



## ANATOMY

Sheet

Slide

Handout

Number

10

Subject

Menstrual Cycle

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Price:



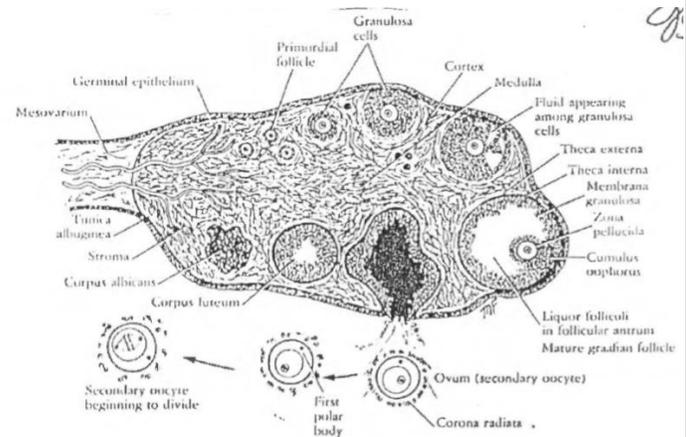
- this sheet was written according to section 1 recording.
- There are many concepts and ideas that will be repeated in the next lecture, so consider this sheet as an introduction.

## ☞ THE OVARIAN FOLLICLES:

- “the ovarian follicles contain immature ovum, oocyte suspended in prophase of 1st meiotic division”
- in the middle of menstrual cycle (14th day), the ovum is ready to go out from the follicle but it's still immature
- the menstrual cycle is 28 days typically & day 14 is for **ovulation**, *(in the handout it's written 15 yet the doc said 14)*
- the growing follicle produces **Estrogen**
- the remnants of the follicle form the **Corpus Luteum**, which gives **estrogen & progesterone**

there are two concepts for the growth of the follicle:

- The old concept says we need FSH from the beginning till the end
- The new concept says, in the first stages we don't need FSH, but in order for the primary multi-laminar to become secondary multi-laminar and the secondary multi-laminar to be mature we do need FSH.

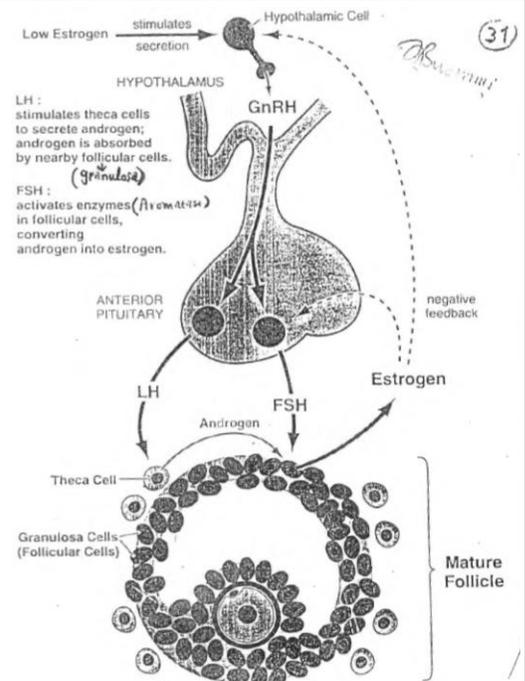


## ☞ Description of the Ovarian Follicle:

- the follicle is at the cortex of the ovary, it has immature ovum, around it single or multiple layers of epithelial cells, the cells around the ovum are called follicular cells or granulosa cells.

