UROGENITAL SYSTEM

#10

PART 1

ANATOMY

PULSE TEAM

Histology of the female reproductive system

Hi everyone and welcome to the 10th lecture of this system, in which we will discuss the histology part of the female reproductive system.

Introduction

➙ So as an introduction its worth mentioning that the developing of reproductive organs and the selection of gender is a result from presence or absence of the Y chromosome, the X chromosome does not have anything to do with it, and now let's start our lecture.

**Starting with the ovaries.

The ovaries

Histology of the coverings & inner part

✪ Coverings:

1. The outer covering is a layer of **simple cuboidal epithelium**, called the surface (or germinal) epithelium, which is continuous with the mesothelium, it is also derived from the peritoneum. (instead of tunica vaginalis in the testes)

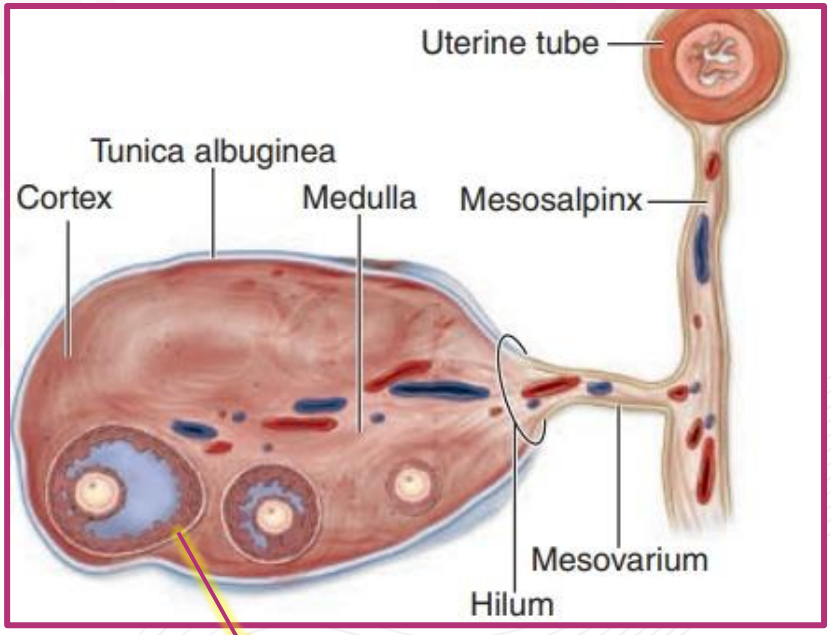
2. On the inner side, each ovary is surrounded by a **dense connective tissue** known as the tunica albuginea like that of the testes.

✪ And, if we look inside the ovary unlike the testes, we will not find lobules, instead we will find:

A. Most of the ovary consists of the cortex which is a region with a stroma of highly cellular connective tissue and many **ovarian follicles** varying greatly in size after menarche.

B. The most internal part of the ovary, the medulla, contains loose connective tissue (fibroblasts) and blood vessels entering the organ through the hilum from mesenteries suspending the ovary.

****There is no distinct border between the ovarian cortex and the medulla.**



**You need to know that the ovaries produce the gamete of the female which is called the ova (oocyte), and this oocytes & ovaries starts developing early in the fetus life, and that's why we need to go somehow more in depth in the developmental growth of the female to discuss this in comparison to the male which started developing sperms after puberty. (and that's why we did not discuss this in the previous lecture).

**And now let us get started.

Developmental growth of the ovaries (picture in page)

- Starting early in the fetus life, and talking specifically about the oocytes:

1. In the first month of embryonic life, a population of gamete stem cells, referred to as "primordial germ cells" or gonocytes, migrates from the yolk sac to the two developing gonads, and as the ovaries develop in chromosomal females, gonocytes there differentiate as progenitor cells called **oogonia** (46 chromatid & cross linking may occur).
2. These proliferate to produce interconnected ~600,000 oogonia, each associated with somatic support, by the end of the 2nd month.

