The female reproductive system consists of the paired ovaries and oviducts (or uterine tubes), the uterus, the vagina, and the external genitalia. This system produces the female gametes (oocytes), provides the environment for fertilization, and holds the embryo during its complete development through the fetal stage until birth. As with male gonads, the ovaries produce steroidal sex hormones that control organs of the reproductive system and influence other organs. Beginning at menarche, when the first menses occurs, the reproductive system undergoes monthly changes in structure and function that are controlled by neurohormonal mechanisms. Menopause is a variably timed period during which the cyclic changes become irregular and eventually disappear.

Ovaries

The two **ovaries** are solid, ovoid structures measuring about 3.5 centimeters in length, 2 centimeters in width, and 1 centimeter in thickness. The ovaries lie in shallow depressions (ovarian fossae) on each side in the lateral wall of the pelvic cavity. A layer of cuboidal surface epithelial cells (**germinal epithelium**) covers the free surface of the ovary. Just beneath this epithelium is a layer of dense connective tissue called the ***tunica albuginea***. The tissues of an ovary can be subdivided into two rather indistinct regions, an inner ***medulla*** and an outer ***cortex***. The ovarian medulla is mostly composed of loose connective tissue and contains many blood vessels, lymphatic vessels, and nerve fibers. The ovarian cortex consists of more compact tissue and has a granular appearance due to tiny masses of cells called ***ovarian follicles***.

Ovary Attachments

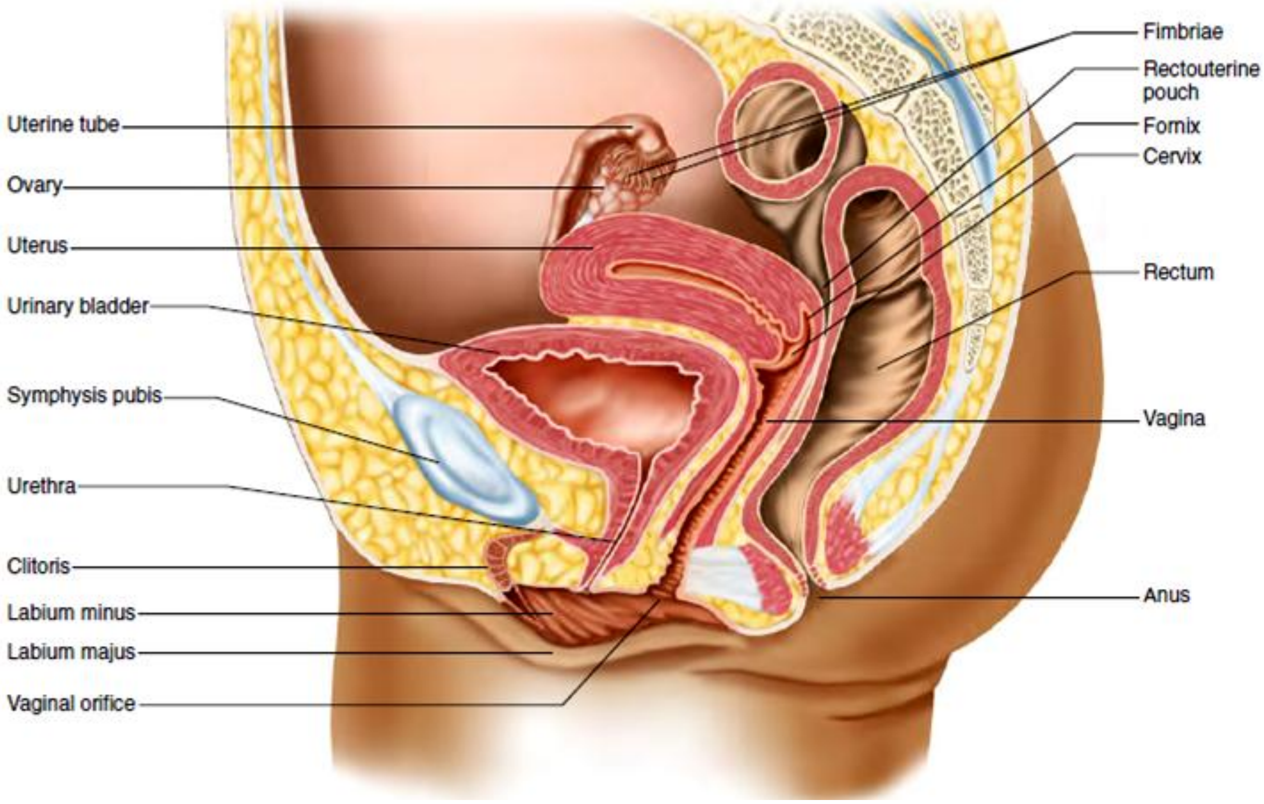
Several ligaments help hold each ovary in position. The largest of these, formed by a fold of peritoneum, is called the ***broad ligament***. It is also attached to the uterine tubes and the uterus. A small fold of peritoneum, called the ***suspensory ligament***, holds the ovary at its upper end. This ligament also contains the ovarian blood vessels and nerves. At its lower end, the ovary is attached to the uterus by a rounded, cordlike thickening of the broad ligament called the ***ovarian ligament.***

