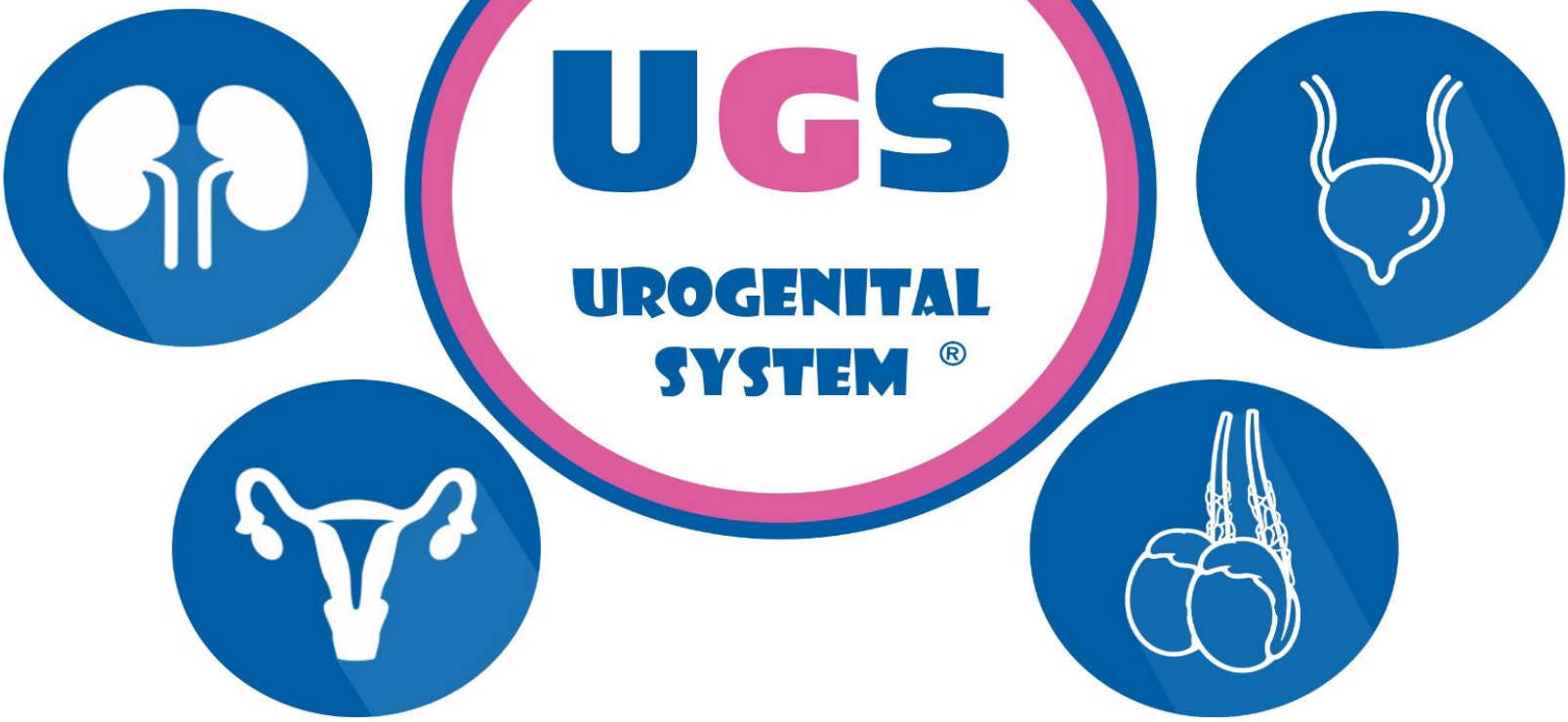


Sheets Physiology

Number	13
Doctor	Mohammad
Done By	Renad zakaria
Correction	---

Before we start:

- I didn't follow the record order, for organizing purposes.

- I added extra information from our text box which is Guyton 12th edition, pages 987- 997, actually I did so because I felt it needed (since there are things that needed further explanation) so pardon me.

- You will find some information in the slides not mention here, so you need to go through them.

- I hope you find this sheet easy to understand, it's a difficult one so I tried my best to make it simple so wish you all the best.

In the previous lecture:

- We talked about male and female reproductive systems in general and we went through some differences between them, in this lecture we may mention some differences.

- In females, we said that the oocyte start as oogonia in the uterine life, then this oocyte will sleep (mostly they will degenerate) for at least 10 years (until puberty). When the puberty state initiate, there will be recruitment of the primordial follicles that will end in production of oocyte.

Primordial follicle consists of an oocyte surrounded by a single layer of flat, supporting granulosa cells

In our lecture we will go through and talk about 3 temporary endocrine glands which haven't consistent pattern of secretions but they are growing, increasing then they will degenerate and because of that we have certain changes in secretions concentration so the homeostasis won't be in the daily basis within a large concept.

- Lets carry on what we were talking about in the previous lecture, In general:

Somehow when reaching the puberty state we will have developmental aspect of hypothalamic- pituitary (don't mind this now), so more important we end up having **follicle stimulating hormone (FSH),** this hormone will initiate the recruitment of the primordial germ cells. These follicles will grow until they ovulate and release the oocyte, the oocyte will be picked by the fimbriated end of the fallopian tube and will go through it.

- Also in the previous lecture we said that the primordial follicle has the original oogonia that will give the destined oocyte. We also talked about how the numbers of the follicles decrease in the intrauterine life and the developmental stage.

