

## UGS physiology sheet #13 lecture 3 Dr.Saleem Khresha .

Now we will start discussing the **female reproductive system** ...

### Ovarian Steroids

Two important cells in female are the theca cells and the granulosa cells.

**Theca cells** are affected by LH and they produce androgens (androstenedione and testosterone) then they pass into granulosa cells.

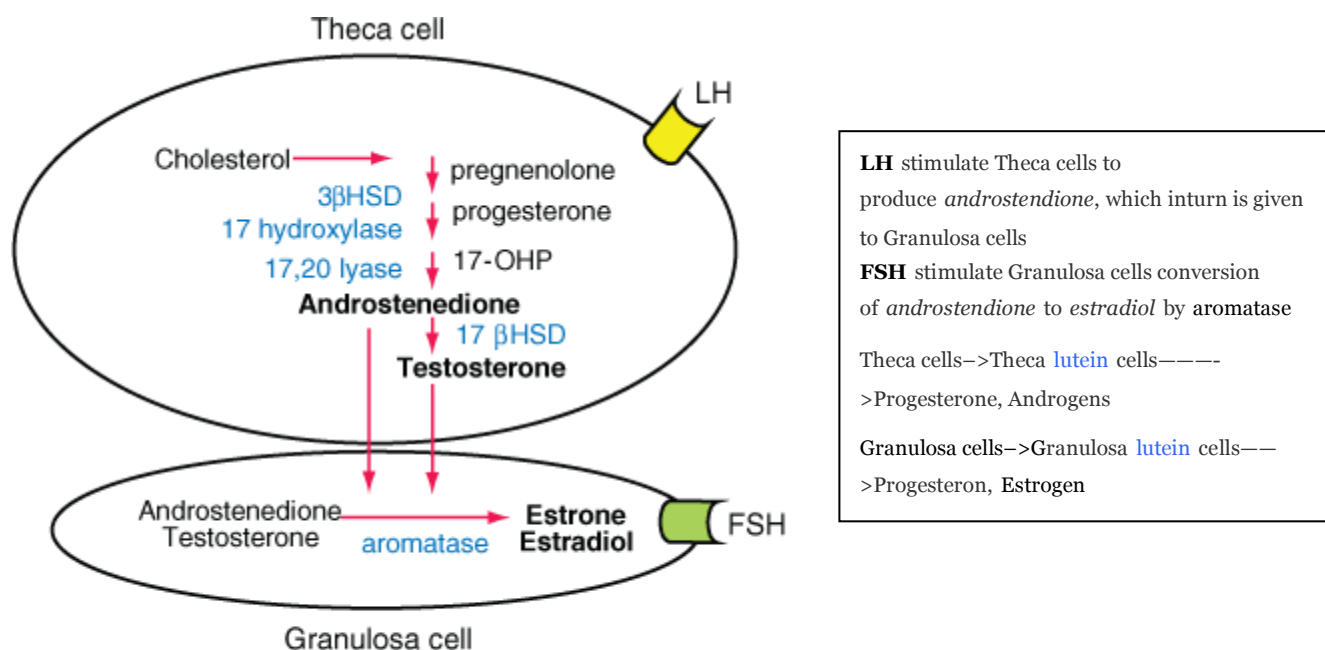
**Granulosa cells** are affected by the two gonadotropin hormones; FSH and LH.

These two cells function as one unit – similar to the cells in the male; Leydig cells and Sertoli cells).

LH affects the granulosa cells to produce progesterone and these processes are important in the luteal phase. Progesterone is not converted to androgens because the necessary enzymes are lacking .

Granulosa cells are also affected by FSH, and under its effect they convert androstenedione (coming from theca cells) and testosterone to 1) estradiol under the effect of aromatase enzyme, and 2) estrons are converted to estradiol, then estradiol diffuses to the circulation to its targets.

So the two cells; theca cells and granulosa cells function as one unit. If we separate either theca cells or granulosa cells, the whole hormone production will not be produced.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>  
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

The reproductive tract in female is almost similar to that in male there is a primary sex organs and secondary sex organs , the difference is the primary sex organs, so instead of testes there are ovaries.

## Hypothalamus-pituitary-ovary axis

You remember that brain centers are affected by some factors including:

1. age
2. environment.
3. Drugs.
4. nutritional status
5. stress level
6. diseases.

**Brain centers affect The hypothalamus** to produce gonadotropin-releasing hormone GnRH which acts on gonadotrophs of anterior pituitary to produce FSH and LH. and it also secretes Dopamine which inhibits prolactin.

[ **anterior pituitary gland** has five types of cells, of which are the gonadotrophs and the lactotrophs].

FSH and LH affects the ovaries to produce estrogen and androgen. **So the ovaries produce both estrogen in the form of estradiol and estron and androgens.**

Both FSH and LH regulate follicular steroidogenesis , androgen and estradiol secretion.

LH regulates the secretion of progesterone from the crpus luteum. ( it act on granulose cells, but these steps *are just important in the luteal phase*).

