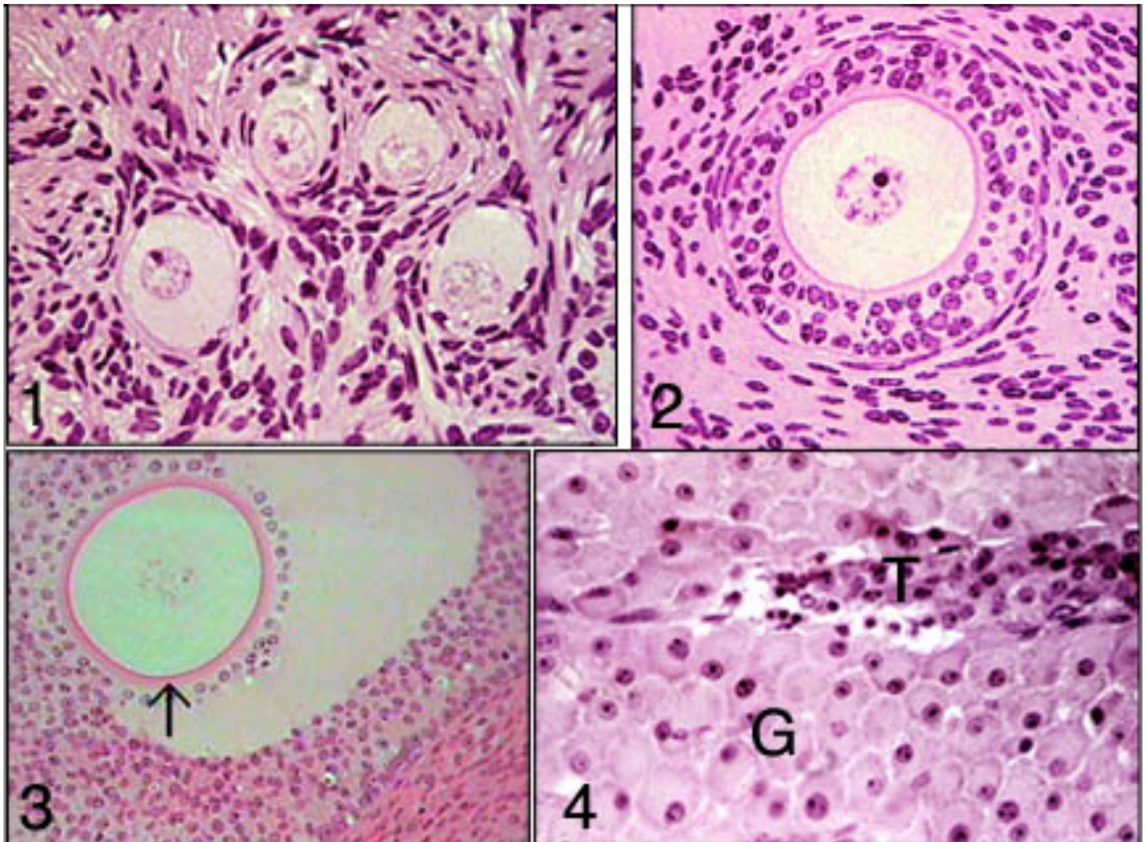
Ovary



1. Primordial follicles.
2. Primary follicle.
3. A region of a mature follicle. Identify the zona pellucida (arrow), corona radiata, and cumulus oophorus.
4. A portion of a corpus luteum illustrating granulosa lutein cells (G) and theca lutein cells (T).

The ovaries are paired oval bodies that lie on each side of the uterus, suspended from the broad ligament by a mesentery, the mesovarium. The ovaries are homologous with the testes and are compound organs with exocrine and endocrine functions. The exocrine secretion consists of whole cells - the ova - and thus the ovary can be classified as a holocrine or cytogenic gland. In cyclic fashion it secretes female sex hormones directly into the bloodstream and therefore is an endocrine gland.

Each ovary is covered by a mesothelium that is continuous with that of the mesovarium. As this membrane extends over the surface of the ovary, the squamous cells become cuboidal and form the surface epithelium of the ovary. Sections of the ovary show an outer cortex and an inner medulla, but the boundary between the two regions is indistinct. The stroma of the cortex consists of a compact feltwork of fine collagenous fibers and numerous fibroblasts. Elastic fibers are associated mainly with blood vessels and otherwise are rare in the cortex. Scattered throughout the cortical tissue are the ovarian follicles, whose size varies with their stage of development. Immediately beneath the surface epithelium, the connective tissue of the cortex is less cellular and more compact, forming a dense layer called the tunica albuginea. The stroma of the medulla consists of a loose connective tissue that is less cellular than that of the cortex and contains many elastic fibers and smooth muscle cells. Numerous large, tortuous blood vessels, lymphatics, and nerves also are present in the medulla.