**Let's talk about some histology just for understanding purposes, in adult female, the ovary look like:

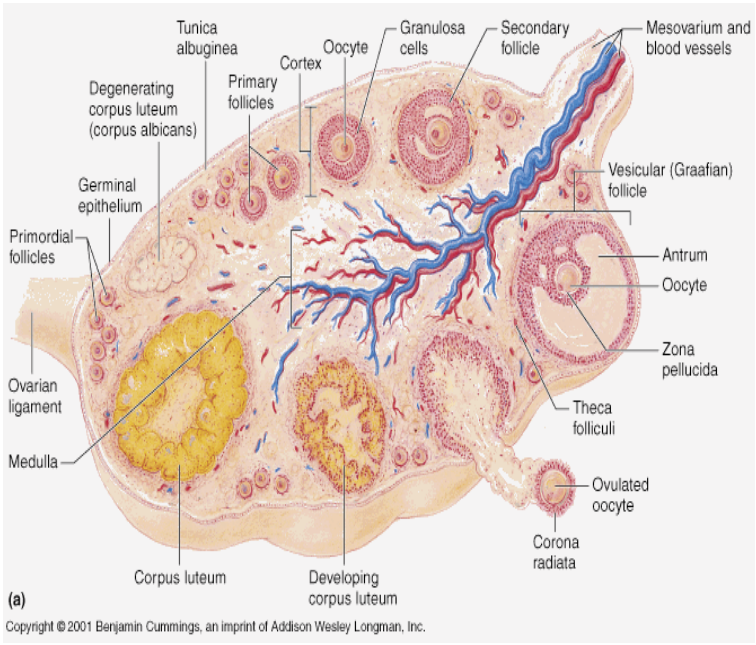


Figure 1:

- The ovary has cortical and medullary areas.

- If you look at the cortex you will notice it's just a few millimeters and inside it you will find all primordial germ cells.

- So in the core of the ovary ovary you won't see any germ cells since they all reside in the cortex.

For explaining purposes please read this extra piece of information:

During fetal life, the outer surface of the ovary is covered by a germinal epithelium, which embryologically is derived from the epithelium of the germinal ridges. As the female fetus develops, primordial ova differentiate from this germinal epithelium and migrate into the substance of the ovarian cortex. Each ovum then collects around it a layer of spindle cells from the ovarian stroma (the supporting tissue of the ovary) and causes them to take on epithelioid characteristics; they are then called granulosa cells. The ovum surrounded by a single layer of granulosa cells is called a primordial follicle. The ovum at this stage is still immature, requiring two more cell divisions before it can be fertilized by a sperm. At this time, the ovum is called a primary oocyte.

After this primordial follicle stimulated by FSH and then follows growth of additional layers of granulosa cells in some of the follicles; these follicles are known as primary follicles.

Guyton. Ch 81, page 987,989

**** So how we start this recruitment? Let's go through the details...**

- keep in mind that in oogenesis we primary concern about the oocyte but don't neglect the importance of what surrounding the oocyte, this crosstalk is all needed to develop the follicle and we define this crosstalk by **maturation**.

So all the things that we will discuss for now concern to the follicle not the oocyte, be careful!!

** After puberty, the pituitary gland start to secrete **FSH** in certain concentration that will stimulate certain development on the primordial follicle, it will awaken the oocyte and stimulate the layer around it. These surrounding layers start to develop in term of mitosis and have the ability to secrete some hormones like estrogen which named granulosa cells.

FSH, secreted from the anterior pituitary gland, and cause accelerated growth of 6 to 12 primary follicles each month (recruitment). The initial effect is rapid proliferation of the granulosa cells, giving rise to many more layers of these cells and so more estrogen production. Such effect last from 5- 14 days.

- The functions of FSH been tested by blocking it, so after such a test proceed there will be no more follicle recruitment.

- The granulosa cells that have receptor for FSH and go under FSH stimulation produce estrogen, these cells are sensitive to their estrogen production so there is will be increasing in their mitotic function (estrogen by itself a strong mitotic element on these cells).

- In the development and recruitment of the follicle there is a mass of cells that developed which named **Theca;** these cells are capable to produce androgens not estrogen!!

So keep in mind the following:

➢The granulosa (follicular) cells are the only ovarian cells that have FSH receptor.

➢ FSH produce estrogen from follicle.

➢ FSH with estrogen will promote the development of LH receptors on thecal and granulosa cell.

➢ So again, we said FSH works on producing estrogen, and LH works on thecal cells to produce androgen.

Physiologically, After few days FSH concentration start to decline which cause reduction in the support of most of the follicles, so no more follicles development and only one follicle will continue to grow.

** But what if we give excess amount of exogenous FSH (pharmacological effect)?

We will recruit more follicles and get them out of their primordial stage and maintain them. So in IVF (In Vitro Fertilization) we give FSH for 6-7 days and they maintain it. If we stop given FSH which is pharmacological not physiological there will decline in the follicle recruitment & maintenance.

So what accelerate & increase follicles growth is the following:

(1) Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors; this causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH.

(2) The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion.

(3) The increasing estrogens from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion as well.

** After the early proliferative phase of growth, lasting for a few days, the mass of granulosa cells secretes a follicular fluid that contains a high concentration of estrogen, Accumulation of this fluid causes an antrum to appear within the mass of granulosa cells (we will have one space)so named the **antral follicle**, this is stimulated mainly by FSH. Once the antral follicles begin to grow, their growth occurs almost explosively, the ovum itself also enlarges.

