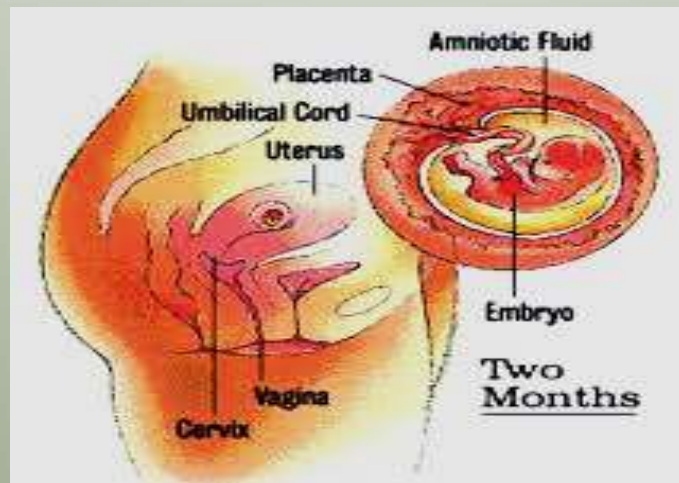




## 7. THE FEMALE REPRODUCTIVE SYSTEM & PREGNANCY.



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# The Female reproductive system

-The female genital system consists of :

2 ovaries (primary sex organs), 2 fallopian tubes , uterus , vagina .

-The ovaries have two important interrelated functions :

1- Production of ova : by a process called **oogenesis** .

2- Production of steroid hormones (**Estrogen and progesterone**) “**steroidogenesis**” .

- The ovaries of young female at **Menarche** (**first** menstrual bleeding) contain about **400.000** follicles . During reproductive life less than 500 of these follicles will complete their maturation to release ova , while others will become atretic and degenerate .

The menstrual cycle: The length of the cycle is 28 days from the start of one menstrual period to the start of the next .

- The sex (menstrual) cycle , is the monthly rhythmic changes in the rate of secretion of female sex hormones with the corresponding changes in the ovaries , uterus , cervix , vagina and breast .

# 1- The ovarian cycle

At puberty , under the ovarian capsule there are many **primordial follicles** containing an immature ovum . Each follicle consists of primary oocyte surrounded by a single layer of squamous follicular cells .

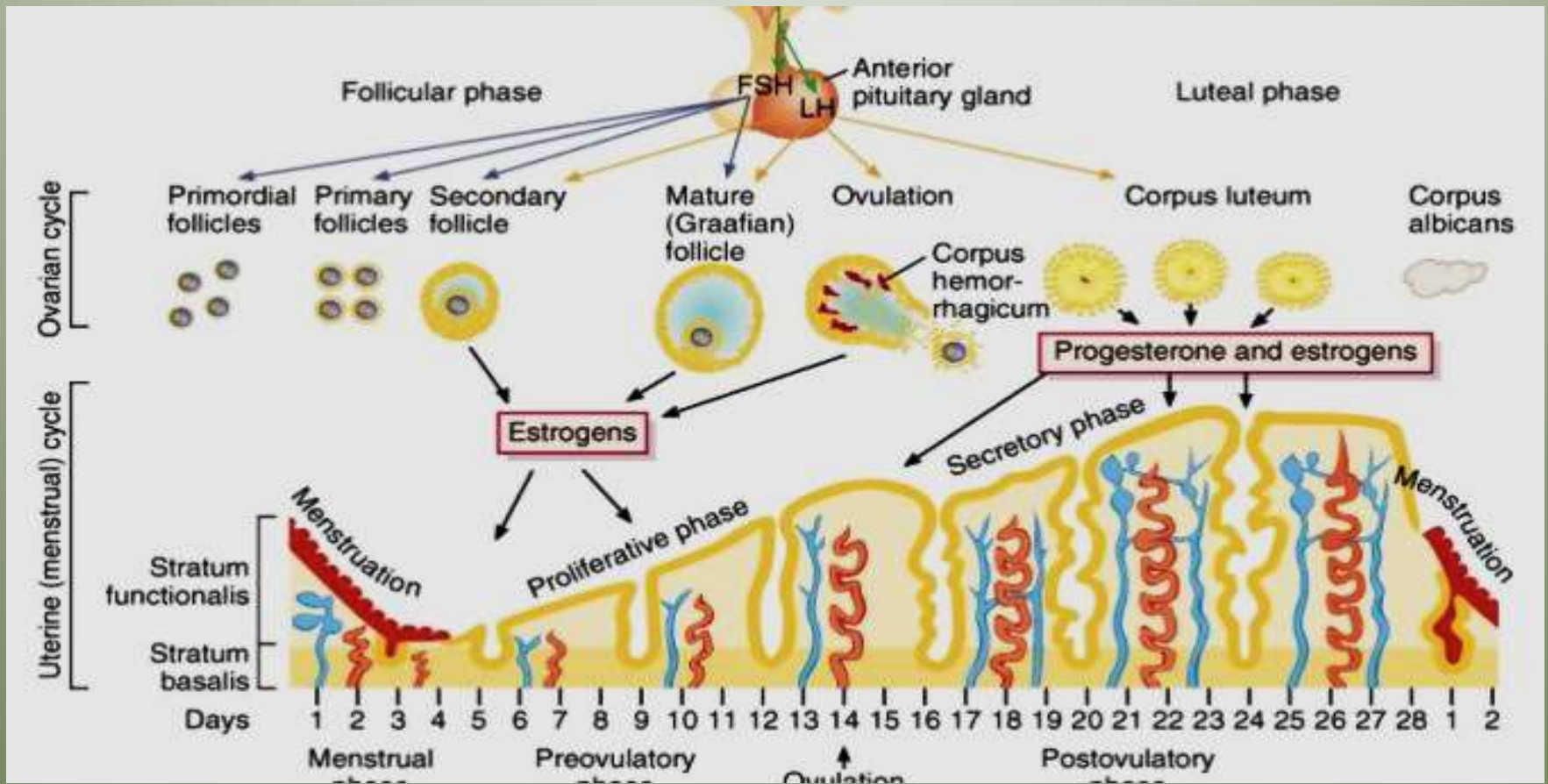
- The ovarian changes during sexual cycle depend on **GnTH** which shows cyclic increase and decrease each cycle to avoid desensitization of the receptors .