## & Follicle stages:

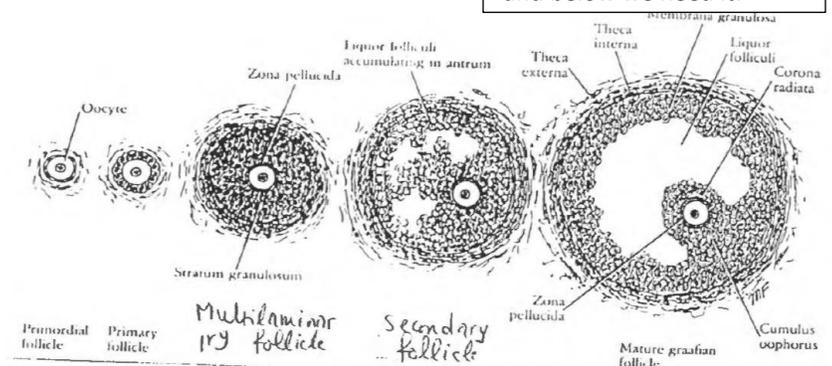
- Primordial follicle: contains immature ovum surrounded by single cells of squamous epithelium, outside it is a connective tissue from the ovary (cortex part)
- if we look at an ovary of a 5 years old, it is full of primordial follicle, why is it suspended and don't continue to grow?
  - because the granulosa (follicular cells) around it secretes "**oocyte maturation inhibiting factor**"
- this follicle grows without FSH to primary follicle (still uni-laminar), the changes are increase in size of the ovum and the number of organelles, and the follicular cells are transformed from simple squamous to cuboidal.
- So, the change from primordial to primary occurs **without the need for FSH**



- the primary uni-laminar grows to primary multi laminar (multiple layers), in this stage the ovum is covered by a membrane consisted of glycoproteins called zona pellucida.

\*Primary uni-laminar & primordial don't need FSH  
From primary multilaminar and below we need it.

- **Zone pellucida** is one of the barriers that the sperm should penetrate in order to fertilize the ovum
- until the stage of primary multi laminar follicle the FSH is not needed, now around this follicle the stroma of the ovary forms two layers: **theca interna** (inner cellular) and **theca externa** (outer fibrous)



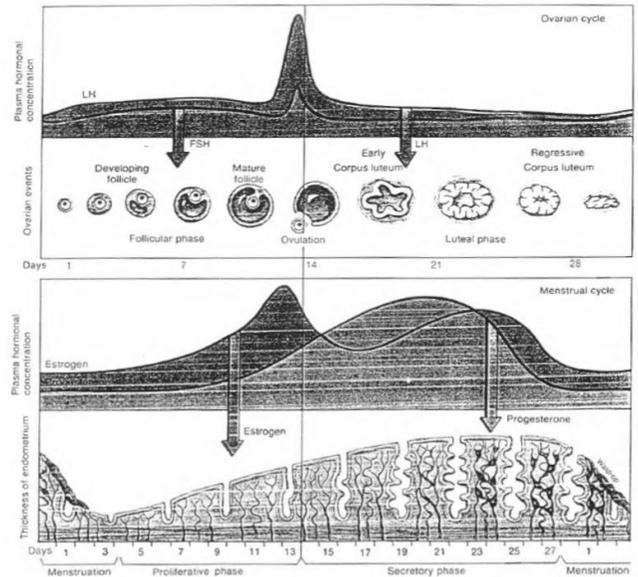
- now we have two types of cells in the primary multi laminar stage, one type in theca interna (the outer part) and the other is in the granulosa "follicular cells" (inner part)
- in this stage, the cells can produce the estradiol "estrogen", how?
  - low estrogen in puberty stimulates the GnRH from the hypothalamus which goes to the anterior pituitary through the portal circulation in the pituitary stalk and stimulates it to produce the LH & FSH
  - LH works on the theca interna cells making them produce the Androgen (testosterone or androstenedione), by stimulating **cholesterol desmolase enzyme** (similar to males), then the androgen will diffuse and gets absorbed by the granulosa cells, and under the effect of FSH the androgen will be

transformed to estrogen, by stimulating the **aromatase enzyme** in the granulosa cells

- “most important estrogen in the female is **17-beta estradiol**”

❖ now we reach a concept:

- FSH and LH makes the follicle able to produce estrogen, so the ovary in the age of puberty under the effect of LH and FSH is going to produce large amounts of estrogen.
- this estrogen will have a negative feedback on the level of the hypothalamus and the pituitary (GnRH, LH & FSH)
- the estrogen will also stimulate the growth of the endometrium,
- these actions happen in about the 1<sup>st</sup> half of the menstrual cycle