Ovary Descent

Like the testes in a male fetus, the ovaries in a female fetus originate from masses of tissue posterior to the parietal peritoneum, near the developing kidneys. During development, these structures descend to locations just inferior to the pelvic brim, where they remain attached to the lateral pelvic wall.

Early Development of the Ovary

In the first month of embryonic life, a small population of **primordial germ cells** migrates from the yolk sac to the gonadal primordia. There the cells divide and differentiate as **oogonia**. In developing ovaries of a 2-month embryo, there are about 600,000 oogonia that produce more than 7 million by the fifth month. Beginning in the third month, oogonia begin to enter the prophase of the first meiotic division but arrest after completing synapsis and recombination, without progressing to later stages of meiosis. These cells arrested in meiosis are called **primary oocytes** (Gr. *oon* , egg + *kytos* , cell). Each primary oocyte becomes surrounded by flattened support cells called **follicular cells** to form an ovarian follicle. By the



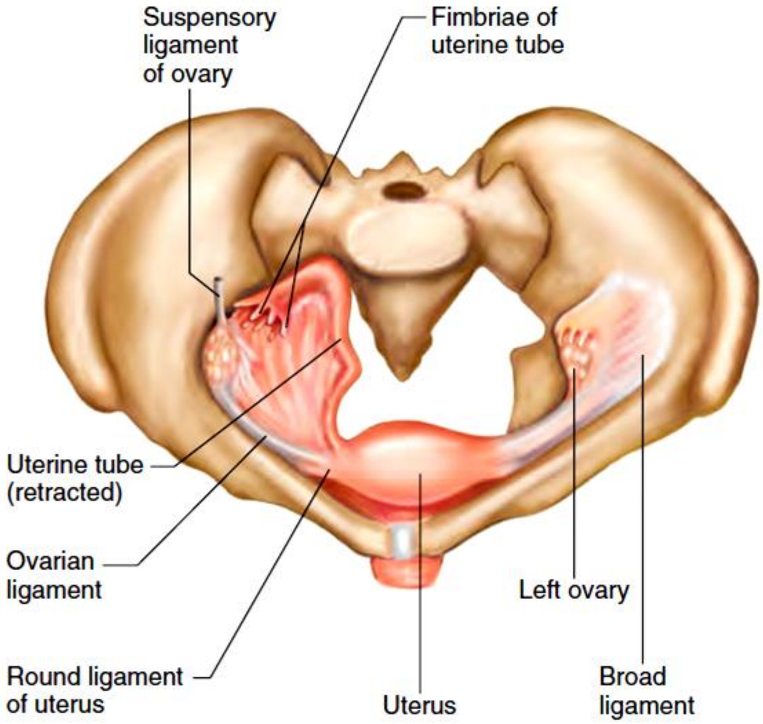


FIGURE. Position of Ovaries in human body.

