Histology of the Female reproductive system

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The female reproductive system consists of the paired ovaries and oviducts (or uterine tubes), the uterus, the vagina, and the external genitalia, and the paired mammary glands, although technically, the mammary glands are part of the integument since they are highly modified sweat glands. 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.

The female reproductive system undergoes marked changes at the onset of puberty, which is initiated by **menarche**. It ranges 11-14 years.

It exhibits monthly menstrual cycles and menses from puberty until the end of the reproductive years, which terminate at **menopause**. It ranges 45-55 years.

Ovaries

Ovaries are almond-shaped bodies approximately 3-cm long, 1.5-cm wide, and 1-cm thick. Each ovary is covered by a single flat to cuboidal epithelium called the surface (or germinal) epithelium that continues with the mesothelium (peritoneum). Underneath this epithelium there is a dense connective tissue capsule (the tunica albuginea).

The ovary consists of two indistinguishable areas, an outer region called the cortex that is predominated by the ovarian follicles in different stages of maturation with a stroma of highly cellular connective tissue. The most internal part of the ovary is the medulla contains loose connective tissue and blood vessels entering the organ through the hilum from mesenteries suspending the ovary.

In the first month of embryonic life, a population of primordial germ cells migrates from the yolk sac to the gonadal primitive organ. These cells undergo mitosis producing millions of oogonia, this mitotic division ends at 11-12 weeks gestation and the clustered oogonia enter a long prophase of a first miotic division. Most of these cells undergo apoptotic cell death, but others survive and called primary oocytes (Gr. *oon*, egg + *kytos*, cell). Each becomes surrounded by flattened cells called follicular cells forming a non-growing follicle called primordial follicle. At birth there are a bout 680,000 such follicles, sometimes called (ovarian reserve), of which about 460,000 remain at puberty, the others having been lost by a process of degeneration called atresia (which mainly ends with menopause).

Ovarian follicles

An ovarian follicle consists of an oocyte surrounded by one or more layers of epithelial cells within a basal lamina.

Primordial follicles are the follicles that are formed during fetal life, consist of a primary oocyte enveloped by a single layer of flattened follicular cells. These follicles are predominating in the superficial ovarian cortex. The oocyte is spherical and about 25 µm in diameter with large nucleus (chromosomes arrested in prophase I), the organelles tend to locate near the nucleus, including mitochondria, several Golgi complexes & extensive RER. The basal lamina surrounding the follicular cells marks a boundary between the follicle and the vascularized stroma acting as a blood-follicle barrier.

Follicular growth and development

At puberty, hypothalamus begins to release GnRH in a pulsatile fashion to stimulate adenohypophysis to produce FSH. A small group of primordial follicles (recruitment) each month begins a process of follicular growth. This process involves:

- Growth of the oocyte: under the influence of FSH (follicular phase), oocyte grows rapidly reaching a diameter of 120 µm, oocyte differentiation includes the following:
    - Cellular and nuclear growth & enlargement
    - Mitochondria become more numerous & uniformly distributed
    - RER become more extensive & Golgi complexes enlarge & move peripherally.
    - Formation of a secretory granule called cortical granule containing proteases inside plasma membrane.
- Proliferation and changes in the follicular cells
- Proliferation and differentiation of the stromal fibroblast around each follicle.

Unilaminar primary follicle: first stage of follicular growth in which the oocyte undergoes growth and differentiation and the follicular cells undergo mitosis and form a simple cuboidal epithelium.

Multilaminar primary follicle: the follicular cells continue to proliferate forming a stratified follicular epithelium, which now called **granulosa cells** (containing aromatase enzyme)**,** in which cells communicated with each other via gap junctions. These cells still surrounded by basement membrane. Between the oocyte and the first layer of the granulosa cells, a layer of glycoproteins is secreted by the oocyte called **zona pellucida** (it constitutes ZP3 and ZP4 which 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 to allow communication.

