#1,2&3Hypothalamic pituitary gonadal axis, Ovarian Cycle & Uterine Cycle

Objectives:

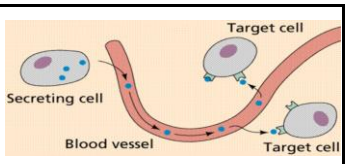
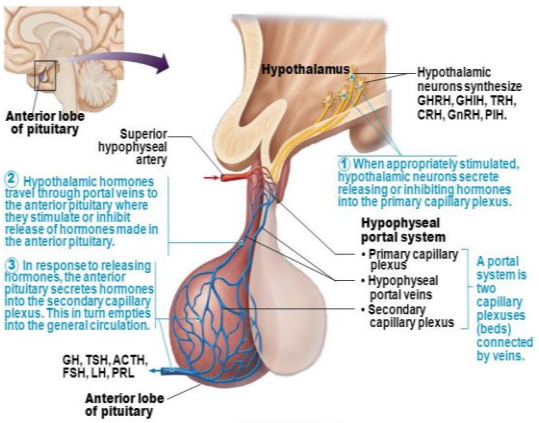
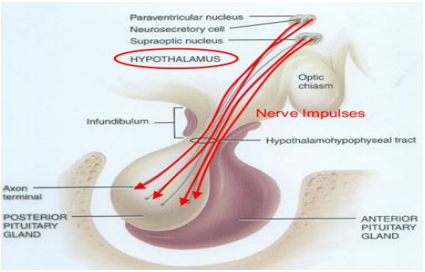
- Characterize hypothalamic pituitary relationship
- Name the hypophysiotropic hormones and outline the effects that each has on anterior pituitary function
- Name anterior pituitary gonadotropic hormones and outline the effects that each has on the gonads
- Describe the negative and positive feedback mechanisms in the hypothalamic-pituitary-gonadal axis and their importance in the control of reproductive function
- List the hormones of female reproductive organs and describe their physiological functions
- Describe the changes that occur in the ovaries during the menstrual cycle
- Describe the hormonal control of the development of ovarian follicles, mature oocytes and corpus luteum
- Describe the pituitary ovarian axis and in correlation with the changes that occur in the ovaries leading up to and following ovulation during an ovarian cycle
- Describe the normal menstrual cycle
- Discuss the structural changes that occur in the endometrium during the menstrual cycle
- Describe phases of the menstrual cycle
- Describe the hormonal control of the menstrual cycle
- Describe the major disorders of the menstrual cycle
- Describe the physiology of menopause

Important
Males notes
Females notes
Extra

Resources: 435 female's slides+435 male's slides
Editing file: Here

Revised by
خولة العماري & هشام الغفيلي

Recall from the endocrine block :')

What is a hormone?	Are secretions of ductless glands that are directly released into the bloodstream. They can act on cells in the vicinity or on distant target cells. 
How hypothalamus controls anterior pituitary?	The Connection between Hypothalamus and anterior pituitary is: <u>Hypothalamic-hypophysial portal vessels</u> 
What are the hormones secreted by anterior pituitary?	• Adrenocorticotropic hormone (corticotrophin, ACTH) • Thyroid-stimulating hormone (thyrotropin, TSH) • Growth hormone (GH) • Follicle-stimulating hormone (FSH) • Luteinizing hormone (LH) • Prolactin (PRL)
How hypothalamus controls posterior pituitary?	The Connection between the hypothalamus and Posterior pituitary gland is:<u>Hypothalamohypophysial tract between the hypothalamic neuclei (supraoptic and paraventricular nuclei) and posterior pituitary gland (neural connection)</u> 
What are the hormones secreted by posterior pituitary?	Oxytocin & ADH

Hypothalamic Pituitary Control of Male & Female Reproduction

Hypothalamus secretes GnRh → Anterior Pituitary secrets LH &FSH → LH & FSH act on the ovaries & the testis

<u>GnRH :</u>

- A peptide secreted by the arcuate nuclei of the hypothalamus through the hypothalamic-hypophysial portal system to Stimulate anterior pituitary to release gonadotropins (LH and FSH).
- GnRH is secreted intermittently(in pulses) for few minutes every 1 to 3 hrs.
- The neural activity that causes pulsatile release of GnRH occurs in the mediobasal hypothalamus, in the arcuate nuclei regulate most of the female & male sexual activity.