After this point the number of oogonia is determined by three ongoing activities:

A. Continued mitosis
B. The onset of meiosis.
C. An apoptotic process in the female gametes called atresia.

3. The number of gametes in the ovaries peaks at ~7 million around the fifth month of gestation, by which time mitotic division has ceased and oogonia have entered **prophase of the first meiotic division**.
(doctor mentioned that it's the 3rd month in his slides but it's not important)

**Most of these cells still undergo apoptotic cell death, but others complete synapsis, genetic recombination, and meiotic arrest in prophase 1 until puberty where it will get completed, and these cells that will be here until puberty arrested is primary oocytes.

- × Each primary oocytes will then be surrounded by flattened, supportive follicular cells in a non-growing primordial follicle which we talked about in the cortex of the ovary.
- × The total number of it is sometimes referred to as the "ovarian reserve" is about 2 to 2.5 million such follicles at birth (in the slides the number is 680,000) and then ~400,000 - 460,000 remain at puberty, the others having been lost through atresia (apoptosis).
- × Because generally only one oocyte completes meiosis and ovulation during each menstrual cycle and the reproductive life of a woman is about 30-35 years, only about 450 oocytes are typically liberated from the ovaries in a lifetime. All others undergo atresia, which itself ends with menopause.

**So here we knew that the in the end of the fetus life and with birth, the growth will be arrested at the prophase of the primary oocytes first meiosis which will be completed after puberty, and also we knew that the primary oocytes will present inside an ovarian follicle, thus, the next thing we are going to talk about is how this primary oocyte with the surrounding follicle going to continue growing after puberty, and before that also, we need to know more about the ovarian follicle.

Describe the ovarian follicle (picture next page)

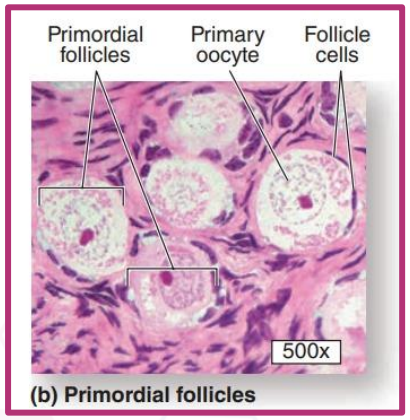
→ An primordial ovarian follicle consists of an oocyte surrounded by one or more layers of flattened epithelial cells within a basal lamina.

→ The follicles are formed during fetal life (primordial follicles), and it 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 arrested 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** surrounding the follicular cells marks a clear boundary between the follicle and the vascularized stroma and acts as a blood-follicle barrier. (instead of occluding junctions in males)



(b) Primordial follicles

Growth of follicles after puberty (picture in page 6 & 7)

And arriving at the puberty:

1. Beginning in puberty with the release of follicle-stimulating hormone (FSH) from the pituitary, which trigger a small group of primordial follicles each month to begin a process of **follicular growth**.

× This involves growth of the oocyte, proliferations, and changes in the follicular cells, as well as proliferation and differentiation of the stromal fibroblasts around each follicle.

× Selection of the primordial follicles that will undergo growth and recruitment early in each cycle, and then selection of the dominant follicle destined to ovulate يعني يتم اختيارها عشان تكون جاهزة للتلقيح that month both involve complex hormonal balances and subtle differences among follicles in FSH receptor numbers, aromatase activity, estrogen synthesis, and other variables.

**Thus, prompted by FSH, an oocyte grows most rapidly during the first part of follicular development, reaching a diameter of about 120 µm.

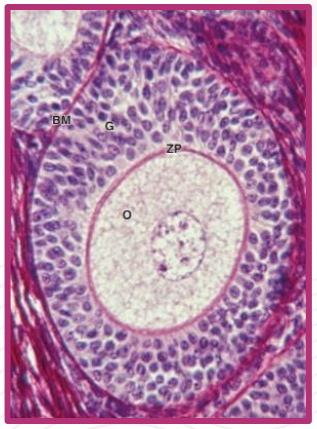
2. Follicular cells form a **simple cuboidal** epithelium around the growing oocyte, and the follicle is now called a **unilaminar primary follicle**.