- the typical menstrual cycle as we said is 28 days
- in the first half happens what we just talked about, the follicles grow and produce the estrogen, and the estrogen will make the endometrium grow and gets filled with glycogen to receive the fertilized ovum
- then...
- ovulation occurs but with no fertilization, the endometrium will get sloughed and destroyed and goes out as a menstrual blood
- if fertilization occurs then estrogen and **progesterone** will continue being produced to maintain the endometrium for the ovum and then the fetus
- now we continue with the growth of the follicle
- primordial uni-laminar → primary uni-laminar → primary multi-laminar → secondary multi-laminar
  - the role of FSH comes in the growth of the follicle from primary to secondary multi-laminar
  - the difference between the primary & the secondary multi-laminar follicles is the presence of more **cavities** filled with a fluid called (**liquor follicluli**), this fluid is rich in estrogen!
  - and we said that the theca interna produces androgen and the granulosa will transform it to estrogen!
  - now for the secondary follicle to be transformed to mature follicle we also need FSH
  - the difference between the secondary and the mature follicle is that the secondary has many cavities while the mature follicle is now having one big cavity, and the ovum now is on the side of the follicle
  - this mature follicle during the middle of the cycle is 1cm in diameter , and it can be seen on the surface of the ovary by using ultrasound

## 🔗 Follicle Layers:

- Theca externa → theca interna → granulosa (follicular) cells
- Now the cells surrounding the inside surface are called **membrana granulosa**.
- Part of them hangs (تعلق) the ovum and are called **cumulus oophorus**
- The cells that surround the ovum directly are called **corona radiata**
- Now the ovum is covered by two layers which are: zona pellucida and corona radiata
- They represent the barrier which must be penetrated by the sperm

"many sperms gather around the ovum but only one will enter and fertilize it!"

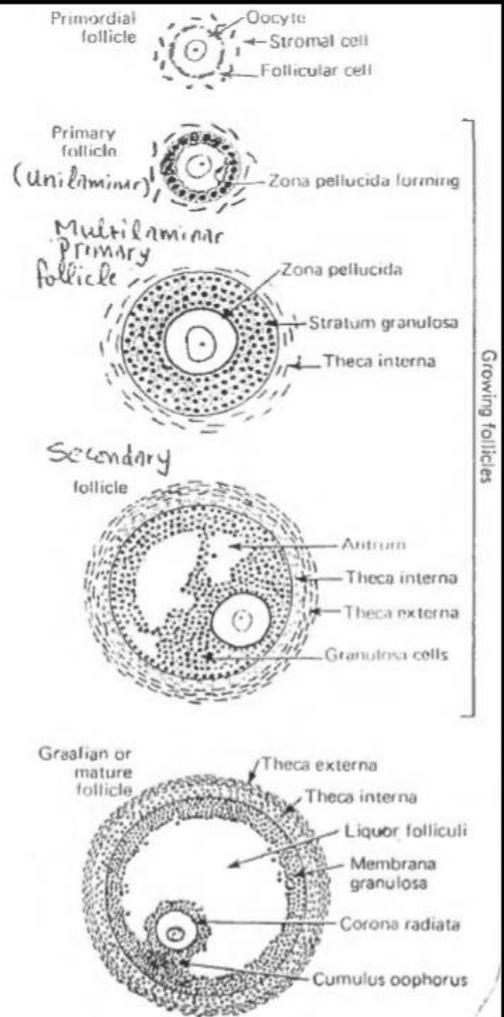
- This is the structure of the mature **Graafian follicle** which is present in the 1<sup>st</sup> half of cycle
- what happens next?
- we said when we reach this stage ovulation occurs!

Q/ what causes and what is the mechanism of **ovulation**?

- the ovum exits the follicle and what's left will form the Corpus Luteum under the effect of **LH**

"corpus luteum secretes estrogen and progesterone!"