- Secretion of anterior pituitary hormone is controlled by "<u>releasing hormones</u>"
- Intermittent, pulsatile secretion of GnRH stimulates pulsatile release of LH (every 90 minutes)(that occur in both female & male) If High dose of GnRH is given, pituitary will not respond and becomes less sensitive

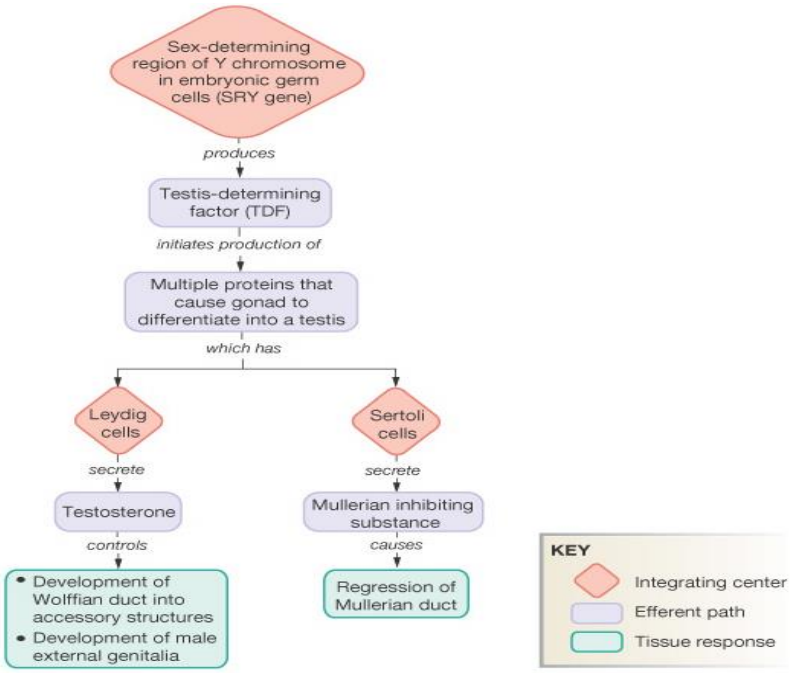
#Why this century puberty is earlier? Because resources are available and body tend to focus on reproductive rather than survival..

#GnRH produced by the arcuate nucleus of the hypothalamus and increased in rapid eye movement (sleep)
GnRH level increase after the third month of pregnancy and after birth and decrease until puberty اذن عندنا زيادتين للجنراتش قبل البلوغ
#in case of prolactinemia GnRH will be suppressed

Male Reproduction

Development of male genital system:

هذي الاضافة الجديده الي بسلايدات العيال ترا نفس الي اخذناه بالامبريو بس حبيت شكل المايند ماب عشان كذا حطيتها



Hormonal Regulation of Testicular Function:

Hypothalamus secretes GnRh to stimulate	Anterior Pituitary secrets LH &FSH	• LH stimulates Leydig cell • FSH stimulates sertoli cell

- **LH stimulates interstitial (Leydig) cells To release:** testosterone.
- **FSH Binds to its receptors on Sertoli cells to induce:** وهذي الاضافه الثانيه الي اضافه الدكتور
  - growth factors important for **spermatogenesis,**
  - Production of androgen-binding protein (ABP),
  - the synthesis of the aromatase enzyme that converts androgens to estrogens,
  - production of inhibin which inhibits FSH secretion. اذا زاد السيرمز كنقتف فيد باك يفرز الانهيبين

-اين تحدث عملية تكوين السبيرم (spermatogenesis)؟ في التيستيس تحديدا في parenchyma داخل تركيب يسمى **seminiferous tubules**

-التيستيس عبارة عن:parenchyma & stroma.

-Parenchyma consist of: "seminiferous tubules (formed of sertoli cell:responsible of spermatogenesis)" + "interstitium(formed of Leydig cell: responsible of testosterone secretion)".