3. The follicular cells continue to proliferate, forming a stratified follicular epithelium, called the **granulosa**, in which the cells communicate by gap junctions, thus now Follicular cells are termed granulosa cells, and the follicle is **multilaminar primary follicle**.

**Until now the follicle is still avascular and surrounded by BM.

→ Between the oocyte and the first layer of granulosa cells of the growing primary follicle, extracellular material accumulates as the zona pellucida, 5-10-µm thick and containing four glycoproteins secreted by the oocyte.

The zona pellucida components 3&4 (ZP3 and ZP4) are **important sperm receptors**, binding specific proteins on the sperm surface and inducing **acrosomal activation**.



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

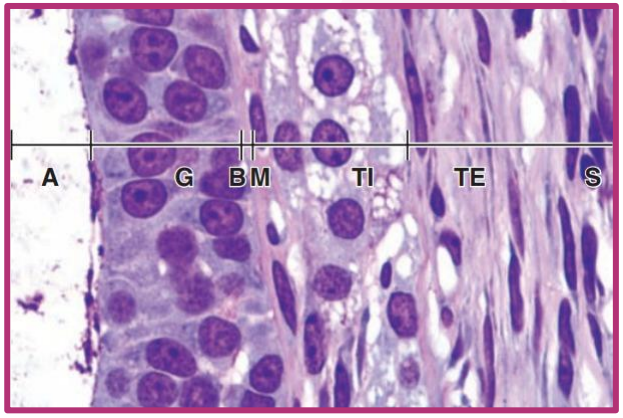
A. A well-vascularized endocrine tissue, known as **theca interna**:

× Has typical steroid-producing cells secreting androstenedione, this precursor molecule diffuses into the follicle through the basement membrane, and in the granulosa cells, then the enzyme aromatase converts it to estradiol (estrogen), and this is an FSH-dependent function, then this estrogen get out to the thecae and stroma around the follicle, enters capillaries, and is distributed throughout the body, inducing the changes characteristic of puberty.

B. A more fibrous layer known as **theca externa** with fibroblasts and smooth muscle merges gradually with the surrounding stroma.

Between the stromal layers and the granulosa cells there is a BM, which account for the blood ovary barrier.

Inside ⟷ Outside



**G: granulosa cells

**BM: basement membrane

**TI: theca interna

**TE: theca externa

**S: stroma

**A: antrum (discussed next half)

4. As the primary follicles grow, they move deeper in the ovarian cortex, and within such follicles, small spaces appear between the granulosa layers as the cells secrete follicular fluid (or antrum), this fluid then accumulates, and the spaces enlarge & unite, and the granulosa cells reorganize themselves around a larger cavity called the antrum, producing follicles now called **secondary or antral follicles**.

× As the antrum develops, the granulosa cells around the oocyte form a small hillock, called the cumulus oophorus, which protrudes into the antrum, while the tightly adhering granulosa cells immediately surrounding the zona pellucida are called corona radiata, and this accompany the oocyte when it leaves the ovary at ovulation.

× 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. {some of them secreted by cumulus oophorus to help in the ovulation later, like prostaglandin which aid in vasoconstriction in this area}

**CR: corona radiata

**CO: cumulus oophorus

**A: antrum

5. The single large antrum of a **mature tertiary (Graafian) follicle** accumulates more follicular fluid and expands to a diameter of 2 cm.

× 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 also has thick thecal layers and normally develops from a primordial follicle during a period of about 90 days.

× Here the oocyte will continue the meiosis 1 to give secondary oocyte with a polar body and a while after that the secondary oocyte will start meiosis 2 and get arrested until fertilization, when it will be completed to give the mature ovum and an additional polar body. (will be discussed in detail)

**We need to know that during the growing of the follicles each month only one managed to complete its growth and the others is gone by atresia, so what is that?