These changes include :

1- Follicular phase .

2- Ovulation .

3- Luteal phase .



## 1- Follicular phase :

At the **start** of each cycle , several (**6-12**) primordial follicles enlarge and develop to **primary** (pre-antral) follicles under the effect of **FSH** which is released from anterior pituitary gland in response to the presence of low basal level of **Estrogen** .

**Primary follicle** : the size of primary oocyte is increased , the follicular cells become cuboidal and proliferate forming many layers of granulosa cells around the oocyte .

- The ovarian stromal cells form theca folliculi

-**Theca** cells synthesize **LH receptors** and form **androgen** under the effect of **LH** hormone and **Granulosa** cells synthesize **FSH receptors** , convert androgen to estrogen under the effect of FSH hormone .

-After **one week** , **one** of the follicle , in **one** ovary , enlarges and highly developed more than other and secrete more estrogen (antral follicle) = **dominant** = secondary follicle and others regress (competing) .

### **Antral follicle :**

The spaces unite and give **one large space**, oocyte is located in a mass of granulosa cells that project into antrum, the first layer of granulosa cells that surround the oocyte and enclose contact with zona pellucida , becomes elongated and is called **corona radiate** .

**The mechanism** : (why **one follicle** enlarges and the **other regress**)

**A- The dominant follicle** secretes more **estrogen**, that causes :

1- **decrease FSH** by **negative feedback** mechanism with hypothalamus and anterior pituitary, decrease the degree of stimulation of competing follicles thus stop its growth and become atretic .

2- **increases granulosa** cells proliferation and increase FSH receptors on granulosa cells, response of granulosa cells to FSH → ↑estrogen secretion from dominant follicle (**+ve feedback** ) → more growth of the dominant follicle becomes.

**B- The dominant** follicle secretes **inhibitory peptides** which impairs binding of LH to its receptors in the competing follicles. In the presence of FSH and increasing quantities of estrogen , the outer layers of granulosa cells of large antral follicle now synthesize LH receptors, moreover LH can induces the formation of its own receptor in FSH primed granulosa cells . thus granulosa cells start to synthesize **Progesterone** instead of estrogen.

At the mid-cycle when estrogen level in the circulation reaches a high critical level and this level is maintained for a critical time , it induces sudden rapid increase in LH (LH surge) ie estrogen → ↑ LH , moreover , presence of progesterone