- in the first half of the cycle the follicle only produce estrogen, in the second half it will also produce progesterone! (corpus luteum)
- and again, both estrogen and progesterone will prepare the endometrium for receiving the fertilized ovum (egg)!



## & MENSTRUAL CYCLE:

- Average (typical) duration is 28 days, normally it's around 21-35 days
- It's divided into two halves.
- we are concerned about the time of ovulation which happens **14** days before menorrhoea

- for example:

- if a female menstruates at day 35, the ovulation then happened at day 21 →  $(35-14=21)$
- this states that ovulation is **stable!**

- the menstrual cycle is really two cycles:  
Endometrial cycle & Ovarian cycle

- Ovarian cycle is the changes that happens in the ovary and we talked about most of it

- the endometrial cycle is the changes that happens in the endometrium

- the menstrual cycle has several phases, the first one is called **menstrual** phase, this phase is called "the period" which is the time when blood comes out "menorrhoea" and lasts for 4-5 days typically

- So, **the first day of bleeding** is the first day of the menstrual cycle

- Bleeding occurs because the endometrium is being destroyed and getting sloughed out

- in the first 4-5 days, we destroy the what we built in the previous cycle

- then we start to build a new endometrium for this cycle hoping for a fertilization to occur

- these changes in the ovaries and the endometrium are under the effect of the hormones coming from the pituitary gland (**LH & FSH**)

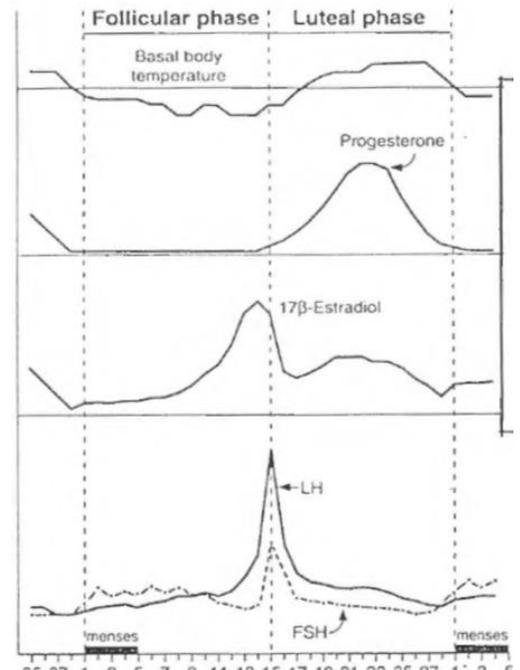
- after this menstrual phase comes the **proliferative phase** (after day 4-5 typically, until day 14), during this phase we start to build the endometrium again, it can also be called **follicular** phase because a follicle in the ovaries starts to grow and produce estrogen which helps in building up the endometrium

- Menstrual phase → Follicular/Proliferative phase:

- here the FSH develops the follicle until reaching the mature **Graafian** follicle, in this period the FSH & LH are relatively low in the blood due to **the negative feedback of the estrogen**

- this low level of FSH helps in the fast growing the follicle, but how?

- the estrogen produced increases the number of FSH receptors in the granulosa cells,



"LH works on the theca interna and makes it produce androgen, granulosa cells have receptors for FSH, the FSH makes these cells transform the androgen to **estrogen**"