Follicular Atresia (Apoptosis)

→ It is worth mentioning that most ovarian follicles undergo the degenerative process called **atresia** during the growth process, in which only one get selected and recruited to complete the process and the other follicular cells and oocytes undergo apoptosis and removal by phagocytic cells, thus follicles at any stage of development, including nearly mature follicles, may become atretic.

→ Atresia involves detachment of the apoptotic granulosa cells, autolysis of the oocyte, and collapse of the zona pellucida, then macrophages invade the degenerating follicle and phagocytose the apoptotic material and other debris.

→ Thus, we surely can say, during a typical menstrual cycle, one follicle becomes dominant and develops farther than the others, this 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 directly used, the large growing follicles surrounding their oocytes will produce much estrogen before becoming atretic each month, thus as described later, **this estrogen** stimulates preparation of the reproductive tract to transport and sustain the embryo if the oocyte from the dominant follicle is fertilized.

Typically, during a woman's fourth decade, menopause begins when atresia and ovulation have reduced the ovarian reserve to fewer than about 1000 follicles.

**And now, let's discuss the oocytes growth after puberty & the ovulation process in detail.

Ovulation & oocytes after puberty (picture in page 6)

→ Ovulation is the hormone-stimulated process by which the oocyte is released from the ovary. Ovulation normally occurs midway through the menstrual cycle, that is, around the 14th day of a typical 28-day cycle.

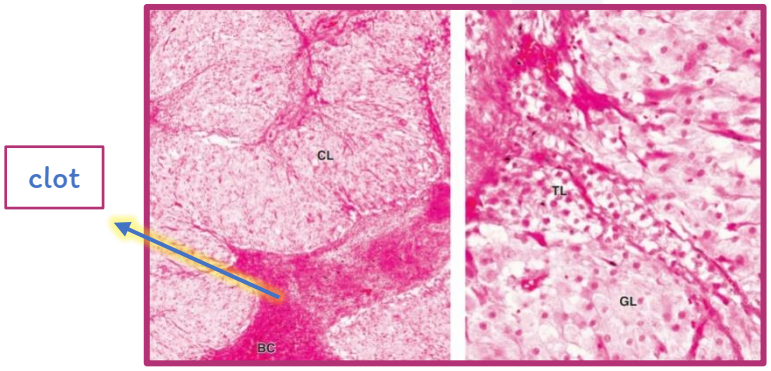
1. In the hours before ovulation, the mature dominant selected follicle bulging against the tunica albuginea develops a whitish or translucent ischemic area, called the **stigma**, in which tissue compaction has blocked blood flow.