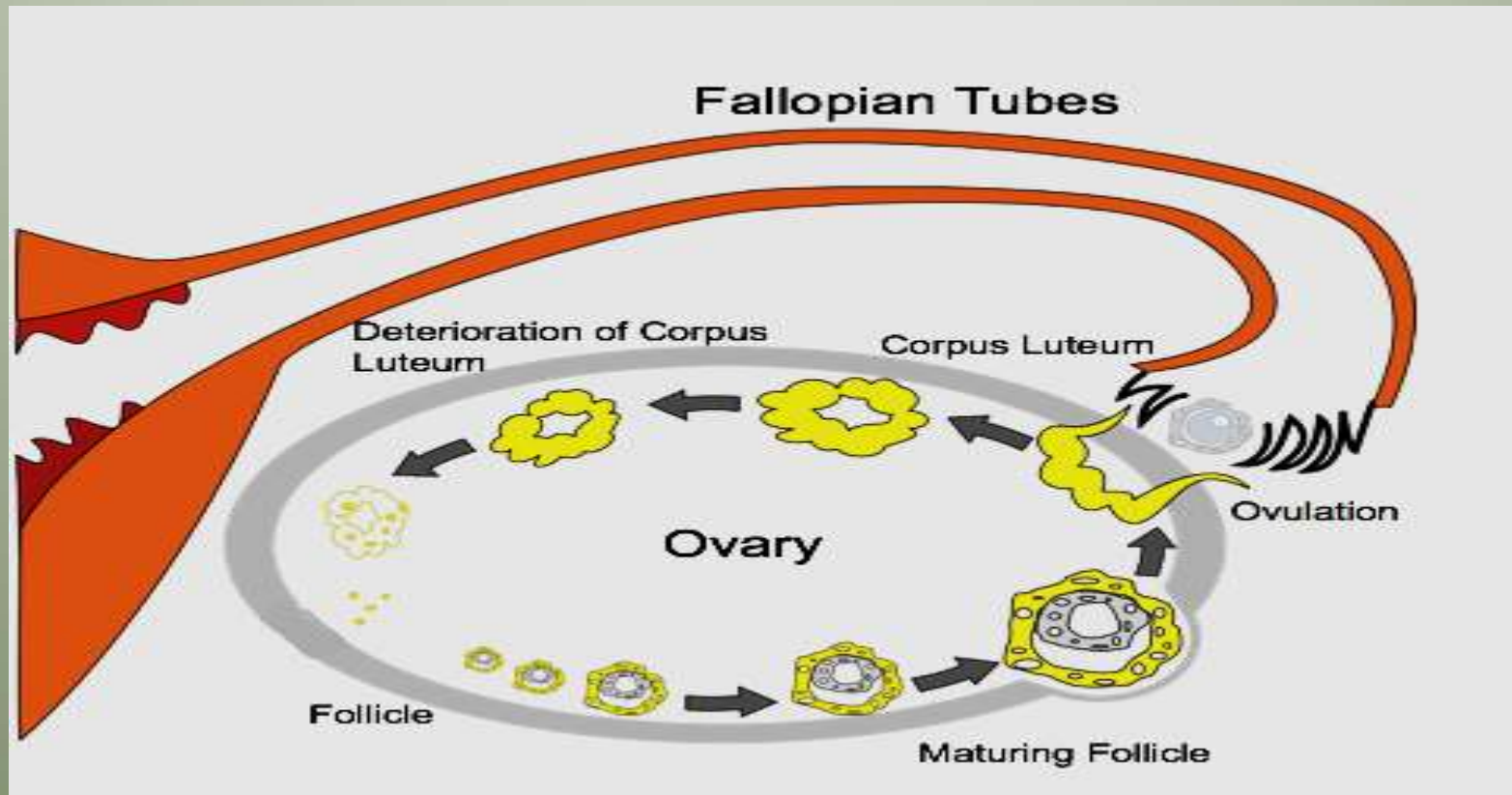
a) Facilitate the +ve feedback mechanism of estrogen on LH .      b) induces FSH surge .

**FSH and LH surge** induce ovulation .

Just before ovulation , the follicle become **mature graafian follicle** (reach 1- 2 cm in diameter and oocyte undergoes meiotic reduction division to produce secondary oocyte and first polar body . The secondary oocyte enters the second meiotic division to arrest again in its metaphase until after ovulation and fertilization .

## 2- Ovulation

- It is the process of rupture of mature Graafian follicle and expulsion of ovum into the peritoneal cavity to be picked up by the fimbriated end of the fallopian tube .
- It takes place approximately in the day **14** of the cycle .
- The cause of ovulation is GnRH surge .
- If the ovum is not fertilized within 24 hours after ovulation , it degenerates .



### 3-Luteal phase

The follicle which ruptures at the time of ovulation, fills with blood forming **corpus haemorrhagicum**, the clotted blood is removed by phagocytosis, the follicle is converted to **corpus luteum** under the effect of LH that accelerates the proliferation and hypertrophy of granulosa cells and incorporation of **theca interna cells** within the follicle .

Now granulosa cells and theca interna cells are called **lutein cells** which are lipid rich cells so corpus luteum is **yellow** in colour. Corpus luteum is a temporary endocrine gland, secretes **progesterone and estrogen** .

- Corpus luteum is maintained by **LH** .

- **Progesterone** reaches its peak level **8-9 days after ovulation** with a second peak of estrogen .

- The high levels of progesterone in presence of estrogen inhibit LH that lead to degeneration of corpus luteum , (luteolysis), and drop of estrogen level 9 days after ovulation. After 14 days of ovulation , it becomes **corpus albicans** .

- **Corpus albicans** persists for some time, then undergoes autolysis and is phagocytosed by macrophages leaving fibrous scar .

- N.B. if fertilization occurs corpus luteum is maintained by human chorionic gonadotropin (HCGn) for **6 months** then converted after **6 months** into corpus albicans.

Drop of estrogen level stimulates FSH secretion by its feedback action on hypothalamus and anterior pituitary gland to start another cycle .

## Ovulation

It is the rupture of mature graafian follicle and expulsion of ovum into the peritoneal cavity to be picked up by fimbriated end of the fallopian tube.