-

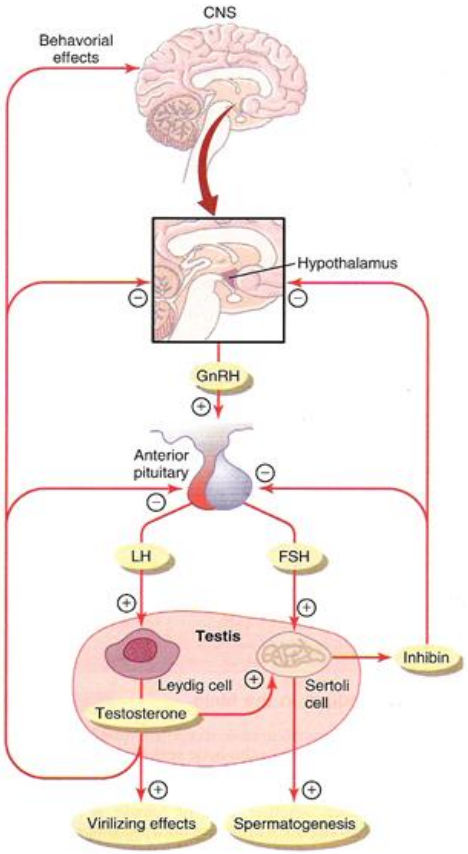
كيف تحدث عملية تكوين السبيرمز؟؟ بكل بساطة السيرتولي سيلز عشان تنتج سبيرمز تحتاج محفزين أحد هذين المحفزين هو FSH

عندما يتحد مع ريسبترز ملتصق بالسرتولي سيلز..و المحفز الاخر هو التيستستيرون الذي يفرز من الليدق سيلز جزء منه يذهب الى السيرتولي سيلز يحفزها على تكوين سبيرمز.. بس خلصنا

Testosterone production: تابعوا الصورة التي عالجنب وانتم تقرؤا

Regulation of Testosterone production by LH:

- Testosterone is secreted by Leydig cells, in the interstitium of the testis, by LH stimulation from the Anterior Pituitary.
- Testosterone release is directly proportional to the amount of LH.
- Mature leydig cells are found in a child's testis few weeks after birth & then disappear until puberty when it appear again.



Negative feedback control of testosterone:

- LH stimulate Testosterone secretion by the testis
- Testosterone inhibit the secretion of LH.
- Most of the inhibitory effect result from direct inhibition of GnRH release from the hypothalamus
- Inhibition of GnRH leads to decrease secretion of both LH & FSH.

Spermatogenesis: تابعوا الصورة التي عالجنب وانتم تقرؤا

Regulation of spermatogenesis by FSH and testosterone: FSH functions in male are 1)Spermatogenesis 2)Produce inhibin 3)Produce Androgen Binding Protein 4)Produce aromatase

- FSH binds with specific FSH receptors attached to the sertoli cell in the seminiferous tubules, which causes these cells to grow & secrete spermatogenic substances.
- Also testosterone & dihydrotestosterone diffuses into the seminiferous tubules from the leydig cells affect the spermatogenesis,
- So both FSH & testosterone are necessary to initiate spermatogenesis. #LH induce spermatogenesis indirectly by testosterone

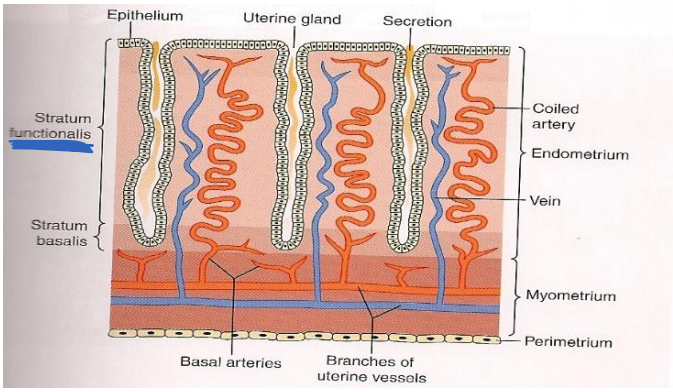
Positive feedback control of seminiferous tubule activity: When the seminiferous tubules fail to produce sperm the secretion of FSH from the AP increases.

Negative feedback control of seminiferous tubule activity
Role of the hormone inhibin:

- Conversely, when spermatogenesis proceeds rapidly pituitary secretion of FSH diminishes.
- This is due to the secretion of **inhibin hormone** from the sertoli cells which strongly inhibit the Ant.Pituitary FSH . inhibin inhibit FSH only
- **Inhibin** has slight inhibitory effect on the hypothalamus to inhibit GnRH secretion.