seventh month of development, most oogonia have transformed into primary oocytes within follicles. Many primary oocytes, however, are lost through a slow, continuous degenerative process called **atresia**, which continues through a woman's reproductive life. At puberty the ovaries contain about 300,000 oocytes. Because generally only one oocyte resumes meiosis with ovulation during each menstrual cycle (average duration, 28 days) and the reproductive life of a woman lasts about 30 to 40 years, only about 450 oocytes are liberated from ovaries by ovulation. All others degenerate through atresia.

Ovarian Follicles

An ovarian follicle consists of an oocyte surrounded by one or more layers of epithelial cells within a basal lamina. The follicles that are formed during fetal life—**primordial follicles**—consist of a primary oocyte enveloped by a single layer of the flattened follicular cells. These follicles occur in the superficial ovarian cortex. The oocyte in the primordial follicle is spherical and about 25 μm in diameter, with a large nucleus containing chromosomes in the first meiotic prophase. The organelles tend to be concentrated near the nucleus and include numerous mitochondria, several Golgi complexes, and extensive RER. The basal lamina surrounds the follicular cells, marking a clear boundary between the follicle and the vascularized stroma. Follicular cells undergo mitosis and form a simple cuboidal epithelium around the growing oocyte. The follicle is now called a **unilaminar primary follicle**. The follicular cells continue to proliferate, forming a stratified follicular epithelium, the **granulosa**, in which the cells communicate through gap junctions.

