lumen of the vagina comes from the glands of the uterine cervix.

The epithelium of the vaginal mucosa of an adult woman is stratified squamous and has a thickness of 150–200 μm. Its cells may contain a small amount of keratohyalin. Intense keratinization, however, with the cells changing into keratin plates, as in typical keratinized epithelia, does not occur. Under the stimulus of estrogen, the vaginal epithelium synthesizes and accumulates a large quantity of glycogen, which is deposited in the lumen of the vagina when the vaginal cells desquamate. Bacteria in the vagina metabolize glycogen and form lactic acid, which is responsible for the usually low pH of the vagina. The acidic vaginal environment provides a protective action against some pathogenic microorganisms

The lamina propria of the vaginal mucosa is composed of loose connective tissue that is very rich in elastic fibers. Among the cells present are lymphocytes and neutrophils in relatively large quantities. During certain phases of the menstrual cycle, these two types of leukocytes invade the epithelium and pass into the lumen of the vagina. The vaginal mucosa is virtually devoid of sensory nerve endings, and the few naked nerve endings that do exist are probably pain fibers.

The muscular layer of the vagina is composed mainly of longitudinal bundles of smooth muscle fibers. There are some circular bundles, especially in the innermost part (next to the mucosa).

Outside the muscular layer, a coat of dense connective tissue, the adventitia, rich in thick elastic fibers, unites the vagina with the surrounding tissues. The great elasticity of the vagina is related to the large number of elastic fibers in the connective tissues of its wall. In this connective tissue are an extensive venous plexus, nerve bundles, and groups of nerve cells.

External Genitalia

The female external genitalia, or vulva, consist of the **clitoris, labia minora, labia majora,** and some glands that open into the vestibulum, a space enclosed by the labia minora.

The urethra and the ducts of the vestibular glands open into the vestibulum. The two **glandulae vestibulares majores,** or **glands of Bartholin,** are situated on either side of the vestibulum. These glands are homologous to the bulbourethral glands in the male. Women frequently experience inflammation of these glands and the formation of

very painful cysts. The more numerous **glandulae vestibulares minores** are scattered, found with greater frequency around the urethra and clitoris. All the glandulae vestibulares secrete mucus.

The clitoris and the penis are homologous in embryonic origin and histological structure. The clitoris is formed by two erectile bodies ending in a rudimentary **glans clitoridis** and a prepuce. The clitoris is covered with stratified squamous epithelium.

The labia minora are folds of skin with a core of spongy connective tissue permeated by elastic fibers. The stratified squamous epithelium that covers them has a thin layer of keratinized cells on the surface. Sebaceous and sweat glands are present on the inner and outer surfaces of the labia minora.

The labia majora are folds of skin that contain a large quantity of adipose tissue and a thin layer of smooth muscle. Their inner surface has a histological structure similar to that of the labia minora. The external surface is covered by skin and coarse, curly hair. Sebaceous and sweat glands are numerous on both surfaces.

The external genitalia are abundantly supplied with sensory tactile nerve endings, including Meissner's and Pacinian corpuscles, which contribute to the physiology of sexual arousal.

Mammary Glands

Each mammary gland consists of 15–25 **lobes** of the compound tubuloalveolar type whose function is to secrete milk to nourish newborns. Each lobe, separated from the others by dense connective tissue and much adipose tissue, is really a gland in itself with its own **excretory lactiferous duct**. These ducts, 2–4.5 cm long, emerge independently in the **nipple,** which has 15–25 openings, each about 0.5 mm in diameter. The histological structure of the mammary glands varies according to sex, age, and physiological status.

Breast Development in Puberty & in the Adult

Before puberty, the mammary glands are composed of **lactiferous sinuses** and several branches of these sinuses, the **lactiferous ducts**.

In girls during puberty the breasts increase in size and develop a prominent nipple. In boys, the breasts remain flattened.

Breast enlargement during puberty is the result of the accumulation of adipose tissue and connective tissue, with increased growth and branching of lactiferous ducts due to an increase in the amount of ovarian estrogens.