- ovulation occurs at the **14th day** of the cycle

### **mechanism of ovulation :**

Gonadotropin surge stimulates a complex series of changes that cause the final maturation of the oocyte and the physical release of the oocyte from the mature graafian follicle .

Gonadotropin surge leads to very rapid growth of follicle and beginning of progesterone secretion that cause :

(a) Hyperaemia of follicle and increase prostaglandins secretion → plasma transudation → swelling of the follicle .

(b) Release of proteolytic enzymes from lysosome and activation of plasminogen → ↑ activity of collagenase enzyme causing → weakening of follicular wall and degeneration of stigma (weak bulging outer pole of follicle) then rupture of follicle and expulsion of ovum into the peritoneal cavity .

Normally premature oocyte maturation and luteinization are prevented by a **local inhibitory factors** :

a- **Oocyte Maturation Inhibitor (OMI)** : It is one of the follicular factors . It is formed by the granulosa cells . It prevents meiosis of the oocyte (prevent premature oocyte maturation) until the preovulatory LH surge that removes this inhibition . Its activity depends upon an intact cumulus oophorus .

b- **Luteinization inhibitor : (LI)** : also originates from the granulosa cells.



## **Purpose of FSH surge :**

- Induction of an adequate number of **LH receptor** on the granulosa cells for luteinization and normal corpus luteum formation.
- **Stimulates** the granulosa cells to produce **plasminogen activator** → conversion of plasminogen to plasmin → provoke collagenase activity → degradation of follicular wall help ovulation .

## **Indications (signs) of ovulation :**

Ovulation and corpus luteum formation is indicated by the presence of signs of progesterone release of which :

- 1- the presence of **pregnandiol** in urine.
- 2- The presence of **early secretory phase** in the endometrium.
- 3- Increased **vaginal secretion** (discharge) and proliferation of the epithelium in vaginal smear examination .
- 4- **Rise** in body temperature by about **0.5 C°** at the time of ovulation , that persists until bleeding occurs.
- 5- **Lower abdominal pain** at the time of ovulation.
- 6- Presence of **thick cervical secretion** that fail to form fern pattern arborization .

## **Failure of Ovulation (Anovulatory Cycles) :**

Some women who are infertile have anovulatory cycles ; they fail to ovulate but have menstrual periods at regular intervals , such cycles are present normally in the first 1 to 2 years after the onset of puberty (**menarche**) and before the menopause bleeding is due to the withdrawal of oestrogens caused by atresia of graafian follicle. Anovulatory cycles occur also in women treated with **contraceptive pills** .

## **2. UTERINE CYCLE**

The histological picture of the endometrium changes from day to day under the influence of the ovarian hormones . the endometrium is prepared to receive an important visitor (the zygote) i.e. for implantation of the fertilized ovum. If it does not arrive the prepared endometrium is destroyed (not needed) and a new cycle starts . (menstruation is the uterus crying for lake of a baby) .

### **1-Proliferative phase (follicular phase) :**

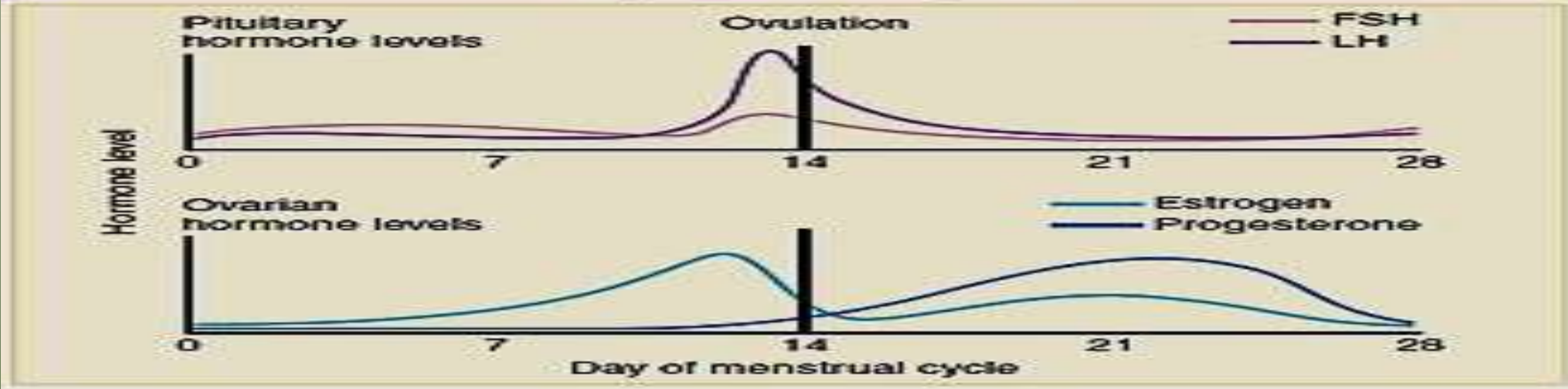
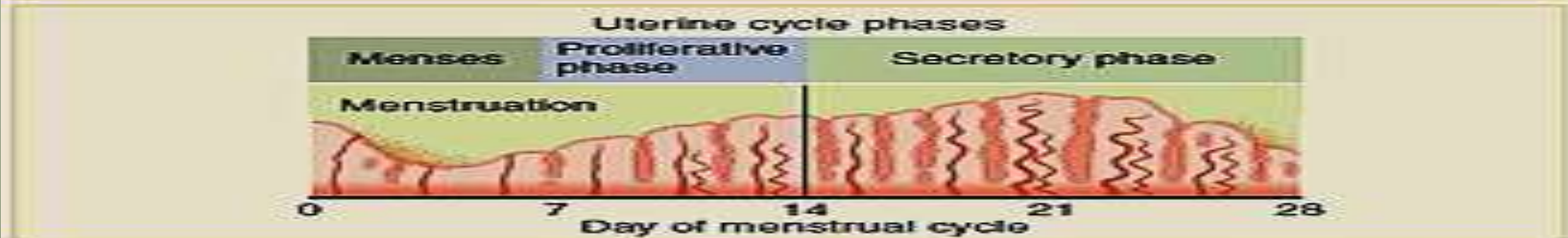
- from the **5th to the 14th day** of the menstrual cycle .
- under the influence of **estrogens** from the developing follicle (follicular state).
- Rapid increase in the endometrium width from **1 mm to 4 mm** .
- The uterine glands increase in length rapidly but with no secretion and finally become wavy .
- Increased **vascularity** , the blood vessels become spiral but not tightly coiled
- the epithelial cells contain little glycogen .