It's worth to know that estrogen have multiple sources for production:

- We have androgens that secreted by adrenal cortex & ovarian thecal cells wich convert to estrogen in the granuluosa cells.

- The granulosa cells of the ovaries also produce estrogen.

- Most of this estrogen will go to circulation.

** So we end with ***rapidly rising pattern of estrogen concentration***.

** Lets summarize all these steps as once:

High FSH production → follicle recruitment & proliferation →multi layers of granulosa layers that produce estrogen and thecal cells that produce androgens → formation of antral follicle → enlargement of this follicle → at the end on follicle will formed and the others will involute.

If you are interested to know the mechanism of Atresia (which means the degeneration of those ovarian follicles which do not ovulate) and how just one follicle goes out, read page 990.

Now let's compare it with the male reproductive system:

In male we said that androgen producing from leydig cells, most of it will goes to the circulation and few of it goes to the serotoli cells. In serotoli cells we have small amount of estrogen secretion mainly for local use and most of goes to the circulaton, comparing to females.

Let's carry on what we were talking about:

So after formation of antral follicle it will increase in size (its diameter will increase up to 10 fold), this will increase pressure inside. Some of the secreted substance has proteolytic activity that lead to weak bond in the wall. The pressure, enlargement and weak bond in the wall all occur under the stimulation of FSH & LH.

-The follicle phases are:

Primordial follicle → primary follicle → antral follicle → big antral follicle

We can call this big follicle, pre ovulatory follicle or big graafian follicle

- what will happen If we go to a certain stage where the follicle is around 5-6 millimeters and aspirate the oocyte?

The oocyte will continue developing to further stages, when place it in vitro.

**look at the figure below:

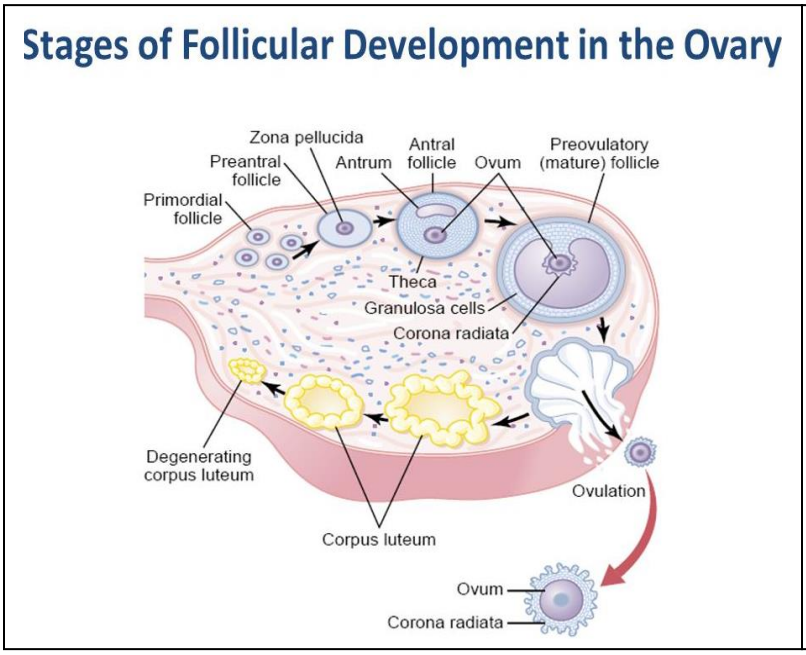


Figure 2; shows:

- Follicular development.
- as we said earliar FSH recruit 6-12 follicles only one of them will go under the stages we mention and the other will degenerate, as you know decrease FSH is one of the causes for this to happen. Since the maintaining of FSH maintain the follicles.

→this is physiological

- But if we give exogenous FSH, FSH will maintain and so as the follicle, so more than one follicle will survive & go through these stages. →pharmacological effect

Estrogen effect:

In the blood circulation the levels of the estrogen vary day by day from low amount, high amount and then huge amount, last for 2-4 weeks but not less than 10 days.

- The estrogen that enters the circulation will reach the hypothalamus and pituitary which induce the production mainly of FSH & LH, now we concerned more about LH.

- We have two hypotheses that explain the mechanism which estrogen stimulates LH production, since we don't really know the mechanism:

1- Continuous progressive increase of exposure to estrogen will alter the responsiveness of the arcuate nucleus in the hypothalamus from suppression to stimulation.

2- We have certain nuclei in the hypothalamus found in deep sleep, but if they expose to continuous rising level of estrogen, they will response in positive feedback.

These two hypotheses end in positive feedback in term of LH secretion due to continuous rising level of estrogen.

- Such effect called **estrogen induced LH surge effect**.

The increase of LH concentration will reach a certain level.

So what are the effects of LH that increase in this positive feedback?

1-LH will stimulate the thecal cells for more androgen production, so we will end up with more estrogen production.

2- Makes changes in the follicle wall by forming weak bonds.

3- Cause follicle enlargement and increase the pressure inside.

All of this will lead to follicle rupture and the release of the oocyte.

** I recommended reading pages 996 and 997 for more explanation on hypothalamus- pituitary relation and this positive feedback mechanism, it's really important to know since I can't put it all in the sheet.