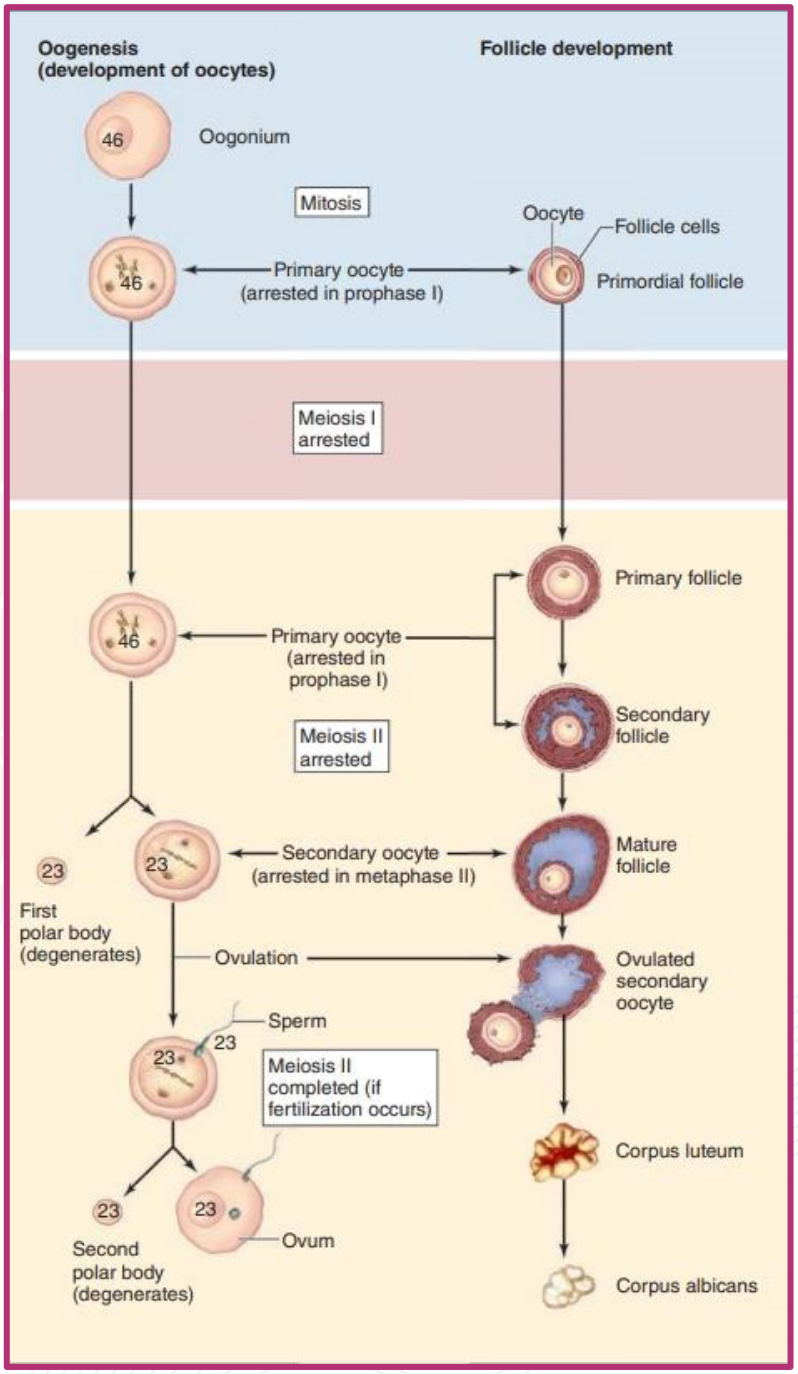
**In humans, usually only one oocyte is liberated during each cycle, but sometimes either no oocyte or two or more simultaneous oocytes may be expelled.

2. Just before ovulation the oocyte completes the first meiotic division, which it began and arrested in prophase during fetal life, the chromosomes are equally divided between the two daughter cells, but one of these retains almost all the cytoplasm, and that cell is now called the **secondary oocyte** (46 chromosome) and the other becomes the **first polar body**, a very small nonviable cell containing a nucleus and a minimal amount of cytoplasm.