## 2-Secretory phase (premenstrual phase) :

- From the **15<sup>th</sup>** day to the beginning of the next cycle .
  - Under the influence of **estrogens and progesterone** from the corpus luteum .
  - The endometrium becomes edematous and thickens from **4 mm to 8 mm** .
  - The endometrial glands become tightly coiled and folded (cork-screw appearance) with thick mucoid secretion rich in glycogen.
  - The connective tissue lamina propria → decidual reaction.
  - At the end of this stage the thick endometrium can be divided into 3 regions :
    - Compact** : neck of the glands.
    - spongy** : dilated part of the glands .
    - Basal** : blind ends of the glands supplied by straight basal arteries .
- the compact and spongy regions are called the **functional layer** supplied by the spiral arteries. At menstruation the functional layer is lost while the basal remains .

## 3-Destructive or Menstrual phase :

- From the **first** to the **5<sup>th</sup>** day of the menstrual cycle .
- When the corpus luteum regresses , hormonal support of the endometrium is removed .
- The spiral arteries **constrict** and so the functional layer becomes **ischemic** and **necrosed** . The spiral arteries then **dilate** one at a time and their necrotic walls rupture producing hemorrhage . Most of the endometrium is shed in patches soaked with blood .
- The menstrual blood does not contain clots because the damaged tissue liberates anti-coagulant (increased fibrinolytic activity) . The bleeding ends when the spiral arterioles constrict again .



### 3- Vaginal cycle

-In the **follicular** stage : under the effect of estrogens the vaginal epithelium becomes cornified (identified in the vaginal smear) and there is **acidic** secretion .

-In the **luteal** stage : under the effect of **progesterone** the epithelium proliferates and a thick mucus is secreted .

### 4- Cyclic changes in cervix

-In the **follicular** stage : under the effect of **estrogen** there is thin , watery , alkaline mucous that help transport and survival of sperm and gives positive fern pattern arborization .

-In the **luteal** stage : under the effect of **progesterone** there is thick , cellular secretion that gives negative fern pattern arborization .

### 5-Cyclic changes in breast

**Ten days before menstruation** , there is swelling , tenderness and pain the breast , probably due to distension of ducts , hyperaemia and edema of the interstitial tissue of the breast , all these changes regress during menstruation .

# Pregnancy

- is characterized by steadily increasing levels of estrogen and progesterone, which maintain the endometrium for the fetus, suppress ovarian follicular function (by inhibiting FSH and LH secretion), and stimulate development of the breasts.

## 1. Fertilization

- If fertilization occurs, the corpus luteum is rescued from regression by human chorionic gonadotropin (HCG), which is produced by the **placenta**.

## 2. First trimester

- The corpus luteum (stimulated by HCG) is responsible for the production of estradiol E2 and progesterone.

