Ovarian Follicles

Recall from the last lecture that:

- Number of germ cells (oogonia) is very large at birth, about 7 million and at puberty age it decreases to reach about 40000 cell.
- Oogonia divide to give primary Oocytes (both have the same no of 46 chromosomes)
- About 500 of the 40000 primary Oocytes will be ovulated and the others become atretic.
- Every month at puberty age from 10-20 primordial follicles begin to grow under the effect of hormones. The hypothalamus releases gonadotrophic hormones that stimulates the anterior lobe of pituitary gland to secret gonadotrops (FSH & LH hormones) that affect the ovaries and stimulates the growth of the primordial follicles.
- On 14th day after the start of each menstrual cycle only one graafain Follicle (mature ovum) reaches maturity and is ovulated whereas the other follicles degenerate and become atretic.
- These follicles before puberty were in the diplotene stage (arrest in prophase of meiosis I) and under the effect of hormones they complete meiosis I and give one mature graafain Follicle (secondary Oocyte).
- Secondary Oocyte completes meiosis I and enter meiosis II before ovulation and after it being released by the ovary it will stay at metaphase phase of meiosis II (lasts for few hours) and is ONLY completed if fertilization takes place. Otherwise after 48 hours if no fertilization took place, the ovum will be degenerated and meiosis II won't be completed!!

The development of Ovarian Follicles

a- primordial follicles: A primary Oocyte, together with its surrounding flat epithelial cells and stromals cell from the cortex of the ovary.

b-Unilaminar primary follicle: the flat cell become cuboidal cells and zona pellucida which is composed of several glycoproteins, is secreted by the primary oocyte and follicular cells and surrounds the oocyte. Zona pellucida is used to protect the oocyte.

Note: zona pellucida disappears in the 5th day of fertilization in the wall of the uterus before implantation.
c- **Multilaminar primary follicle**: the follicular cells become granulosa cells that divides by mitosis to increase their number. Note that the follicular cells lies on the basal lamina.

d- **Antral follicle**: the formation of antrum (follicular spaces) and thecal cells (formed outside the basal lamina from the stromal cells) begin to form and forms theca interna and theca externa.

- **Note**: Fluids (liquor folliculi) start to form in the antral spaces and this would increase the pressure forming one big space called antrum. The 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.

- A group of granulosa cells concentrates around the oocyte and forms the corona radiata. These granulosa cells accompany the oocyte when it leaves the ovary.

- During the reorganization of the granulosa cells to form the antrum, some cells of this layer concentrate at a certain point on the follicular wall. This group forms a small hillock of cells, the cumulus oophorus, which protrudes toward the interior of the antrum and contains the oocyte.

E- **MATURE GRAAFAIN FOLLICLE (Very Important)**: contain all the following parts

1. antrum  
2. Follicular fluid  
3. granulosa cells  
4. Theca interna  
5. theca externa  
6. Basal lamina  
7. Cumulus oophorus  
8. corona radiata.

**Important:**

- the parts of the mature graafain follicle that are released during ovulation are: secondary oocytes, corona radiata and some of cumulus oophorus while the other parts remain in the ovary to form corpus luteum.

- The cells of the theca interna, when completely differentiated, acquire the ultrastructural characteristics of cells that produces steroids. 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.

**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. Only a mature graafian follicle doesn’t 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.
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 noticed just after birth, when the effect of maternal hormones ceases, and during puberty and pregnancy, when marked qualitative and quantitative hormonal modifications take place.

**Interstitial Cells (theca interna 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.

**Ovarian Cycle**

- At puberty, the female begins to undergo regular monthly cycles.
- These sexual cycles are controlled by the hypothalamus. **Gonadotropin-releasing hormone (GnRH)** produced by the hypothalamus acts on cells of the anterior pituitary gland, which in turn secrete **Gonadotropins**.
- These hormones, **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** stimulate and control cyclic changes in the ovary.
- Progesterone, together with estrogenic hormones, causes the uterine mucosa to enter the **progestational or secretory stage** in preparation for implantation of the embryo.
- At the beginning of each ovarian cycle, 15 to 20 primary (preantral) stage follicles are stimulated to grow under the influence of FSH.
- Thus, FSH rescues 15 to 20 of these cells from a pool of continuously forming primary follicles.
- Under normal conditions, only one of these follicles reaches full maturity, and only one oocyte is discharged; the others degenerate and become atretic.
- In the next cycle, another group of primary follicles is recruited, and again, only one follicle reaches maturity.
- Consequently, most follicles degenerate without ever reaching full maturity.
• Primordial follicle follows 2 paths: 1) Goes from being primordial to maturing and then become atretic

2) Goes from being primordial to ripe and then forms the corpus luteum. And the growth of these cells are controlled by growth family factors.