Female Monthly Sexual Cycle (The Menstrual Cycle)

Anatomy of the uterine layers:



What is the menstrual cycle & its results:

هي دورة من التغيرات الطبيعية التي تحدث في الرحم والمبيض بهدف تمكين عملية التكاثر ففيها يتم إنتاج البويضات وتجهيز الرحم للحمل

- Monthly rhythmical changes in the rates of secretion of female hormones & corresponding physical changes in the ovaries & other sexual organs,This rhythmical pattern is called the female monthly sexual cycle (or, less accurately, the menstrual cycle)
- Duration of the cycle average 28 days (It may be as short as 20 days or as long as 45 days in some women).
- There are 2 significant results of the female sexual cycle:
    1. Single ovum is released from the ovaries each month
    2. Uterine endometrium is prepared for implantation for the fertilized ovum.

female monthly sexual cycle (Menstrual cycle)
هي دورة من التغيرات التي تحدث في الرحم والمبيض

- Ovarian cycle (تنقسم بناء عى الاحداث التي تحدث بالمبيض إلى ثلاثة اطوار): Follicular phase → ovulation → Luteal phase
- Uterine cycle (تنقسم بناء عى الاحداث التي تحدث بالرحم إلى ثلاثة اطوار): Mensural phase → proliferative → Secretory phase

Physiology of Ovarian Cycle

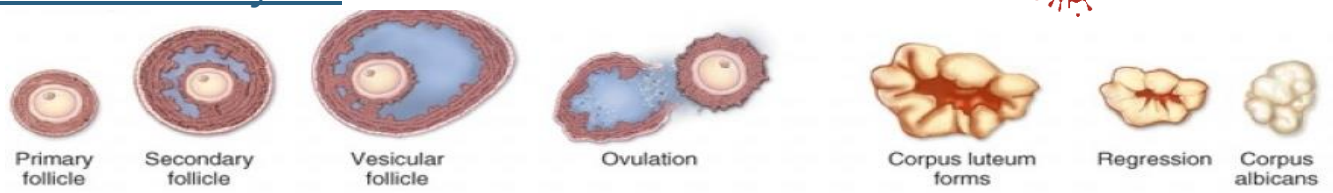
Gonadotropic hormones and their effects on the ovaries:

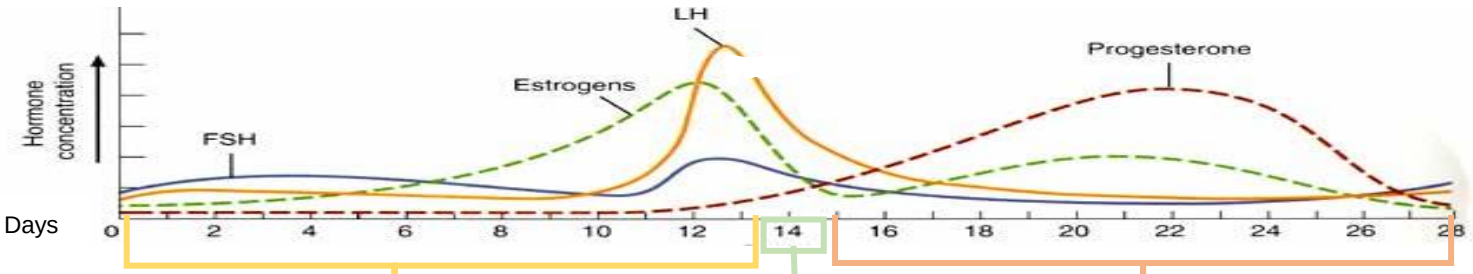
- The ovarian changes during the reproductive cycle depend on FSH & LH secreted by AP.
- In the absence of these hormones, the ovaries remain inactive throughout childhood, At puberty the AP starts to secrete FSH & LH which lead to the beginning of monthly reproductive cycles.
- First menstrual cycle is called menarche.
- Both FSH and LH stimulate their ovarian target cells(keep in mind LH& FSH NEVER stimulate the uterus ONLY stimulate ovaries) by combining with highly specific receptors to increase Rates of secretion, Growth & proliferation of the cells.

we start counting the days of the cycle when the bleeding starts

Events of ovarian cycle:

The ovarian cycle(khan academy) 10 min





ovarian follicle growth"Follicular" phase | **Ovulation** | **Luteal phase**

نبدا نتكلم من لما تنولد البنت يكون عندها ملايين من البرايموردیال فوليكل(عبارة عن بويضة يغطيها طبقة وحيدة من الخلايا نسميها قرانيولاوزا سيلز) هذي البرايموردیال فوليكل تقعد زي ماهي ماتكبر ولا يصير لها شيء إلى سن البلوغ...