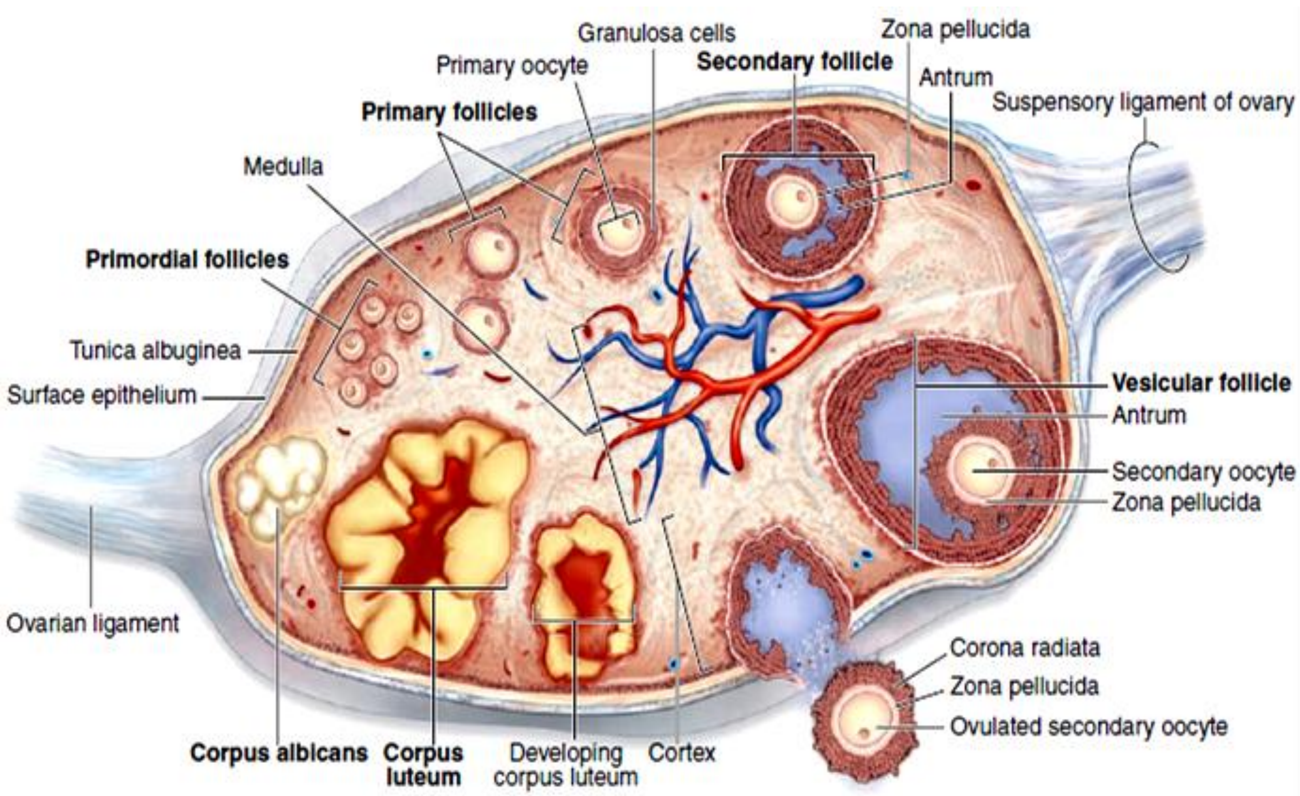


FIGURE. Cross section of Ovary.

Follicular cells are now termed **granulosa cells** and the follicle is a **multilaminar primary follicle** still surrounded by a basement membrane. Between the oocyte and the first layer of granulose cells of the growing primary follicle, extracellular material accumulates as the **zona pellucida**, 5 to 10 μm thick and containing four glycoproteins secreted by the oocyte. The zona pellucida components ZP3 and ZP4 are important sperm receptors, binding specific proteins on the sperm surface and inducing acrosomal activation. Filopodia of granulosa cells and microvilli of the oocyte penetrate the zona pellucida, allowing communication between these cells via gap junctions.

Stromal cells immediately outside each growing primary follicle differentiate to form the follicular theca (Gr. *theca*, outer covering). This subsequently differentiates further as two distinct tissues around the follicle :

■ A well-vascularized endocrine tissue, the **theca interna**, with typical steroid-producing cells secreting androstenedione. This precursor molecule diffuses into the follicle through the basement membrane, and in the granulose cells the enzyme aromatase converts it to estradiol, an FSH-dependent function. This estrogen returns to the thecae and stroma around the follicle, enters capillaries, and is distributed throughout the body.

■ A more fibrous **theca externa** with fibroblasts and smooth muscle merges gradually with the surrounding stroma.

As the primary follicles grow, they move deeper in the ovarian cortex. Within such follicles small spaces appear between the granulosa layers as the cells secrete **follicular fluid** (or **liquor folliculi**). This fluid accumulates, the spaces enlarge and gradually coalesce, and the granulosa cells reorganize themselves around a larger cavity called the **antrum**, producing follicles now called **vesicular** or **antral follicles**. Follicular fluid contains the large GAG hyaluronic acid, growth factors, plasminogen, fibrinogen, the anticoagulant heparan sulfate proteoglycan, and high concentrations of steroids (progesterone, androstenedione, and estrogens) with binding proteins. As the antrum develops, the granulosa cells around the oocyte form a small hillock, the **cumulus oophorus**, which protrudes into the antrum. Those granulosa cells that immediately surround the zona pellucid make up the **corona radiata** and accompany the oocyte when it leaves the ovary at ovulation. The single large antrum of a mature or **preovulatory follicle** (or **graafian follicle** named after the 17th-century reproductive biologist Regnier De Graaf) accumulates follicular fluid rapidly and expands to a diameter of 2 cm or more. A preovulatory follicle forms a bulge at the ovary surface visible with ultrasound imaging. The granulosa layer becomes thinner at this stage because its cells do not multiply in proportion to the growth of the antrum. A mature follicle has thick thecal layers and normally develops from a primordial follicle over a period of about 90 days.