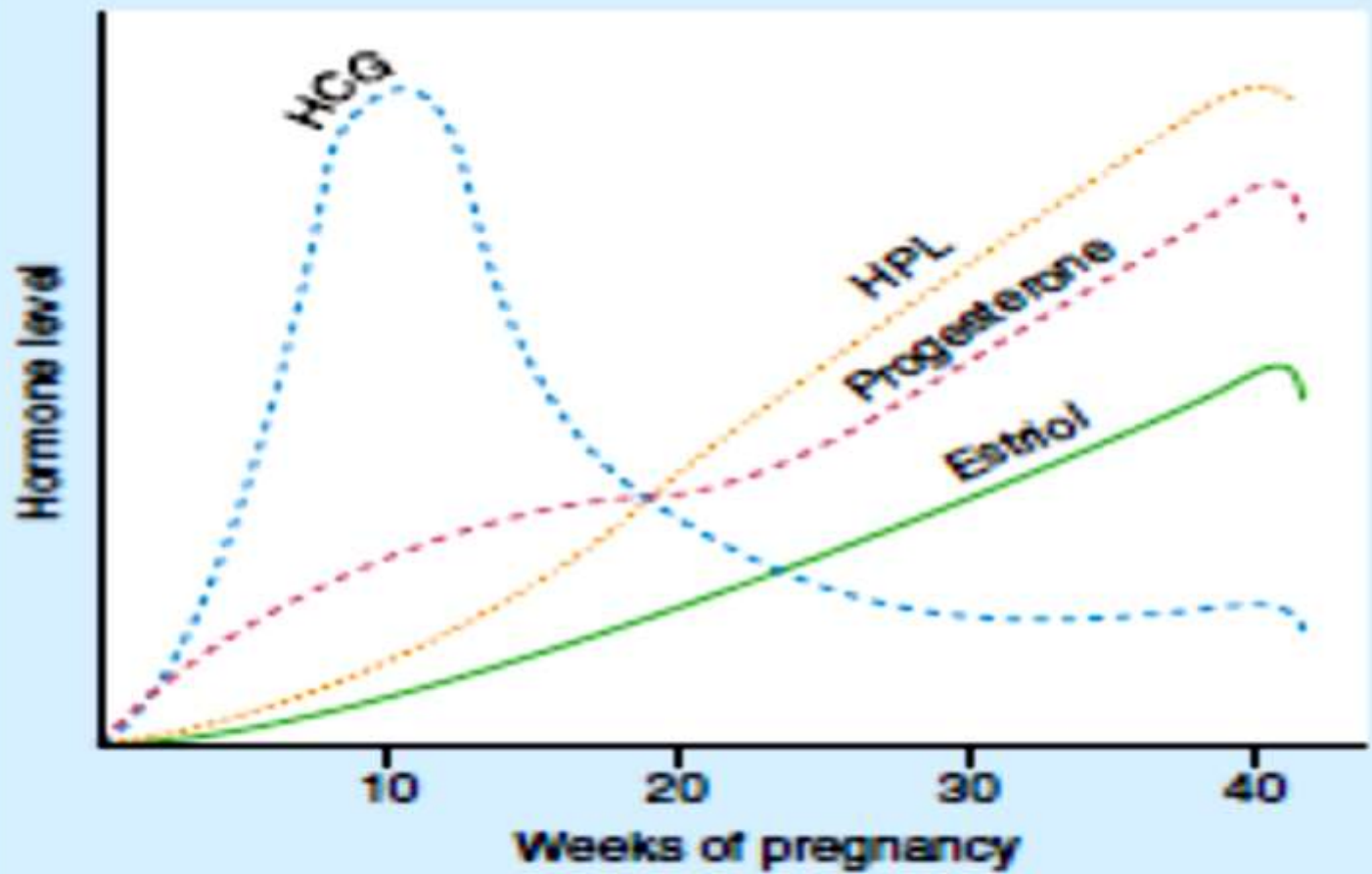
- Peak levels of **HCG** occur at gestational **week 9** and then decline.

## 3. Second and third trimesters

- Progesterone is produced by the placenta.

- Estrogens are produced by the interplay of the fetal adrenal gland and the placenta. The fetal adrenal gland synthesizes Dehydro-epiandrosterone-sulfate (DHEA-S), which is then hydroxylated in the fetal liver. These intermediates are transferred to the placenta, where enzymes remove sulfate and aromatize to **Estrogens**. The major placental estrogen is estriol E3.

- Human placental **lactogen** is produced throughout pregnancy. Its actions are similar to those of growth hormone and prolactin.



Corpus luteum

Placenta

# FUNCTIONS OF THE PLACENTA

The Feto-placental unit :

The placenta is the site where fetal and maternal circulations are closely associated . Most of the gaseous and metabolic exchanges between fetus and mother take in this region of close proximity , although the place also functions as a barrier to the transfer of large molecules and cells .

A- The placenta is a site of **selective exchange** :

- Site of transport of nutrient materials for the fetus .
- Site of exchange of respiratory gases .
- It acts as a kidney for the excretion of waste products .
- It prevents the passage of harmful materials to fetus .

B- The placenta as an Endocrine organ for maintaining pregnancy and preparing the mother for labor and lactation : It secretes 5 main hormones :

1- **Estrogens** :

- Cause enlargement of the breast tissue .
- Cause enlargement of the female external genitalia as a preparation for labor .
- Relax the sacroiliac joint and symphysis pubis ligaments to make easy passage of the fetus through the birth canal .