So all the things that we went through concern with the follicles not the oocyte, Remember when we said there is crosstalk between the oocyte and its rurrounding. We also explain the fuction of FSH and few about LH on the follicles. What secreted from these follicles needed for further development of the oocytee that concern with resuming the mitotic devision of the oocyte.

Now let's go in details about oocyte development:

Actually before start talking about it, remember what we took in the 1st year with doctor Amjad that All eggs are arrested at an early stage (prophase I) of the first meiotic division as a primary oocyte (primordial follicle). 

Once the follicle rupture and release the oocyte, the first meiotic division takes place in the oocyte. It's important to know that ovulation start with this meiotic devision. If there is no follicle rupture there is no ovulation.

- This 1st meiotic division has criteria's which are:

1- A diploid cell becomes 2 haploid (23 chromosomes) daughter cells, each chromosome has two chromatids. One cell becomes the secondary oocyte the other cell forms the first polar body.

2- So it will give two cells, big one that has most of the cytoplasm (2nd ry oocyte) and the other small cell has few cytoplasms (polar body).

The polar body is a small cytoplasmic exclusion body formed to enclose the excess DNA formed during the oocyte (egg) meiosis and following sperm fertilization.

- So the big cell (oocyte) will go out from the ovaries to the fallopian tube. The other cells are essential structure to the ovary.

By now we end talking about the first endocrine gland which start from primordial follicle (recruitment) and end with its rupture (ovulation). Special characteristic of it is the progressive rapid increase of estrogen.

Ovulation

- We know that the typical menstrual cycle is 28 day, at day 14 the ovulation will occur.

- And by now you also knew that follicular or proliferative phase (day 4 →14).

** Let's review what we said before:

The follicle before ovulation is growing under the effect of FSH→ This Graafian follicle will keep growing under the effect of FSH until part of its wall becomes thin → then it will rupture releasing the ovum outside.

** Once the oocyte comes out from the ovary to the pelvic cavity, we have almost seization of all the secretion.

The remaining granulosa and thecal cells will change rapidly. Such changes occur due to LH secretion. LH will stimulate these cells to increase their lipid material, cause acute enlargement of these cells and increase their vascularization. So we retain the capacity to produce the two hormones estrogen and progesterone (remember from the beginning we have the ability to produce estrogen). The whole process named **luteinization**.

** It's worth to know that these granulosa and thecal cells will transform to **lutien cells**, the total mass of these cells together named **corpus luteum**.

** In the previous lecture we said that progesterone is a precursor for estrogen, since it's a precursor for all steroid hormones.

- The progesterone will be released to the circulation and some estrogen released outside.

So what left in the ovaries will be:

1- Stimulated by ovulation.
2- Maintained by luteinizing hormone LH.
3- Increase secretion of estrogen and progesterone.
4- Change their structure for around 7- 10 days then it will start to degenerate.

- By 14 days from this, programmed cell deaths (apoptosis) take place and the cells die.

- After the death of these cells, progesterone and estrogen level will reach zero.

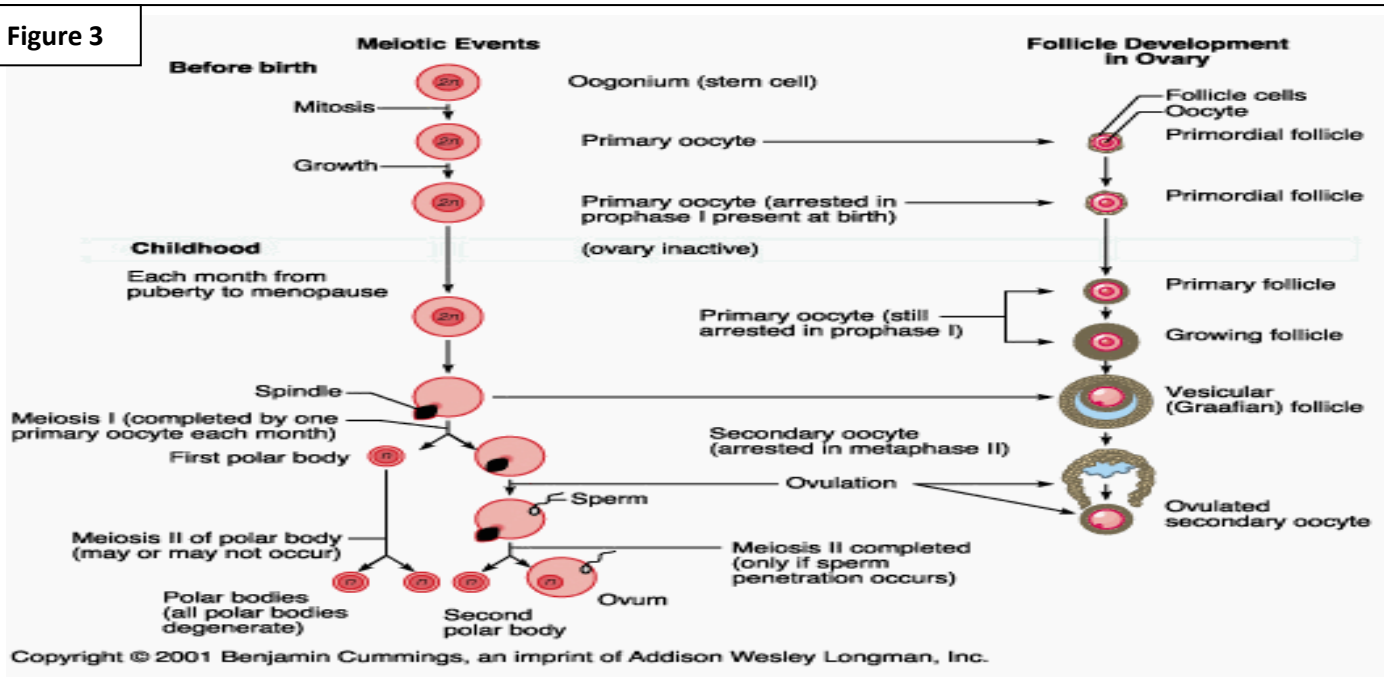
By now we end talking about the 2nd endocrine gland that start by ovulation and ended by death. It's characterized by increase secretion of estrogen and progesterone.