Follicular Atresia

Most ovarian follicles undergo the degenerative process called **atresia**, in which follicular cells and oocytes die and are disposed of by phagocytic cells. Follicles at any stage of development, including nearly mature follicles, may become atretic.

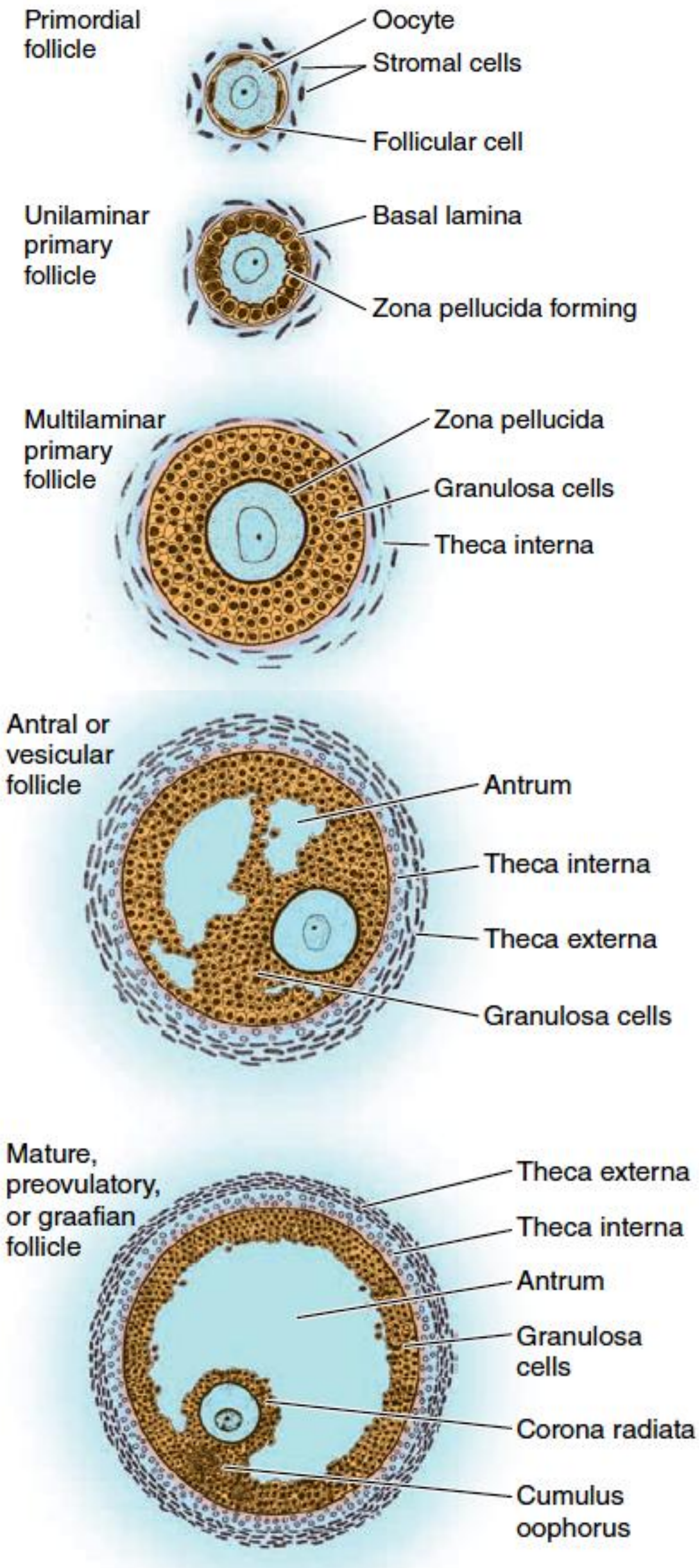


FIGURE. Stages of follicular development.