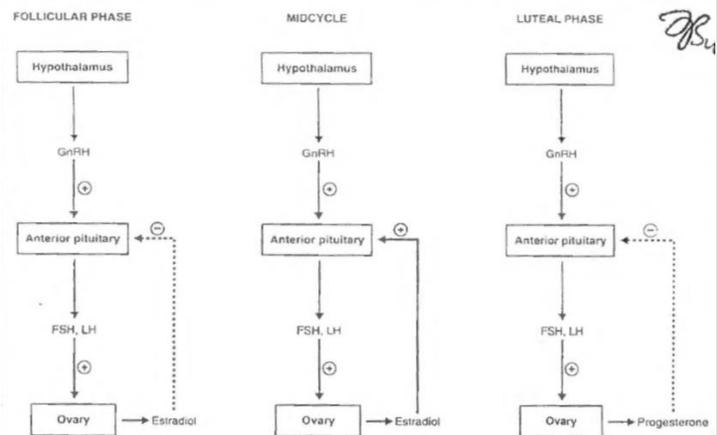
- so, in the proliferative phase, the glands in the endometrium grow under the effect of estrogen secreted by the growing follicles
- before the midpoint of the menstrual cycle, the estrogen works as negative feedback on the FSH & LH
- at the midpoint of the cycle or just before it (**day 13 typically**) the estrogen levels in the blood rises and the effect on FSH & LH turns to **positive feedback**, increasing their levels in the blood "especially LH"
- this induces something called **LH surge** "massive increase in its blood level" which happens at the midpoint of the cycle,
- So, the estrogen induces LH surge, LH surge causes **ovulation**

\*so, we can say that ovulation occurs due to the **estrogen induced LH surge**

- after the ovulation, the **LH** will be responsible for transforming what's left of the follicle to **Corpus Luteum**
- the Corpus Luteum will produce estrogen & progesterone
- the main hormone in the first half of the cycle is the **estrogen** but after the formation of the Corpus Luteum in the second half, the main hormone becomes the **progesterone**
- in the first half of the cycle the endometrium thickness was 2-3mm, yet in the second half it becomes thicker, the glands becomes longer and more numerous and stores glycogen and Amino Acids, all of that occur to get ready for receiving the ovum if it gets fertilized!
- if the ovum didn't get fertilized, the Corpus Luteum survives for only 14 days (day 14 to day 28 typically), then degenerates and transforms to Corpus Albican, estrogen & progesterone levels decline and the endometrium starts to shed due to constriction of the arteries → ischemia & necrosis → menstruation phase of next cycle

- if fertilization occurs it will survive for 3 months after pregnancy and keep growing producing estrogen & progesterone until it gets replaced by the **placenta**

- LH & FSH at the first half are low (**negative feedback** of estrogen), at the middle are high due to high amounts of estrogen (**positive feedback**), at the second half they become low again due to the effect of progesterone (**negative feedback**)



- so first and second half negative feedback, positive feedback in the middle (LH surge)
- the immature ovum was suspended in the prophase of first meiotic division, the **LH surge** makes the immature ovum exits the first meiotic division, and enters the second meiotic division & becomes a secondary oocyte suspended in the metaphase, and the secondary oocyte will continue the meiotic division only when it gets fertilized!
- So, these changes are in the ovaries (ovarian cycle), And changes in endometrium (endometrial cycle) under the effect of

❖ **Three effects of LH surge:** (*LH increment is more important*)

1. **Complete the first mitotic division**
2. **Ovulation**
3. Formation of **Corpus luteum** from the remaining follicle

- In the first half, the estradiol (*estrogen*) becomes more and more and it reaches the maximum in the middle of the cycle
- During ovulation, the production of estrogen decreases a little and then it will increase again.
- there's no progesterone in the first half, only after the formation of the Corpus Luteum in the second half
- Progesterone will work on the hypothalamus and will rise the body temperature in the middle of the cycle

## & OVULATION:

- The ovum determines the time of its (3) ovulation!
- Q/what induces the ovulation?
- The ovulation is due to (2) estrogen induced LH surge
- Q/when does the estrogen increase in large amount, when the follicle is small or large?
- When the (1) follicle is large (mature follicles in the middle of the cycle)