• In cooperation, granulosa and thecal cells produce estrogens that: (Very important)
  • (a) cause the uterine endometrium to enter the follicular or proliferative phase
  • (b) cause thinning of the cervical mucus to allow passage of sperm
  • (c) Stimulate the pituitary gland to secrete LH and LH is used to convert

LH hormone reaches its highest level in the 14th day of the Menstrual Cycle (LH surge) that:
  • a) elevates concentrations of maturation-promoting factor, causing oocytes to complete meiosis I and initiate meiosis II;
  • b) stimulates production of progesterone by follicular stromal cells (luteinization)
  • (c) Causes follicular rupture and ovulation.

OVULATION:

• In the days immediately preceding ovulation, under the influence of FSH and LH, the secondary follicle grows rapidly to a diameter of 25 mm and can be viewed on the surface of the ovary.

• Coincident with final development of the secondary follicle, there is an abrupt increase in LH that causes the primary oocyte to complete meiosis I and the follicle to enter the preovulatory stage.

• Meiosis II is also initiated, but the oocyte is arrested in metaphase approximately 3 hours before ovulation. (Diplotene stage of meiosis II)

• In the meantime, the surface of the ovary begins to bulge locally, and at the apex, an avascular spot, the stigma, appears. (it’s the site of ovulation on surface of ovary)

• The high concentration of LH increases collagenase activity, resulting in digestion of collagen fibers surrounding the follicle.
• Prostaglandin levels also increase in response to the LH surge and cause local muscular contractions in the ovarian wall

• Those contractions extrude the oocyte, which together with its surrounding granulosa cells from the region of the cumulus oophorus, breaks free (ovulation) and floats out of the ovary.

**Corpus luteum:**

• After ovulation, granulosa cells remaining in the wall of the ruptured follicle, together with cells from the theca interna, are vascularized by surrounding vessels.

• Under the influence of LH, these cells develop a yellowish pigment and change into **lutean cells**, which form the corpus luteum and secrete the hormone **progesterone**

• Progesterone, together with estrogenic hormones, causes the uterine mucosa to enter the **progestational or secretory stage** in preparation for implantation of the embryo.

The corpus luteum consists of the remaining parts of mature Graafian follicle in the ovaries which are:

1- theca interna
2- theca externa
3- granulosa cells

• If fertilization occurs then: - the corpus luteum of pregnancy is formed

• If no fertilization occurs: - mature ovum degenerates

  - corpus albicans is formed

• The importance of the corpus luteum is secretion of the hormone **progesterone**.

**Corpus albicans:**

• If fertilization does not occur, the corpus luteum reaches maximum development approximately 9 days after ovulation.

• It can easily be recognized as a yellowish projection on the surface of the ovary

• the corpus luteum shrinks because of degeneration of lutean cells and forms a mass of fibrotic scar tissue, the corpus albicans.

• Simultaneously, progesterone production decreases, precipitating menstrual bleeding.
**Corpus luteum of pregnancy:**

- If the oocyte is fertilized, degeneration of the corpus luteum is prevented by human chorionic gonadotropin (HCG); a hormone secreted by the syncytiotrophoblast. (implanted egg after 9 days of fertilization and is used to form placenta) of the developing embryo. The corpus luteum continues to grow and forms the corpus luteum of pregnancy (corpus luteum graviditatis).
- By the end of the third month, this structure may be one-third to one-half of the total size of the ovary.
- Yellowish luteal cells continue to secrete progesterone until the end of the fourth month because placenta will start secreting progesterone by then.
- Removal of the corpus luteum of pregnancy before the fourth month usually leads to abortion.

**Uterus at Time of Implantation:**

Uterus parts are: fundus, body, cervix, vagina, internal orifice (os), external orifice(os)

The wall of the uterus consists of three layers:

- (a) **endometrium** or mucosa lining the inside wall;
- (b) **myometrium**, a thick layer of smooth muscle; important during labor as it’s the one that contracts.
- (c) **perimetrium**, the peritoneal covering lining the outside wall and has blood vessels like uterine artery.
**Endometrium:** it's the most important layer and shed during the Menstrual Cycle. It consists of 2 layers:

- (1) The **basalis** is the deepest one, adjacent to the myometrium; it contains lamina propria (loose connective tissues), blood vessels and uterine glands and causes proliferation (growth)

- 2) The **functionalis** contains the remainder of the lamina propria and the glands, as well as the surface simple columnar epithelium. It builds up for implantation or shed during menstrual cycle.

- Whereas the functionalis undergoes profound changes during the menstrual cycles, the basalis remains mostly unchanged.

- **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.

*Three distinct layers can be recognized in the endometrium:

- a superficial **compact layer**, an intermediate **spongy layer**, and a thin **basal layer**

- Normally, the human blastocyst implants in the endometrium along the anterior or posterior wall of the body of the uterus

- where it becomes embedded between the openings of the glands

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