Ovarian Follicles

The follicles are located in the cortex of the ovary, deep to tunica albuginea, and consist of an immature ovum surrounded by one or more layers of epithelial cells. At puberty, the human ovary contains 300,000 to 400,000 ova embedded in the cortical stroma, but only a few reach maturity and are ovulated. Approximately 300 to 400 ova are ovulated by a normal woman during her lifespan. During the menstrual cycle, several follicles (15-25) begin to grow and develop, but only one attains full maturity; the rest degenerate. The size of the follicle and the thickness of the epithelial envelope vary with the stage of development. During their growth, the follicles undergo a sequence of changes in which primordial, primary, secondary, and mature follicles can be distinguished.

Primordial Follicles

In the mature ovary, follicles are present in all stages of development. Most, especially in young women, are primordial or unilaminar follicles, which are found in the peripheral cortex, just beneath tunica albuginea. These follicles consist of an immature ovum surrounded by a single layer of flattened follicular cells that rest on a basement membrane. At this stage, the ovum is a primary oocyte, suspended in the diplotene stage of the meiotic prophase. The primary oocyte is a large cell with a prominent vesicular nucleus and nucleolus. The Golgi apparatus is well developed, and spherical mitochondria tend to concentrate in the region of the centrosome. As the primordial follicle develops into a primary follicle, changes occur in the ovum, follicular cells, and adjacent connective tissue of the cortex.

Primary Follicles

During growth of a primary follicle, the oocyte increases in size, and the Golgi complex, originally a single organelle next to the nucleus becomes a multiple structure scattered throughout the cytoplasm. Free ribosomes increase in number, mitochondria become dispersed, and granular endoplasmic reticulum, although not prominent, becomes more extensive. A few lipid droplets and lipochrome pigments appear in the cytoplasm, and yolk granules accumulate; these, however, are smaller and less numerous than in nonprimate species. As the oocyte grows, a clear refractile membrane, the zona pellucida, develops between the oocyte and adjacent follicular cells. The zona pellucida consists of glycoproteins (ZP1, ZP2, ZP3) secreted primarily by the oocytes, although surrounding granulosa cells may produce a lesser amount. Microvilli extend from the oocyte into the zona pellucida. As the ovum grows, the flattened follicular cells of the primordial follicles become cuboidal or columnar in shape and proliferate to form several layers. These cells now are referred to as granulosa cells, and the layer of stratified epithelium that they form is called stratum granulosum. Mitochondria, free ribosomes, and endoplasmic reticulum increase and the Golgi element become prominent. Irregular, slender cytoplasmic processes extend from the granulosa cells and penetrate the zona pellucida to make contact with processes from the oocyte. Gap junctions unite the processes of the oocyte and granulosa cells. While these changes occur in the oocyte and follicular cells, the adjacent stroma becomes organized into a sheath or capsule, the theca folliculi, which surrounds the growing primary follicle. The theca folliculi is separated from the stratum granulosum by a distinct basement membrane. The cells differentiate into an inner secretory layer, the theca interna, and an outer fibrous layer, the theca externa, but the boundary between the layers is somewhat indistinct. The theca externa merges imperceptibly into the surrounding stroma. Many small blood vessels penetrate the theca externa to provide a rich vascular network to the theca interna. The stratum granulosum remains avascular until after ovulation. Follicle stimulating hormone (FSH) promotes the growth of a group of follicles resulting in an increase in the production of estradiol and inhibin by the granulosa cells. As estradiol and inhibin levels rise, secretion of FSH is decreased. By the end of the first week of the cycle falling FSH levels result in the selection of a dominant follicle, the one that is most sensitive to FSH. The dominant follicle continues to grow, produces large amounts of estradiol, and is the one destined to ovulate while the others of the group are destined to become atretic. As estradiol levels increase there is an increase in the amount of LH produced by gonadotrophs in the anterior pituitary that is not secreted.

Secondary Follicles

As the follicular cells continue to proliferate, the growing follicle assumes an ovoid shape and gradually sinks deeper into the cortex. When the stratum granulosum has become 8 to 12 cell layers thick, fluid-filled spaces appear between the granulosa cells. The fluid, the liquor folliculi, increases in amount and the spaces fuse to form a single cavity called the follicular antrum. Liquor folliculi contains several growth factors, steroids, gonadotrophic hormone, and other substances many times their concentration in blood plasma. The follicle is now a secondary or antral follicle, and the oocyte has reached its full size and undergoes no further growth. The follicle, however, continues to increase in size, due in part to continued accumulation of liquor folliculi. The ovum is eccentrically placed in the follicle, surrounded by a mass of granulosa cells that projects into the fluid-filled antrum, forming the cumulus oophorus. The cells of the cumulus are continuous with those granulosa cells lining the antral cavity. Granulosa cells that immediately surround the oocyte form the corona radiata and are anchored to the zona pellucida by cytoplasmic processes.