Stromal cells immediately adjacent to the basement membrane of the growing follicle differentiate to form vascularized **theca cells** (Gr. theca, outer covering), which further differentiate into two distinct types of theca cells:

- **Theca interna cells**, with typically steroid-secreting cells producing androgen (androstenedione) under the influence of LH. This precursor diffuses into granulosa cells through basement membrane, in which aromatase enzyme converts it into estrogen (estradiol) under FSH effect. This estrogen returns to theca cells to be distributed through out the body to induce puberty changes.
- **Theca externa**; which is more fibrous and containing smooth muscle cells.

As the primary follicles mature, they move deeper in the ovarian cortex.

Secondary (antral) follicle: it is established when the granulosa cells begin to produce follicular fluid (liquor folliculi) that start to accumulate within spaces between the cells. The fluid-filled spaces begin to coalesce eventually form a single large cavity called an **antrum** around which granulosa cells reorganize themselves.

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 protein.

Tertiary (Graafian, mature, dominant or preovulatory) follicle: is the one follicle among the secondary follicles that will ovulate. It measures 2 cm in diameter and appears as a large bulge on the ovarian surface can be seen by ultrasound. The primary oocyte is located off center on a small hillock of granulosa cells called **cumulus oophorus** that projects into follicular fluid within the antrum. Some of the granulosa cells remain surrounding the oocyte as well as the zona pellucida, these cells called **corona radiata** and accompany the oocyte when leaving the ovary at ovulation. Granulosa cells become thinner at this stage as their division as out of proportion to the growth of the antrum. Tertiary follicle produces inhibin that shuts off FSH release by anterior pituitary to stop other follicles from growing.

Follicular atresia

It is a process by which most of the ovarian follicles undergo degeneration, when the granulosa cells and oocyte undergo apoptosis (programmed cell death) and removal by phagocytic cells. Follicles at any stage of development, including nearly mature follicles, may become atretic. During a typical menstrual cycle, one follicle becomes dominant and develops farther than the others. The dominant follicle usually reaches the most developed stage of follicular growth and undergoes ovulation, while the other primary and antral follicles undergo atresia. Although their oocytes are never used, these growing follicles produce much estrogen before atresia which is essential for preparation of the reproductive tract for a potential fertilization and pregnancy.

Ovulation

It is the hormone-stimulated process by which the oocyte in the Graafian follicle is released from the ovary. Ovulation occurs 14 days from the end of the menstrual cycle (at day 14 of a typical 28-day cycle). In the hours before ovulation, the mature dominant follicle bulging against the tunica albuginea develops a whitish or translucent ischemic area, the **stigma**, in which its blood flow has been blocked. In humans usually only one oocyte is liberated during each cycle, but sometimes either no oocyte or two or more being expelled. The stimulus for ovulation is a surge of LH in response to high levels of circulating estrogen produced by the growing follicles.

Just before ovulation the oocyte completes its first meiosis in which the chromosomes are equally divided between the two daughter cells but one cell keeps almost all of the cytoplasm called **secondary oocyte** and the other small one called first polar body. Immediately after expulsion of the first polar body the nucleus of secondary oocyte enters the second meiotic division but arrests at metaphase, and never completes meiosis unless fertilization occurs.

The increasing pressure within the follicle and weakening if the wall lead to rupture of the ovarian surface at the stigma. The oocyte and its surrounding corona radiata along with some follicular fluid are all expelled by local smooth muscle contraction. The ovulated secondary oocyte is drawn into the opening of the uterine tube where fertilization may occur. If not fertilized within about 24 hours, the secondary oocyte begins to degenerate.

It takes approximately 290 days to go from primordial to a completely developed secondary follicle and another 60 days or so for that follicle to become ovulated.

polycystic ovary syndrome (PCOS) *is the most common cause of infertility in women. It is characterized by enlarged ovaries with multiple cysts and an anovulatory cycles (irregular menses and with no follicles completing*

maturation successfully), associated with increased testosterone by ovaries and adrenals (leading to hirsutism and alopecia) and obesity and insulin resistance. Its etiology is unclear.

Hormonal regulation of ovarian growth and ovulation