\*\*\*\* ثلاث تعبيرات تتبع بعض  
1 → 2 → 3

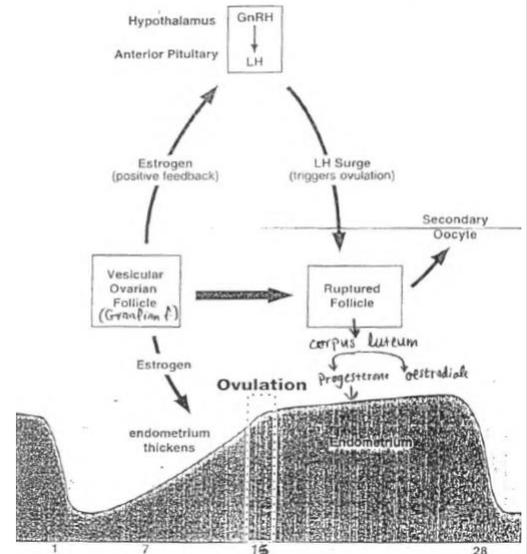
- The granulosa (follicular) cells are the **only** ovarian cells that have FSH receptor
- FSH produce estrogen from follicle
- FSH with estrogen will promote the development of LH receptors on theca interna and granulosa cell
- So again, we said FSH works on producing estrogen, and LH works on theca interna to produce androgen

Q/ But who is going to change androgen to estrogen?

- **Granulosa** cell under the effect of FSH
- And to change the remnants of the follicle into Corpus Luteum under the effect of LH, there must be receptors for LH on both granulosa cells and theca interna (which is due to the effect of FSH and estrogen)

Q/ how does the follicles change into corpus luteum?

- Under the effect of LH , the follicles will change **شكلا و وظيفة** , so instead of saying granulosa cell we say granulosa lutein and theca interna to theca lutein



## Ovulation Mechanism:

- ❖ We said that the typical menstrual cycle is 28 day
- ❖ At day 14 the ovulation will occur
- Menstrual phase (day 0 ⇨ 4-5 ) → follicular or proliferative phase (day 4 ⇨ 14) → **ovulation** (day 14) → secretory or **luteal** phase (day 15 ⇨ 28)
  - ❖ We said before that the follicle before ovulation is growing under the effect of FSH, it is called the Graafian follicle yet the physiologists like to call it (vesicular ovarian follicle), and of course Dr. Faraj don't like this name so stick to Graafian follicle
  - ❖ This Graafian follicle will keep growing under the effect of FSH until part of its wall becomes thin and ischemic → necrotic, then it will rupture releasing the ovum
  - ❖ theca **externa** will also help in releasing the ovum by producing proteolytic enzymes that will work on the thin part of the wall
  - ❖ Now the estrogen induced LH surge effect or mechanism is still unknown inducing this ovulation

➤ **Once again:**

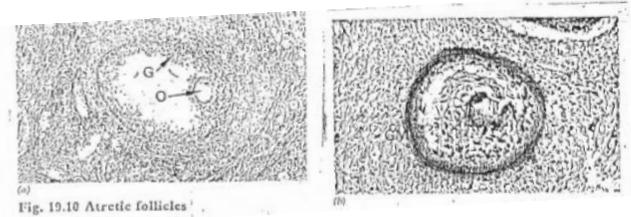
- After the ovulation, (i.e. secretory phase), The Corpus Luteum will be formed and now we will have Estrogen & Progesterone
- The endometrium will be **thickened**, the glands will be **tortuous** instead of being straight

“if we look at a part of the endometrium, we can know if it was in the 1<sup>st</sup> half (follicular & proliferative phase) or 2<sup>nd</sup> half (secretory & luteal phase) histologically by looking at the glands → straight vs. tortuous”

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## Follicular Atresia:

- Each month, a number of primordial follicles starts to grow (5-15 follicles)
- Only one of them will reach the mature Graafian follicle state, the others will have follicular atresia and degeneration
- The atresia may occur at the primordial, primary or secondary state
- Now in the follicle that will undergo atresia, the ovum will shrink and degenerate, the cells around it will have degenerative changes, and the most important change is that the basement membrane between the granulosa cells and the theca interna will persist and get thickened and becomes the **Glassy membrane**
- This glassy membrane when seen in the ovary will reflect the fact that this follicle has become atretic!