Mature Follicles and Ovulation

In women, a follicle requires 10 to 14 days to reach maturity. The dominant follicle continues to make more and more estradiol as the follicle continues to acquire an increase in the number of FSH and later LH receptors. In addition to estradiol the growing follicle produces a small amount of progesterone. At maximum size, the follicle occupies the thickness of the cortex and bulges from the surface of the ovary. Fluid spaces appear between granulosa cells of the cumulus oophorus, and the connection between the ovum and stratum granulosum is weakened. The theca folliculi has attained its greatest development, and the theca interna assumes the cytologic characteristics of a steroid-secreting endocrine gland. Androstenedione and testosterone are important androgens secreted by the theca interna that serve as substrates for estrogen biosynthesis by the granulosa cells. The theca is thought to be influenced primarily by luteinizing hormone. An aromatase enzyme complex within the granulosa cells converts the substrates to estradiol, a form of estrogen. Estradiol then diffuses back across the limiting basement membrane of the stratum granulosum to enter the circulation via capillaries within the theca interna. Just before ovulation, the oocyte completes the first meiotic division and gives off the first polar body. Thus, at ovulation a secondary oocyte is liberated. Rupture of the mature follicle and liberation of the ovum constitute ovulation, which normally occurs at the middle (day 14) of the menstrual cycle. Immediately before ovulation, further expansion of the follicle occurs due to increased secretion of liquor folliculi. Where the follicle bulges from the ovary, its wall becomes thinner, and a small, avascular, translucent area appears. This is the stigma, or macula pellucida. The tunica albuginea thins out, and the surface epithelium of the ovary becomes discontinuous in this area. A collagenase produced by granulosa cells adjacent to the tunica albuginea appears to be responsible for the breakdown of collagen fibers at the site of the stigma. The stigma protrudes as a small blister and ruptures, and the ovum, with its surrounding zona pellucida and adherent corona radiata, is extruded along with follicular fluid. Ovarian contractility aids in ovulation. The released ovum measures about 120 µm in diameter.

Corpus Luteum

The maturing follicle that acquires LH receptors is the one of the group of developing follicles that goes on to ovulate and is critical for subsequent corpus luteum formation after ovulation. Following ovulation, the follicle is transformed into a temporary endocrine structure, the corpus luteum, which elaborates estrogens, progesterone and inhibin. The walls of the follicle collapse, and stratum granulosum is thrown into folds. Bleeding from capillaries in the theca interna may result in a blood clot in the center of the corpus luteum. At this time it is sometimes referred to as a corpus hemorrhagicum. Granulosa cells increase greatly in size, take on a polyhedral shape, and transform into large, pale-staining granulosa lutein cells. Lipid accumulates in the cytoplasm of the cells, smooth endoplasmic reticulum becomes abundant, and mitochondria show tubular cristae. Cells of the theca interna also enlarge and become epithelioid in character to form theca lutein cells. The lutein cells derived from the theca interna are somewhat smaller than granulosa lutein cells. The process of formation of granulosa and theca lutein cells is called luteinization. With the depolymerization of the basement membrane between the theca interna and the granulosa cells, capillaries from the theca interna invade the lutein tissue to form a complex vascular network throughout the corpus luteum. Connective tissue from the theca interna also penetrates the mass of lutein cells and forms a delicate network about them. The fully formed corpus luteum secretes estrogens, inhibin, and progesterone; secretion of progesterone increases rapidly during luteinization, and high levels are maintained until the corpus luteum involutes.

If the ovum is not fertilized, the corpus luteum persists for about 14 days and then undergoes involution. The cells decrease in size, accumulate much lipid, and degenerate. Hyaline material accumulates between the lutein cells and an irregular white scar of dense connective tissue, the corpus albicans, gradually replaces the corpus luteum. Over the following months, the corpus albicans itself disappears. If fertilization occurs, the corpus luteum enlarges further and persists for about the first 6 months of pregnancy and then gradually declines. Following delivery, involution of the corpus luteum is accelerated, resulting in the formation of a corpus albicans.

Estradiol, progesterone and inhibin initially suppress FSH production by gonadotrophs in the anterior pituitary, but if pregnancy does not occur and the corpus luteum declines, FSH levels rise and a new group of ovarian follicles is stimulated to develop and the cycle repeats.