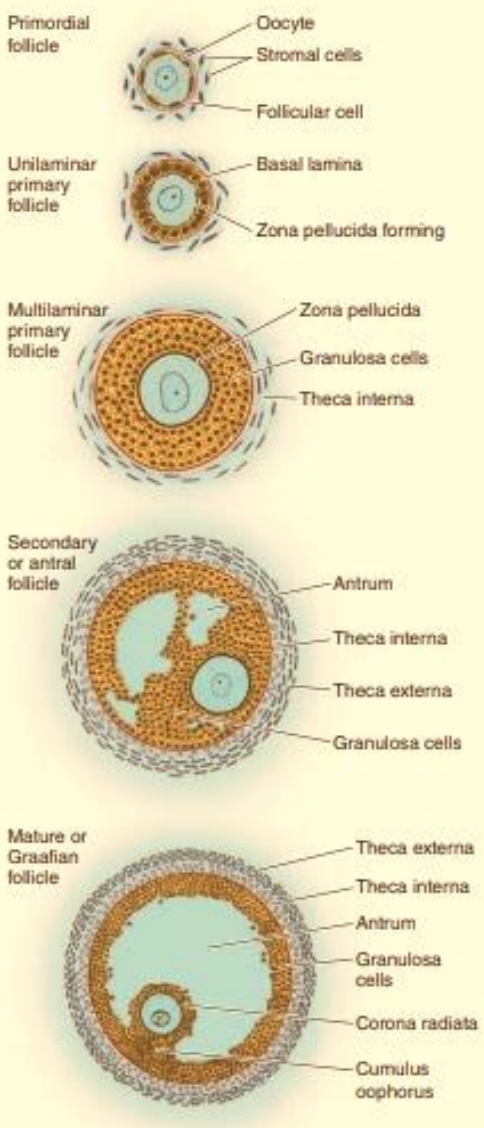
3. Immediately after expulsion of the first polar body, the nucleus of the oocyte **begins the second meiotic division** **but arrests at metaphase** and never completes meiosis unless fertilization occurs, where it will complete the meiosis process giving a mature **ovum** & **another polar body**.

✪ **After ovulation**, the granulosa cells and theca interna of the ovulated follicle reorganize to form a larger temporary endocrine gland, called the **corpus luteum**, in the ovarian cortex, thus we can say that ovulation is followed immediately by the collapse and folding of the granulosa and thecal layers of the follicle's wall to form a new structure, and blood from disrupted capillaries typically accumulates as a clot in the former antrum, and the granulosa is now invaded by capillaries, and after a while this corpus luteum degenerates to form what is known as corpus albicans.





Another picture for the follicles



****And now, because all these processes are heavily influenced by hormones, lets talk about the hormonal regulations upon them.**

Hormonal regulations after puberty

Before we start you need to know that (FSH & LH**) are both hormones that are secreted from the anterior pituitary gland by stimulation of the hypothalamus, both hormones together with the female (**estrogen, progesterone**) and male (testosterone) hormones influence each other secretion all along, oh, and there is another hormone (which you already knew) called the **inhibin**, and this hormone will work as negative feedback, whenever its secreted alongside other hormones.

Follicular Development

× Follicular development begins in the ovaries under the influence of FSH (Follicle-Stimulating Hormone) from the pituitary gland. FSH secretion is stimulated by GnRH (Gonadotropin-Releasing Hormone) from the hypothalamus.

Dominant Follicle Development

× In the days preceding ovulation, one dominant follicle starts secreting higher levels of estrogen.

Surge & peak of LH (Luteinizing Hormone)

× Higher estrogen leads to increased GnRH levels which will trigger a surge (peak) of LH release from the pituitary gland which will induce ovulation after a while.

Events in and around the Dominant Follicle

× These events are induced by LH and happens before ovulation:

A. Meiosis I is completed, yielding a secondary oocyte and a first polar body.
B. Granulosa cells produce follicular fluid with various components.
C. The ovarian wall at the stigma weakens.
D. Smooth muscle contractions begin in the theca externa, leading to the rupture of the ovarian surface at the stigma, preparing for ovulation.

Ovulation

× The oocyte, along with its surrounding corona radiata and follicular fluid, is expelled from the ovary due to smooth muscle contractions and **leaves the corpus luteum behind**, and this is induced by the LH.

× And here the ovulated secondary oocyte adheres loosely to the ovarian surface in the viscous follicular fluid, to be then drawn into the uterine tube to either be:

A. Fertilized there within 24 hours.
B. Degenerated after 24 hours of being not fertilized.

**And now, because we talked about the fate of the oocyte after ovulation either fertilization or degeneration, we will also have to talk about the surrounding follicle which became corpus luteum.