## 2- Progesterone :

- Increases decidual reaction development .
- Inhibits uterine contraction and prevents spontaneous abortion .
- Prepares the breast for lactation

## 3- Chorionic Gonadotrophin :

- It is a glycoprotein having the same function of **LH**. It replaces the anterior pituitary LH which by the **24<sup>th</sup> day** of the menstrual cycle is only being secreted in small basal quantities because of the steroid feedback inhibition.
- It stimulates the growth of the **corpus luteum** to be the **C.L of pregnancy** to increase its secretion of estrogen and progesterone .
- It stimulates the **interstitial cells of leyding** in the **testes** of the male fetus to secrete **testosterone** hormone which causes descend of the testes into the scrotum and stimulates the development of the male sex organs .
- Its detection is the bases of pregnancy tests as it can be detected in maternal blood 6 – 8 days after fertilization .

## 4- Placental Lactogen (Somato-mammo-trophin):

Recently discovered and secreted about the **5<sup>th</sup> week** of pregnancy .

- It has a luteotropic function stimulating the corpus luteum to secrete estrogen and progesterone (previously ascribed to be the function of chorionic gonadorophin) .
- It stimulates breast development (mammatrophic).
- It stimulates cellular growth (growth-promoting effect) and it inhibits glucose transport (inhibits insulin effect) i.e. it is similar to growth hormone .

## **5- Relaxin hormone (Relaxing Factor) :**

It is secreted from the **placenta** and **corpus luteum** . It softens and relaxes the pelvic ligaments to help in the process of delivery (there are at least 3 closely related polypeptides with molecular weight of about 9000 have relaxin activity )

## **EARLY PREGNANCY TEST**

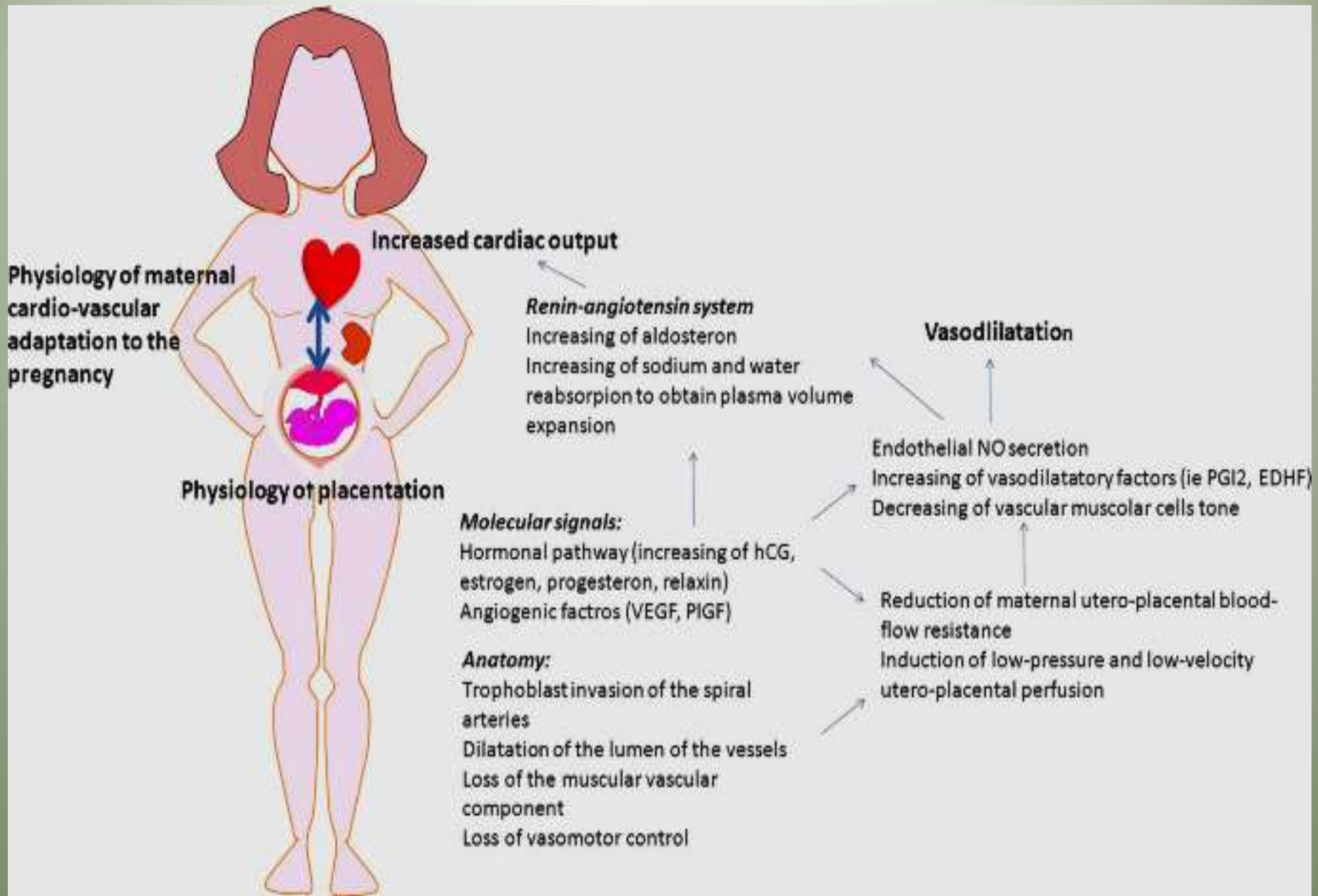
It depends upon detection of chorionic gonadotrophin in urine of pregnant females .