Atresia of Follicles

During the early part of each menstrual cycle, several primordial follicles begin to grow, but usually only one attains full development and is ovulated. The remainder undergoes a degenerative process called atresia, which may occur at any stage in the development of a follicle. In atresia of a primary follicle, the ovum shrinks, degenerates, and undergoes cytolysis; the follicular cells show similar degenerative changes. The follicle is resorbed, and the small space that is left is rapidly filled by connective tissue from the stroma. Similar degenerative changes occur in larger follicles, but the zona pellucida may persist for a time after dissolution of the oocyte and follicular cells. Macrophages invade the atretic follicle and engulf the degenerating material, including fragments of the zona pellucida. Cells of the theca interna persist longer than those of the stratum granulosum but also show degenerative changes. The theca cells increase in size, lipid droplets appear in the cytoplasm, and the cells assume an epithelioid character, similar to that of lutein cells. The cells assume a cordlike arrangement, the cords being separated by connective tissue fibers and capillaries. The basal lamina between granulosa cells and the theca interna frequently becomes thicker and forms a hyalinized, corrugated layer, the glassy membrane. This structure is characteristic of growing follicles that have undergone atresia and aids in distinguishing a large atretic follicle from a corpus luteum. Other differences include degenerative changes in the granulosa cells and the presence of fragments of zona pellucida at the center of a follicle without an associated oocyte. Ultimately, the degenerated remains of the follicle are removed and a scar resembling a small corpus albicans is left. This, too, eventually disappears into the stroma of the ovary. In some mammals, especially rodents, clusters of epithelioid cells are scattered in the stroma of the cortex. These interstitial cells contain small lipid droplets and bear a marked resemblance to luteal cells. It is thought that these interstitial cells arise from the theca interna of follicles that are undergoing atresia. In humans, interstitial cells are most abundant during the first year of life, the period during which atretic follicles are most numerous. In women, they are present only in widely scattered, small groups. Their exact role in ovarian physiology is unknown; in humans they elaborate androgens. Other large epithelioid cells, the hilus cells, are found associated with vascular spaces and unmyelinated nerves in the hilus of the ovary. The cells appear similar to the interstitial cells of the testis and contain lipid, lipochrome pigments, and cholesterol esters. Hilus cells are most commonly found during pregnancy and at menopause, but their function is unknown. Tumors arising from these cells have a masculinizing effect.

The Ovarian Cycle

During the ovarian cycle gonadotrophin-releasing hormone (GnRH) is synthesized by neurons in the arcuate nucleus of the hypothalamus and released in pulsatile fashion to stimulate follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and release by gonadotrophs within the anterior pituitary. The receptor for GnRH on the gonadotrophs is a G-protein. The gonadotrophic hormones also are released in pulsatile fashion corresponding to the GnRH pulses. Both the FSH and LH glycoprotein molecules bind to a G-protein linked cell-surface receptor, which increases the production of cAMP in the appropriate cell. Maturation of ovarian follicles, their endocrine functions, and the phenomenon of ovulation are regulated by the follicle stimulating and luteinizing hormones. Follicle-stimulating hormone is responsible for the growth of follicles and stimulates the aromatase enzyme complex within granulosa cells to produce estrogens and inhibin. Together with FSH, luteinizing hormone induces ripening of the mature follicle and ovulation. Alone, LH converts the ovulated follicle into a corpus luteum and induces it to secrete progesterone, estrogen and inhibin. The cyclic nature of follicle formation and ovulation is the result of reciprocal interaction between the hypothalamic-pituitary axis and ovarian hormones. As production of estrogens and inhibin by the granulosa cells increases, release of FSH from the pituitary is inhibited, and the level of FSH falls below that needed for maturation of new follicles. However, the rising level of estrogen does stimulates a surge in the release of LH from the pituitary, resulting in ovulation, formation of a corpus luteum, and secretion of progesterone, estrogen and inhibin by this structure. Increasing levels of progesterone from the corpus luteum now inhibit release of LH from the pituitary, and as the level of LH declines, the corpus luteum can no longer be maintained. With decline of the corpus luteum, progesterone and estrogen levels diminish, the pituitary no longer is inhibited from secreting FSH, and a new cycle of follicle formation is initiated. The ovarian steroid hormones have only minor effects on the pituitary directly; their primary action is mediated through neurons in the hypothalamus. Both FSH and ovarian androgens stimulate granulosa cells to synthesize and release a glycoprotein called inhibin. Inhibin preferentially suppresses the synthesis and secretion of FSH by gonadotrophs in the anterior pituitary.

Age and the Ovary

The ovary looses its ability to produce viable ova with age. In women at 42 years of age the ability of the ovary to produce viable ova is reduced to about 50%. By 45 years of age ovarian failure in women is nearly 100%.