But what about the secondary oocyte with its polar body that completed the 1st meiotic division?

This oocyte surrounded by a cluster of granulosa cells and corona radiata and its polar body, It will survive for 16hours and maximum 24 h (it will live along with the polar body). After that it will degenerate, so degeneration of the oocyte takes place when it completed its1st meiotic division. This occurs every month unless we have fertilization which will survive and complete the 2nd meiotic division (that's not important now).

** The figure below summarizes all the stages:

Figure 3



** Look at the figure below that shows the plasma concentrations of the hormones we were talking about; we will go in further details on each hormone:

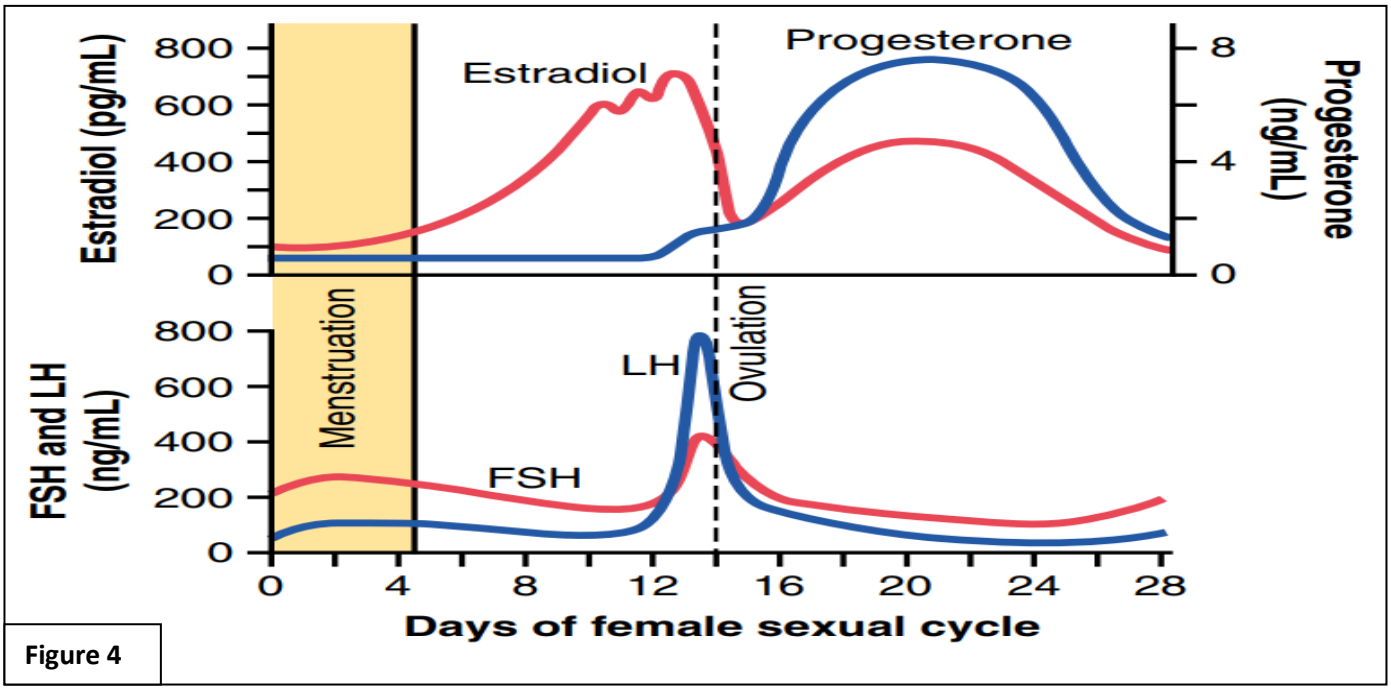


Figure 4

1- **Estrogen**; will rise (due to the mechanism we explained before) then decline when the apoptosis occur. Estrogen decline in small levels after ovulation since the granulose and thecal cells are no longer there after follicle rupture, so what maintain and keeps it production is the corpus luteum.

2- **LH**; will increase due to estrogen positive feedback. Then it will decrease suddenly, so it shunts from positive to negative feedback. As you see on the figure the LH increase with estrogen because of positive feedback. Essential for ovulation if not found we will have failure in ovulation. The reduction of LH caused by small amount of estrogen and to lesser extent by progesterone (negative feedback). Corpus luteum may also reduce it in such a mechanism. If you interested read page 997.

3- **FSH**; as you see in the figure also increase then decline especially after ovulation when follicle recruitment and maintain not needed. Its mechanism of decline follow the mechanism of LH declining. It's essential for development & recruitment of the follicles.

4- **Progesterone**; its rising level occur after ovulation as we said before. And its decline to the same reason of estrogen when the oocyte go through apoptosis.