عند سن البلوغ أول شي يبدأ يفرز اف اس اتش هذا الهورمون يحفز الفوليكل انها تكبر وتزيد طبقاتها تقعد البرايموردیال فوليكل تكبر تكبر ويتغير شكلها تحت تأثير اف س اتش **فقط**..لكن عندما تصل الى مرحلة اسمها انترال فوليكل(او سكندري فوليكل)هنا عشان تنمو وتكبر بعد هذي المرحلة لا يكفيها اف اس اتش بل تحتاج الى هورمون اضافي يساعدها انها تنمو اكثر عشان تصير ماتشيور فوليكل هذا الهورمون هو ال اتش ..يله اقروا التكمله تحت ماودي احرق القصه زياده :)

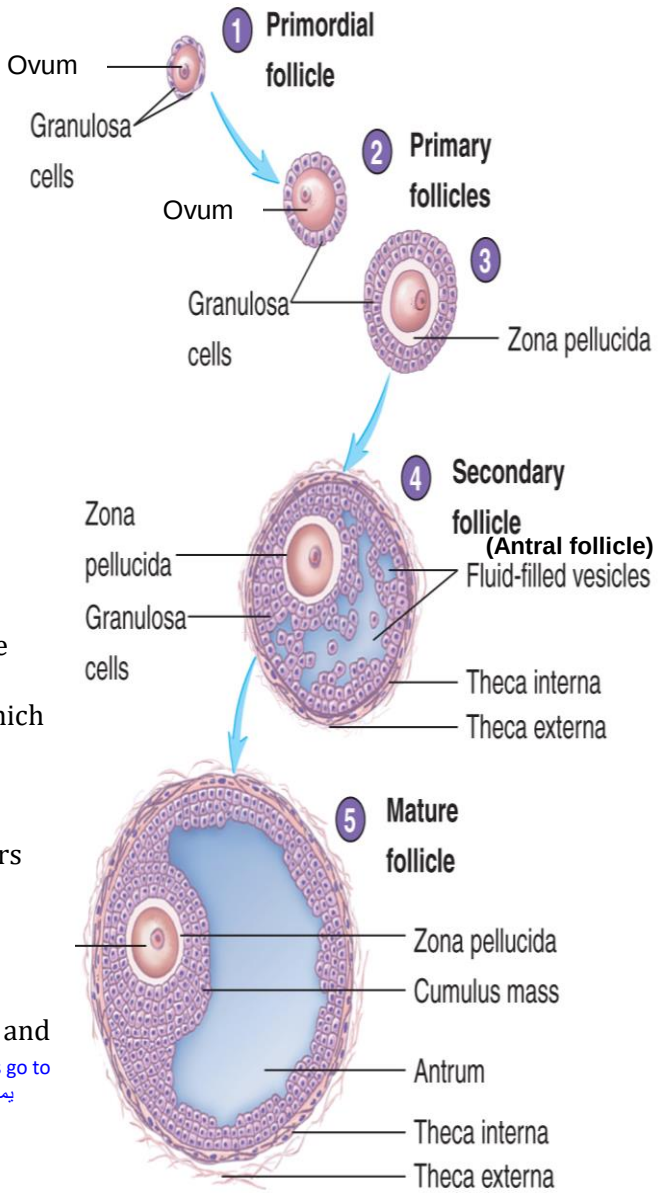
1. In female child each ovum is surrounded by single granulosa cell sheath called primordial follicle.
   During childhood, the granulosa cells:
   - Provide nourishment for the ovum
   - Secrete oocyte maturation inhibiting factor which keeps the ovum suspended in its primordial state.