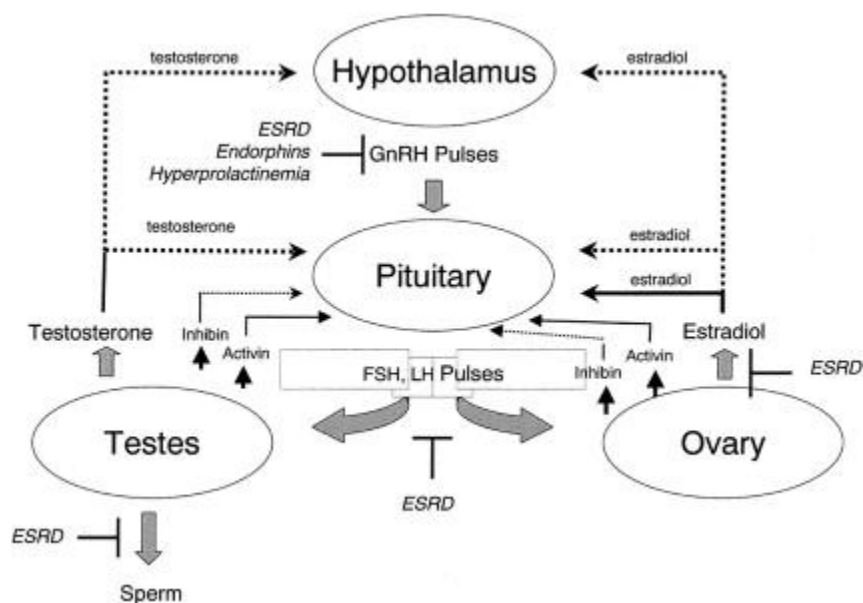
There are three polypeptide hormones; inhibin, activin and follistatin. All these hormones function at the level of FSH “only” Inhibin inhibits FSH totally while follistatin reduces FSH, that is similar to the feedback control.

Regarding activin and inhibin binding proteins, activin is not found with inhibin at the same time. Anyway, these three hormones secreted by granulose cells affect FSH.

Very very important:

There are many isoforms of inhibin because of the difference in the subunits and they are produced by “other” tissues including the pituitary glands, brain, adrenal glands, kidney, bone marrow, corpus luteum and the placenta. But the whole activity of inhibin is primarily confined to the reproductive system.

Activin is produced in the same tissues as inhibin, but it stimulate FSH rather than inhibiting it and it also has many isoforms.



## Female hormones and the ovarian cycle

Primary sex organs in female are the ovaries that have two functions; production of hormones and ova.

Estrogens are called in general female hormones الهرمونات الأنثوية while progesterone or progestins are called in general pregnancy hormone هرمون الحمل , so without progesterone on pregnancy takes place.

There are two cycles in female; the ovarian and the uterine cycles which take place typically every 28 days from puberty till menopause, and they do not stop unless there is pregnancy or disease.

The two cycles occur at the same time and the ovarian cycle dominates the uterine cycle. so if we prevent the ovarian cycle, the uterine cycle does not appear.

Ovarian cycle is divide into 3 phase; follicular (13days), ovulation (at 14 day) and luteal phase (13 days) considering a typical cycle.

Follicular phase in which the follicles develop. Ovarian phase in which one follicle ovulate and the luteal phase in which the corpus luteum “remnant of the ovulated follicle” is formed. If there is pregnancy, the corpus luteum continues to grow otherwise it is converted to corpus albicans.

**Follicular phase** begin with the activation of the primordial follicles which then form the primary follicles.

Activation of the primordial follicles is genetically determined two to three days before the onset of the previous cycle. So even if there is no any hormone, the primordial follicles can still be activated, but the difference is that the process continues in the presence of hormones while it terminates somewhere in the absence of hormones thus all the cells become atretic.

Now, the number of activated primordial follicles depends on :

1. The number of stored follicles in each ovary.
2. Genetics.
3. Nutrition.
4. Environment.

Illustration of the first factor “The number of stored follicles in each ovary”:

At the 30 week of gestation 7 million ova are present in the two ovaries.

2 million are activated and the others degenerate.

Only 300,000 – 400,000 ova reaches puberty during all the reproductive years (13-50) years and even before 13 and after 50 okay. And this is for the improvement of the life style. Statistics revealed that the average age of menopause is around 55 yrs – even at age 55 or 60 some women got pregnant. While menopause age in Uganda is from (37-42) years.

Usually the two ovaries alternate in ovulation, but sometimes the two ovaries ovulate, or one ovary ovulate two ova, or one ovary ovulate one ovum which further divides into two producing identical twin .

At menopause few of the follicles remains and sometimes all of them got degenerated.

Now, **throughout the reproductive life (90-95)% of all follicles are primordial follicles.**

In fetal life and childhood some primordial follicles develop all the way to later states. However, all these follicles undergo atresia.

“one” of the primary follicles continue to grow and become dominant. Why??