The characteristic structure of the gland the **lobe** in the adult woman is developed at the tips of the smallest ducts. A lobe consists of several ducts that empty into one terminal duct. Each lobe is embedded in loose connective tissue. A denser, less cellular connective tissue separates the lobes.

Near the opening of the nipple, the lactiferous ducts dilate to form the lactiferous sinuses. The lactiferous sinuses are lined with stratified squamous epithelium at their external openings. This epithelium very quickly changes to stratified columnar or cuboidal epithelium. The lining of the lactiferous ducts and terminal ducts is formed of simple cuboidal epithelium covered by closely packed myoepithelial cells.

The connective tissue surrounding the alveoli contains many lymphocytes and plasma cells. The plasma cell population increases significantly toward the end of pregnancy; it is responsible for the secretion of immunoglobulins (secretory IgA) that confer passive immunity on the newborn.

The histological structure of these glands undergoes small alterations during the menstrual cycle, eg, proliferation of cells of the ducts at about the time of ovulation. These changes coincide with the time at which circulating estrogen is at its peak. Greater hydration of connective tissue in the premenstrual phase produces breast enlargement.

The **nipple** has a conical shape and may be pink, light brown, or dark brown. Externally, it is covered by keratinized stratified squamous epithelium continuous with that of the adjacent skin. The skin around the nipple constitutes the **areola.** The color of the areola darkens during pregnancy, as a result of the local accumulation of melanin. After delivery, the areola may become lighter in color but rarely returns to its original shade. The epithelium of the nipple rests on a layer of connective tissue rich in smooth muscle fibers. These fibers are disposed in circles around the deeper lactiferous ducts and parallel to them where they enter the nipple. The nipple is abundantly supplied with sensory nerve endings.

The Breasts during Pregnancy & Lactation

The mammary glands undergo intense growth during pregnancy as a result of the synergistic action of several hormones, mainly estrogen, progesterone, prolactin, and human placental lactogen. One of the actions of these hormones is the proliferation of **alveoli** at the ends of the terminal ducts. Alveoli are spherical collections of epithelial cells that become the active milk-secreting structures in lactation. A few fat droplets and membrane-limited secretory vacuoles containing from one to several dense aggregates of milk proteins can be seen in the apical cytoplasm of alveolar cells. The number of secretory vacuoles and fat droplets greatly increases in lactation. Stellate myoepithelial cells are found between the alveolar epithelial cells and the basal lamina. The amounts

of connective tissue and adipose tissue, relative to the parenchyma, decrease considerably during lactation.

During lactation, milk is produced by the epithelial cells of the alveoli and accumulates in their lumens and inside the lactiferous ducts. The secretory cells become small and low cuboidal, and their cytoplasm contains spherical droplets of various sizes containing mainly neutral triglycerides. These lipid droplets pass out of the cells into the lumen and in the process are enveloped with a portion of the apical cell membrane. Lipids constitute about 4% of human milk.

In addition to the lipid droplets, there are a large number of membrane-limited vacuoles that contain granules composed of caseins and other milk proteins . Milk proteins include several caseins, lactalbumin, and plasmocyte-produced IgA. Proteins constitute approximately 1.5% of human milk. Lactose, the sugar of milk, is synthesized from glucose and galactose and constitutes about 7% of human milk.

Postlactational Regression of the Breasts

With cessation of breast-feeding (weaning), most alveoli that develop during pregnancy undergo degeneration through apoptosis. This includes sloughing of whole cells as well as autophagic absorption of cellular components. Dead cells and debris are removed by macrophages.

Senile Involution of the Breasts

After menopause, involution of the mammary glands is characterized by a reduction in size and the atrophy of their secretory portions and, to a certain extent, the ducts. Atrophic changes also take place in the connective tissue.

Cancer of the Breast

About 9% of all women born in the United States will develop breast cancer at some time during their lives. Most of these cancers (carcinomas) arise from epithelial cells of the lactiferous ducts. If these cells metastasize to the lungs, brain, or bone, breast carcinoma becomes a major cause of death. Early detection (eg, through self-examination, mammography, ultrasound, and other techniques) and consequent early treatment have significantly reduced the mortality rate from breast cancer.