** Then this cycle will repeat itself every month, started by increase FSH releasing.

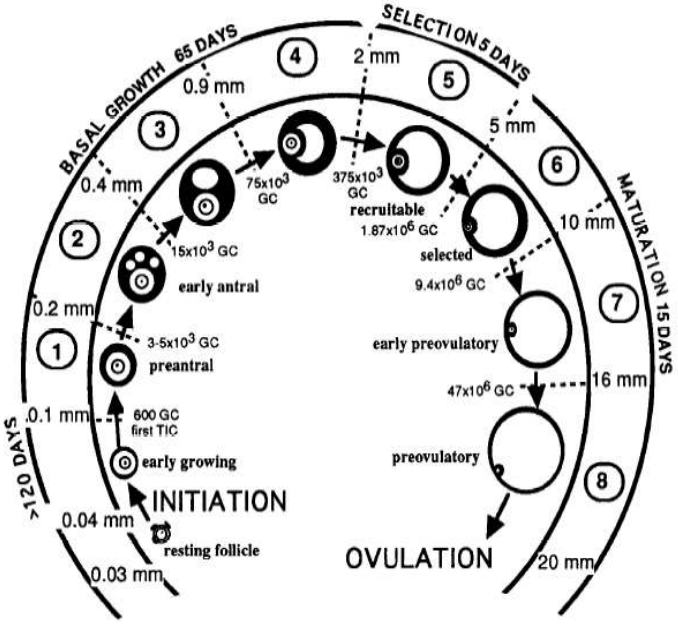


Figure 5;shows:

- The different diameters of the follicles through its phases.

- It starts with small diameter .1mm and end with follicle with big diameter which is 1 inch.

- If we still have FSH, what recruited won't be degenerated.

** For an ovulation to occur we need:

1- LH.
2- Certain structure and volume.
3- Certain developmental pattern.
   If something wrong happen with one of them, the ovulation won't take place, where the oocyte won't leave the follicle and the follicle will stay in the ovary. Staying of the follicle in the ovary will develop disease such as cysts and tumors.

** In the previous lecture; we talked about FSH & LH regulation, such regulation happen through testerone regulate and inhbin that released from serotoli cells. That was in male reproductive system **<u>so what about females?</u>**

We have what called ***mullerian inhibitory factor*** or ***anti mullerian hormone (AMH)***. This hormone produced from growing small to medium sized follicle, its FSH independent.

AMH function, we don't its exact function but we suggest:

It's a developmental marker for the follicle since its express the recruitment. If we have less recruitment and less small to medium size follicle, AMH concentration will be high.

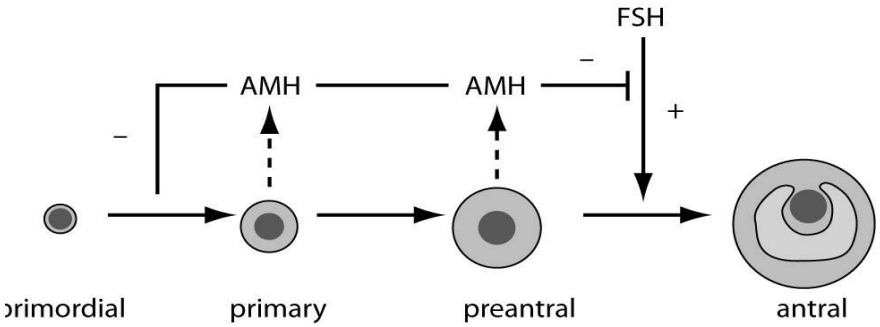


Figure 6; summarizes its function.

It's Stable under various conditions like:

–OCP

–Pregnancy

–Menstrual cycle

Remember; we said that there is a crosstalk between the oocyte and its surrounding. Actually there is multiple communications you just need what we took. So the take home message is that oocyte sense and receives messages from its surrounding. You need to know this communication is more complex than that but you need to know what we talked before.

In the previous lecture we also talked about aromatase and its function and it secreted from serotoli cells in the males. Here in female system you will find aromatase in the granulosa cells which convert androgen to estrogen. Be aware there is no aromatase in thecal cells!!

** Now let's go through hormonal secretion once again:

- Why we have rising in FSH & LH?

We said that estrogen produced from corpus luteum level will decrease due to cell death, so because of that the inhibition effect of estrogen on LH & FSH will be released, so FSH level will increase.

** So what the time difference between LH surge and ovulation?
In IVF, we give them ***human chorionic gonadotropin*** which is a glycoprotein that similar mainly to LH & lesser extent to FSH. Once we give it ovulation will take place after 34-364h. Physiologically; after the high level of natural LH, ovulation happen in less than one day.