Oogenesis

Oogenesis (o′o-jen′e˘-sis) is the process of egg cell formation. Beginning at puberty, some primary oocytes are stimulated to continue meiosis. As in the case of sperm cells, the resulting cells have one-half as many chromosomes (23) in their nuclei as their parent cells, constituting one chromosome set. Unlike a primary spermatocyte, when a primary oocyte divides, the cytoplasm is distributed unequally. One of the resulting cells, called a ***secondary oocyte***, is large, and the other, called the ***first polar body***, is small. The large secondary oocyte represents a future *egg cell* (ovum) that can be fertilized by uniting with a sperm cell. If this happens, the oocyte divides unequally to produce a tiny ***second polar body*** and a large fertilized egg cell, or **zygote** (zi′go¯ t), that can divide and develop into an **embryo** (em′bre-o). An embryo is the stage of prenatal development when the rudiments of all organs form. The polar bodies have no further function, and they begin to degenerate fifteen hours post fertilization. Formation of polar bodies may appear wasteful, but it has an important biological function. It allows for production of an egg cell that has the massive amounts of cytoplasm and abundant organelles required to carry a zygote through the first few cell divisions, yet the right number of chromosomes.

Ovulation

As a follicle matures, its primary oocyte undergoes meiosis I, giving rise to a secondary oocyte and a first polar body. A process called **ovulation** (o″vu-la′shun) releases these cells from the follicle. Release of LH from the anterior pituitary gland triggers ovulation, which rapidly swells the mature follicle and weakens its wall. Eventually the wall ruptures, and the follicular fluid, accompanied by the secondary oocyte, oozes outward from the surface of the ovary. After ovulation, the secondary oocyte and one or two layers of follicular cells or the **corona radiata** surrounding it are usually propelled to the opening of a nearby uterine tube. If the secondary oocyte is not fertilized within hours, it degenerates.

Corpus Luteum

After ovulation, the granulosa cells and theca interna of the ovulated follicle reorganize to form a larger temporary endocrine gland, the **corpus luteum** (L., yellowish body), in the ovarian cortex. Ovulation is followed immediately by the collapse and folding of the granulosa and thecal layers of the follicle's wall, and blood from disrupted capillaries typically accumulates as a clot in the former antrum. The granulosa is now invaded by capillaries. Cells of both the granulosa and theca interna change histologically and functionally under the influence of LH, becoming specialized for more extensive production of progesterone in addition to estrogens. Granulosa cells increase greatly in size (20-35 μm in diameter), without dividing, and eventually comprise about 80% of the corpus luteum. They are now called **granulose lutein cells.** The former theca interna forms the rest of the corpus luteum, as **theca lutein cells**. These cells are half the size of the granulose lutein cells and are typically aggregated in the folds of the wall of the corpus luteum, which, like all endocrine glands, becomes well vascularized. LH causes these cells to produce large amounts of progesterone as well as androstenedione.

The corpus luteum that persists for part of only one menstrual cycle is called a **corpus luteum of menstruation**. Remnants from its regression are phagocytosed by macrophages, after which fibroblasts invade the area and produce a scar of dense connective tissue called a **corpus albicans** (L., white body).

The short-term fate of the corpus luteum depends on whether a pregnancy occurs. If pregnancy occurs, the uterine mucosa must not be allowed to undergo menstruation because the embryo would be lost. To prevent the drop in circulating progesterone, trophoblast cells of the implanted embryo produce a glycoprotein hormone called **human chorionic gonadotropin** (HCG) with targets and activity similar to that of LH. HCG maintains and promotes further growth of the corpus luteum, stimulating secretion of progesterone to maintain the uterine mucosa. This **corpus luteum of pregnancy** becomes very large and is maintained by HCG for 4 to 5 months, by which time the placenta itself produces progesterone (and estrogens) at levels adequate to maintain the uterine mucosa. It then degenerates and is replaced by a large corpus albicans.