**1- Asheim Zondek Test :** Injection of small amount of urine under investigation in immature female **mice** for 3 days . On the **5<sup>th</sup>** day kill the animal and examine the ovary for the presence of corpus haemorrhagicum and corpus luteum .

**2- Friedman's Test :** Injection of small amount of urine under investigation into an isolated virgin female **rabbit** (isolated from males for at least one month) . The rabbit is killed after 24 to 48 hours to examine the ovaries for the presence of corpus luteum .

**3- Toads and Frogs test :** Injection of small amount of urine in the dorsal lymph sac of a male **frog** , within 3 hours the cloaca will be full of sperms .

**4- Immunological tests :** Very accurate , the presence of human chorionic gonadotropin can be detected when using specific antibodies (prepared in rabbits).



**TLC** = Total lung capacity  
**IRV** = Inspiratory reserve volume  
**VT** = Tidal volume  
**ERV** = Expiratory reserve volume  
**RV** = Residual volume

**Functional effects**

Increased respiratory drive resulting in reduced  $\text{PaCO}_2$   
 Minimal change in TLC  
 Increased VT  
 Reduced FRC predominantly caused by reduction in ERV

**Anatomic effects**

Airway edema and friability  
 Widened anteroposterior and transverse diameters

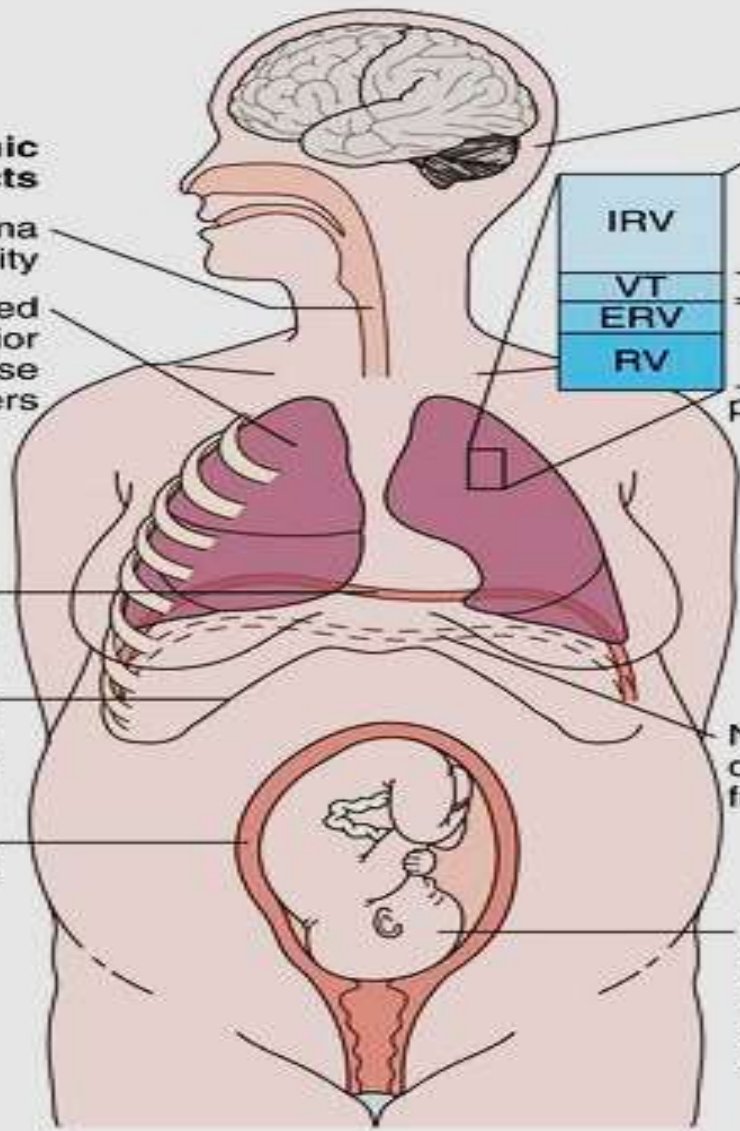
Elevated diaphragm

Widened subcostal angle

Enlarging uterus

Normal diaphragmatic function

Increased oxygen consumption and  $\text{CO}_2$  production



Thank You