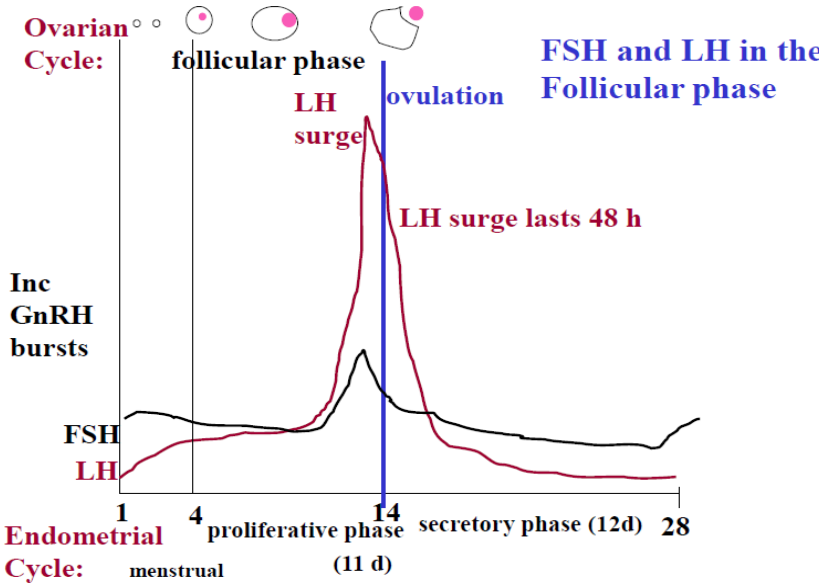


Figure 7:

- The high level of FSH will recruit follicles and induce their development.

- When the FSH level decrease, all the follicles will degenerate except on which will survive due to rapid increase in size, estrogen secretion and LH surge.

- LH surge & FSH will induce ovulation as you see it does occur at the day 14.

- This is the normal homeostasis, which occurs every month.

* We have multi changes of these hormones during the month or in their daily basis, so if you find high level of FSH in certain time (after 17 days of the cycle for example), it will be abnormal and so on.

** With decreasing of estrogen and progesterone level, FSH and LH inhibition will decrease and we will start a rising pattern of FSH & LH to recruit more and new follicles.

** All the estrogen that produced in the follicles by thecal and granulosa cells will be used locally where all enzymes functioning (like aromatase in thecal cells for androgen). What produced from corpus luteum will go to the circulation and some of it will be converted to estrogen.

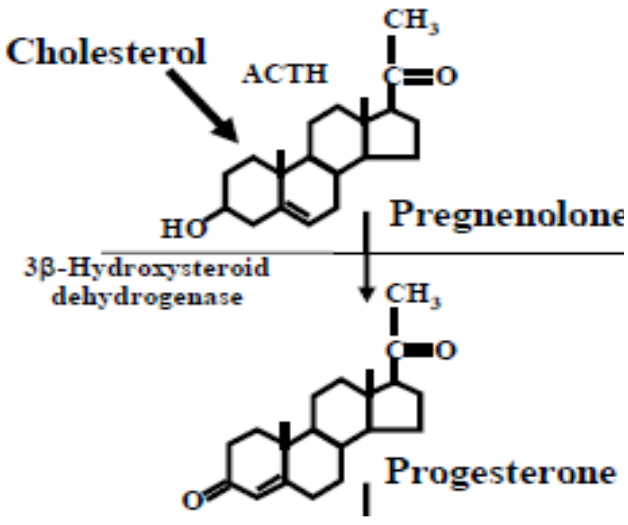


Figure 8; shows:

The synthesis of the steroidal hormone progesterone from cholesterol that converted to pregnenolone which will be converted finally to progesterone.