Because it is richly vascularized in comparison to the others and because it is very sensitive to FSH.

The dominant follicle – particularly- secretes estrogen “ estradiol” which has two functions: reduces FSH level (-ve feedback ) and increases the number of receptors on the same follicle for FSH, so that it becomes very sensitive to FSH even if its concentration is very low while the other follicles degenerate since they need too much FSH.

So **dominant follicle produce a lot of estrogen.**

**Ovulation:** There is a limit for estrogen level to inhibit LH and FSH. Above that limit the negative feedback is altered to positive feedback.

In fact, The high amount of estrogen does not increase the secretion of LH only but FSH as well. However, FSH role in ovulation is minor.

It is not only estrogen that stimulate LH and FSH , it is also progesterone and activin .

**How estrogen stimulate LH secretion??**

It has two functions.

First, when estrogen reaches to a certain level it activates neurons in the hypothalamus to produce too much GnRH and of course, it modulate the secretion of these hormones down to the gonadotrops.

Second, estrogen increases the sensitivity of gonadotrops to GnRH as well as the receptors thus increasing the release of LH.

**So estrogen works at both the hypothalamus and the pituitary levels.**

**What are the causes of ovulation??**

1. LH surge .
2. Ovarian proteins are also produced : 1- Progesteron receptors 2- Cyclooxygenases 3- cyclin D 4- transcription factor C/EBP $\beta$  ( their specific function is not known till now).
3. Vasodilators (histamine,bradykinines, and PGs). When these vasodilators are produced the graafian follicle becomes hyperemic, edematous and it swell.
4. Enzymes (plasminogen activators , collagenase and lysosomal enzymes) the lysosomal enzymes are produced by PGE and PGF.

So ovulation occurs.

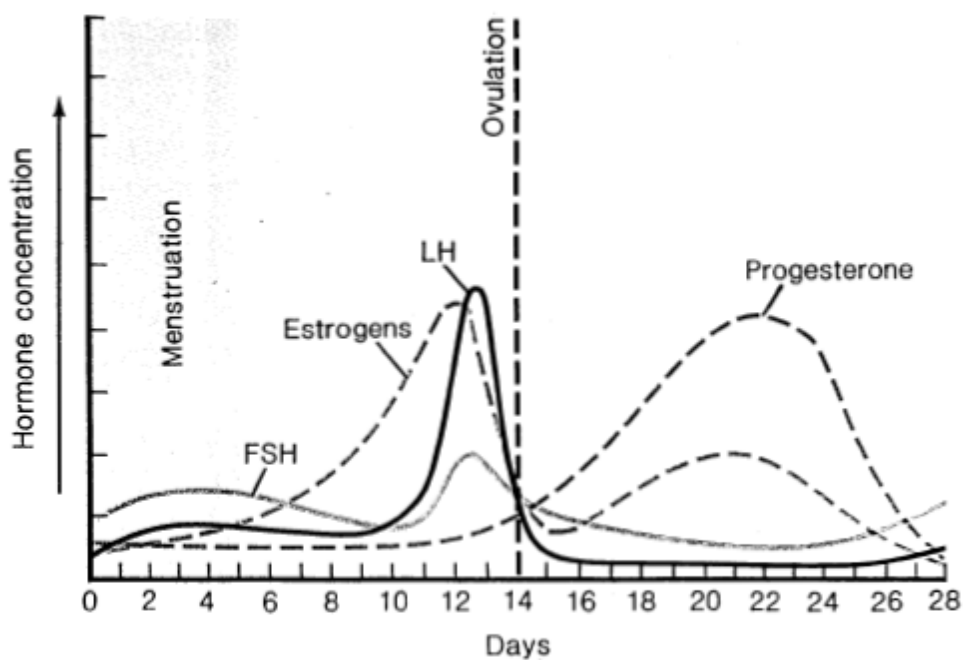
**Luteal phase :**

The follicle ovulates and the remnant becomes the corpus luteum. If pregnancy occurs it secretes more progesterone and less estrogen.If there is no pregnancy, it starts shrinking within two weeks and within two months it disappears and becomes the corpus albicans. This is the luteal phase.... 13 days before ovulation..ovulation...13 days after.

- The follicle must be exposed to an appropriate sequence of hormones to mature probably : first FSH followed by estradiol and LH for normal maturation and function.
- Sometimes the ovarian cycle doesn't end in ovulation. These non-ovulatory cycles are usually seen at the beginning of puberty (first year or two) and at the beginning of menopause.

The characteristics for these non-ovulatory cycles:

1. Graffian follicle doesn't rupture so no Corupus Luteum and consequently no progesterone.
2. So we conclude that this cycle is shorter than usual normal. It ranges between (21-26 days).



**Figure 28-19**  
 Tortora/Anagnostakos: Principles of Anatomy and Physiology, 5/e  
 Copyright © 1987 by Harper & Row, Publishers, Inc. All rights reserved.

We notice here that during the first 5 days , low levels of hormones are present .

---