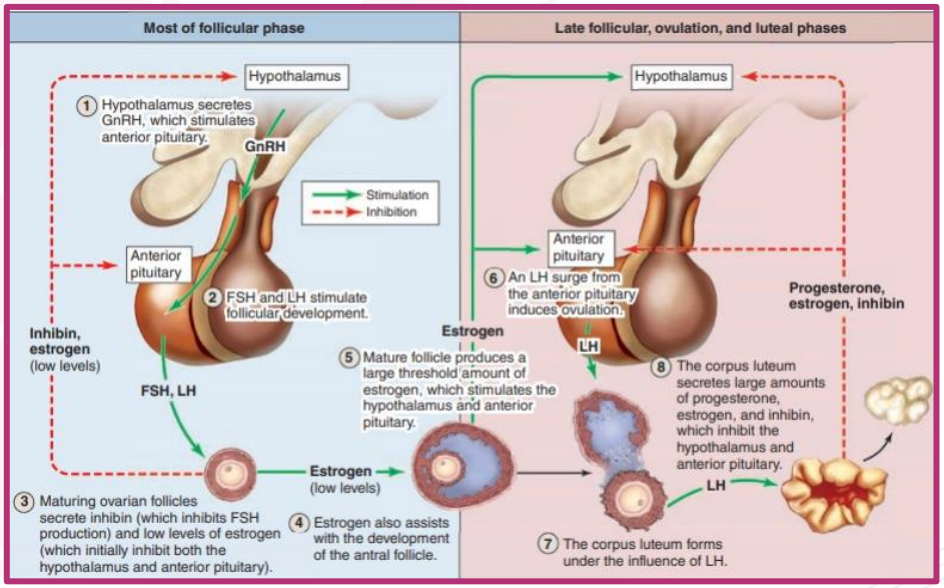
Fate of the Corpus Luteum

A. Complete of menstruation: **without fertilization** of oocytes pregnancy would not occur, thus, the corpus luteum secretes progesterone (& estrogen) normally for about 10-12 days, after which it undergoes apoptosis and regresses to **leave the corpus albicans as remnant**.

× The secretion of progesterone from the regressing corpus luteum leads to menstruation, which involves the shedding of part of the uterine mucosa.
× Also, the Estrogen produced by the active corpus luteum inhibits FSH release from the pituitary, thus, after the corpus luteum degenerates, FSH secretion increases back to normal, stimulating the growth of another group of follicles and initiating the next menstrual cycle.

**thus, they have negative feedback with inhibin in this stage

B. Pregnancy: If **the oocyte is fertilized**, pregnancy occurs, and hCG (human chorionic gonadotropin) maintains and promotes the corpus luteum's growth to secrete progesterone to maintain the uterine mucosa, because in pregnancy **if the corpus luteum degenerate here and complete the menstruation, this will lead to the embryo death**, thus it maintain the corpus luteum for several months before being replaced by a large corpus albicans, and that's when the placenta can produce adequate progesterone independently of the corpus luteum.



Extra information about corpus luteum

× Both granulosa cells and theca interna change histologically and functionally under the influence of LH to form the corpus luteum, thus, becoming specialized for more extensive production of progesterone in addition to estrogens:

A. 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 **granulosa lutein cells** and have lost many features of protein-secreting cells to expand their role in conversing androstenedione into estradiol (estrogen).

B. The former theca interna forms the rest of the corpus luteum, as **theca lutein cells**, and these cells are half the size of the granulosa lutein cells and are typically aggregated in the folds of the wall of the corpus luteum, which, like all endocrine glands, becomes well vascularized. Luteinizing hormone causes these cells to produce large amounts of progesterone as well as androstenedione.

****Estrogen & Progesterone here will have a negative feedback effect**

× Remember that there are remnants from the regressing corpus luteum that are phagocytosed by macrophages, and fibroblasts invade the area, producing a scar of dense connective tissue called a corpus albicans.

Oocytes	Spermatocytes
Limited	Nearly unlimited
Started during fetal life	Started after puberty
Every oogonium give one oocyte	Every spermatogonium give 4 sperms

End of part 1