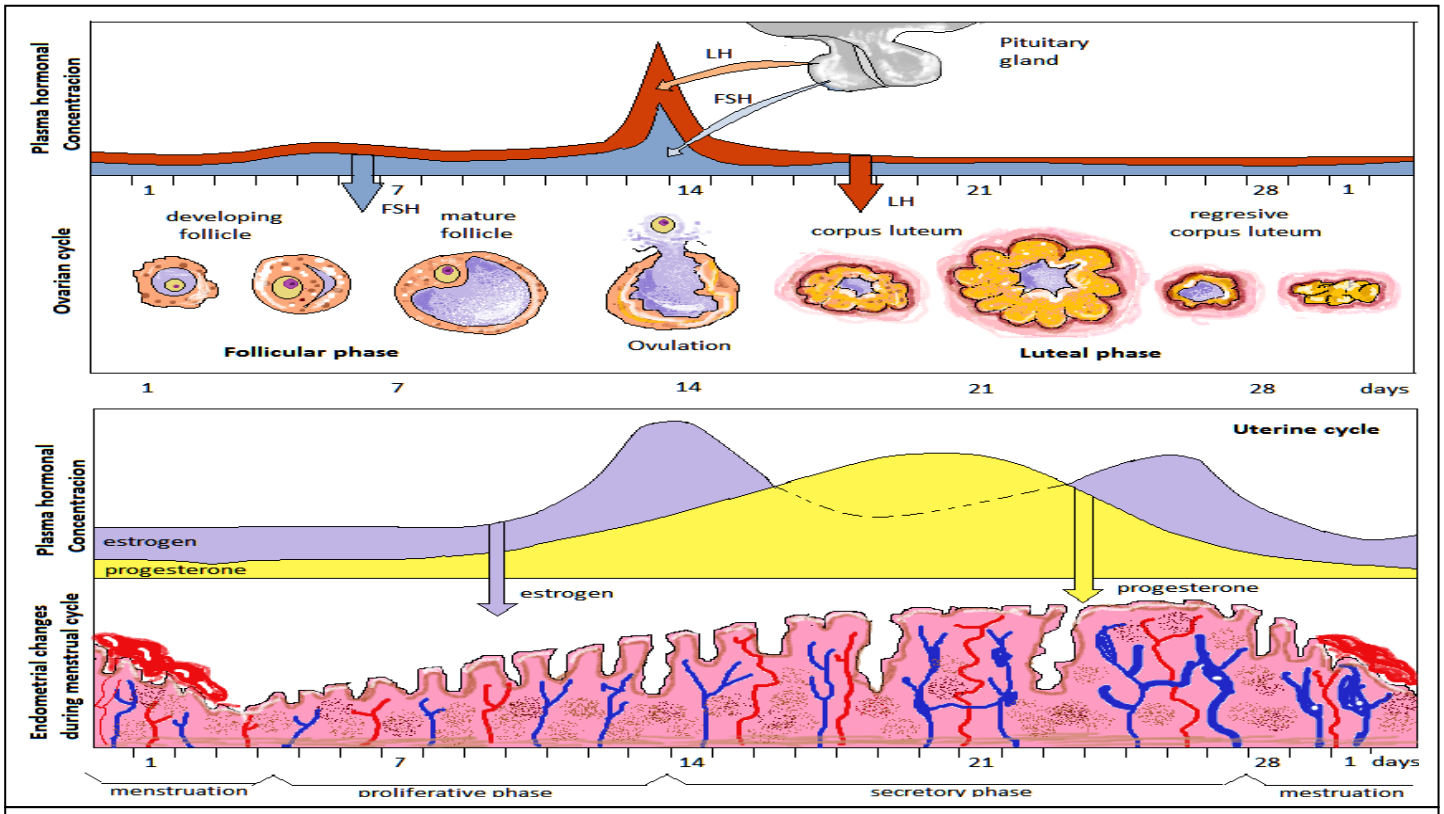


Figure 9; summarizes all the ovarian and hormonal changes let's go through it briefly:

The follicle recruitment and increasing of its size start by the stimulation of FSH. Then they start to be responsive to LH and secrete estrogen. Estrogen secretion come from the growing follicles (either thecal or granulosa cells) this rapid increase of estrogen will shift the hypothalamus from negative to positive feedback and we will end up with LH surge that will induce ovulation. No fertilization so the cell will die so will have estrogen suppress so no more activity. Then it will regain activity to produce estrogen and progesterone once more since it's a cycle.

- don't mind the uterine cycle for now we will go through it in the next lectures.

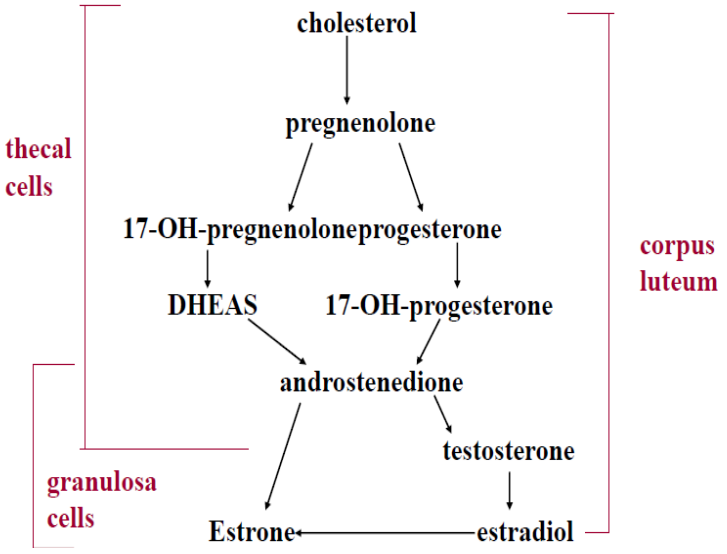


Figure 10; shows:

The production of testosterone in males, Just to show the similarities with estrogen and progesterone.

Leydig cells the same as thecal cell

Seritoli cells the same as granulosa cell

They have receptor for LH that will induce androgen production. They produce estrogen since they have aromatase 1 & 2.

Now let's talk about estrogen and progesterone functions:

- We have rising pattern of estrogen, so what its function?

Inside the ovaries:

1- It will stimulate mitosis locally in the granulosa cells.

2- It will stimulate the positive feedback of LH.

Outside the ovaries:

1- At puberty, increase in size of fallopian tubes, uterus and vagina, external genitalia deposition of fat in mons pubis. Also change vaginal epitheliafrom cuboidal to stratified type endometrium by increase their mitotic division and proliferation of cells and endometrial glands (important in nutrition of fertilized ovum).

2- Its increase the contractility of the uterus. And stimulate mitosis in the endometrial cells, so more cells production and more thickness, that will lead to high numbers of cells found far away from the base that supply them with nutrients and that will cause more capillary infiltration to supply these far cells. We end with decline in estrogen level so we start with estrogen and progesterone release.

Progesterone function:

1- Anti estrogenic effect which reduce mitotic activity.

2- Greater metabolic effect on the endometrial cells. The endometrial cells start to produce glycoproteins, proteins and other secretary elements. So more blood flow and the capillaries will increase in length but in limited space, since it occurs in narrow space it will form coils so more blood supply. The endometrial layer increase in thickness due to high blood flow and secreted materials that mean it filled with fluid so we call it **spongy endometrium.**

** The progesterone level starts to decrease, so the metabolic effect on the endometrial cells starts to decrease. With no more estrogen and progesterone this layers lose its support and start to die.

** Once the endometrial cells die we will have sloughing and bleeding. This blood will leave through the vagina and the menstrual cycle start. Refer to figure 10 for full picture.

"The way I see it, every life is a pile of good things and bad things. The good things don't always soften the bad things, but vice versa, the bad things don't always spoil the good things and make them unimportant."
_Doctor Who