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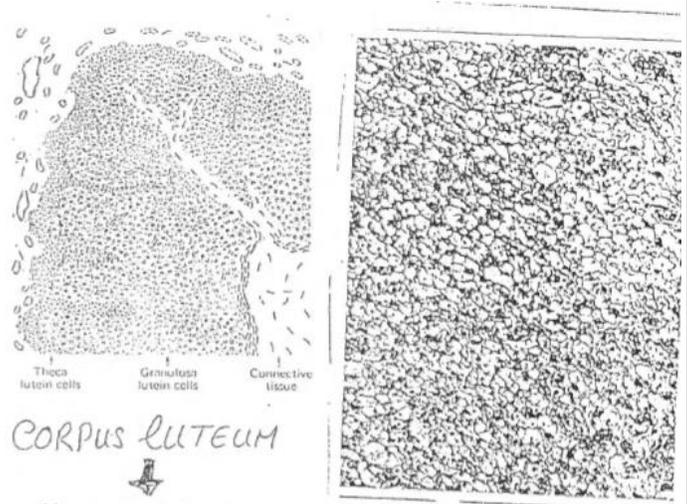
## ↳ CORPUS LUTEUM:

- Q/ How the remnants of the follicle are transformed to corpus Luteum? :
  - The corpus luteum is a temporary endocrine gland, survives for 14 days if fertilization didn't occur, then it will degenerate. (from day 15⇒28)
- Q/ Under the effect of LH, the remnants of the follicles will transform, how?

- The theca interna & the granulosa cells will transform to cells similar to that of the endocrine system under the effect of LH, which means they will have a pad of fats which provides cholesterol that is essential for hormones production, these cells will also have spaces that contain the cholesterol
- The follicle after the ovulation is collapsed, and may contain some blood clots due to bleeding from blood vessels of the theca interna
- The Granulosa cells will get bigger, store fats, will have larger SER, and will be capable of producing Estrogen & Progesterone.
- And the progesterone is responsible for changing the endometrium from the proliferative to secretory state

Before ovulation, the theca interna will produce androgen under the effect of LH, the granulosa cells will absorb this androgen and under the effect of FSH will be transformed to estrogen

Now the granulosa lutein and theca lutein under the effect of LH will produce not only estrogen, but will also produce progesterone and androgen



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#### - Q/ How the menstrual phase starts?

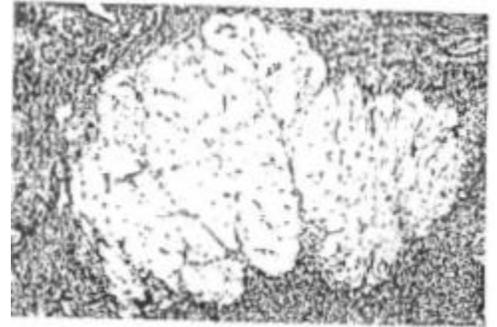
- After the degeneration of the corpus luteum, the estrogen & progesterone levels will be lowered suddenly will cause constriction in the arteries of the endometrium → ischemia → necrosis → shedding. (loss of endometrium)
- Menstrual blood contains venous blood, epithelial cells, secretions from the endometrium glands
- If fertilization does occur the corpus luteum will survive for 3 months after the pregnancy until the placenta takes its place in forming estrogen & progesterone, it will be called Corpus Luteum of pregnancy
- If we remove the corpus luteum in the first 3 months of pregnancy, abortion will occur!

“That’s because the estrogen & progesterone are important for maintaining pregnancy”

- ❖ If a woman is having multiple spontaneous early abortions, it’s advised that she should take progesterone to prevent these abortions and maintain the fetus.
- ❖ Her problem is probably that the corpus luteum isn’t producing enough progesterone, so progesterone is given until the 3<sup>rd</sup> month to give time for the placenta to be formed and starts producing the progesterone.

## & CORPUS ALBICAN:

- Q/ How does the Corpus Luteum is transformed to **Corpus Albican**?
    - If we look at a human ovary we can see scars of connective tissue at the surface
    - If fertilization didn't occur, Corpus Luteum will degenerate and transform to a white mass of collagen fibers called Corpus Albican
    - That occurs due the entrance of fibroblast that will produce **collagen type I** which will be responsible for the scar formation
- 



*Le Fin.*

Done by: *Omar Saffar*