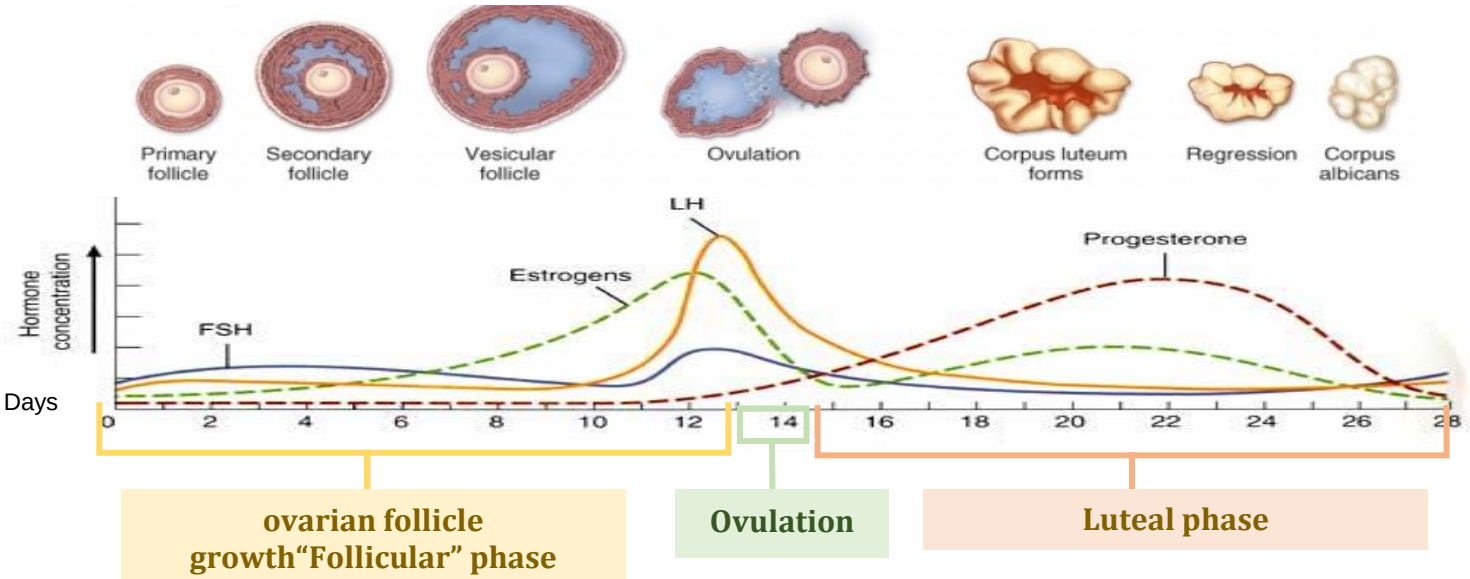
2. 3. After puberty, AP secrete FSH and LH which
   - Stimulate the ovaries and result in growth of some follicles.
   - Growth of the follicle begins with increase in size of the ovum to & growth of additional layers of granulosa cells of some follicles
   - At this stage it is known as primary follicles.

4. During the first few days of the monthly female reproductive cycle there is increase in secretion of **FSH and LH,**
   - Increase in FSH is slightly more & earlier than LH which causes the acceleration of growth of many primary follicles each month.
   - There is proliferation of the granulosa cells to many layers. The ovary interstitium collect in several layers outside the granulosa cells to form a second mass of cells called **theca.**

     This theca is divided into 2 layers:

     1. Theca interna, the cells have epitheloid characteristics and similar to the granulosa cells and secrete sex hormones (**ANDROGENS**)then androgens go to granulosa cells to convert into estrogen by aromatase enzyme يمكن تجيكم سؤال اين يفرز الاندروجين
        LH stimulates theca INTERNA to produce ANDROGEN.(MCQ)
     2. Theca externa, the outer layer, develops into a highly vascular connective tissue capsule of the developing follicle. خلوها ببالكم ان الثيكا اكسترنا ماتفرز هورمون هي عبارة عن كابسول يحاوط القرانيولوزا



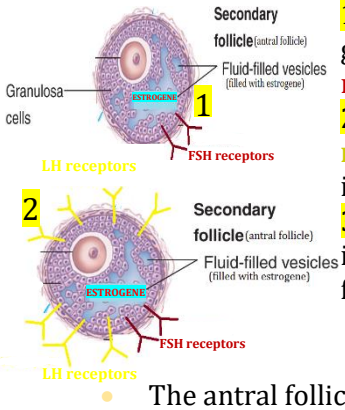


ovarian follicle growth"Follicular" phase | **Ovulation** | **Luteal phase**

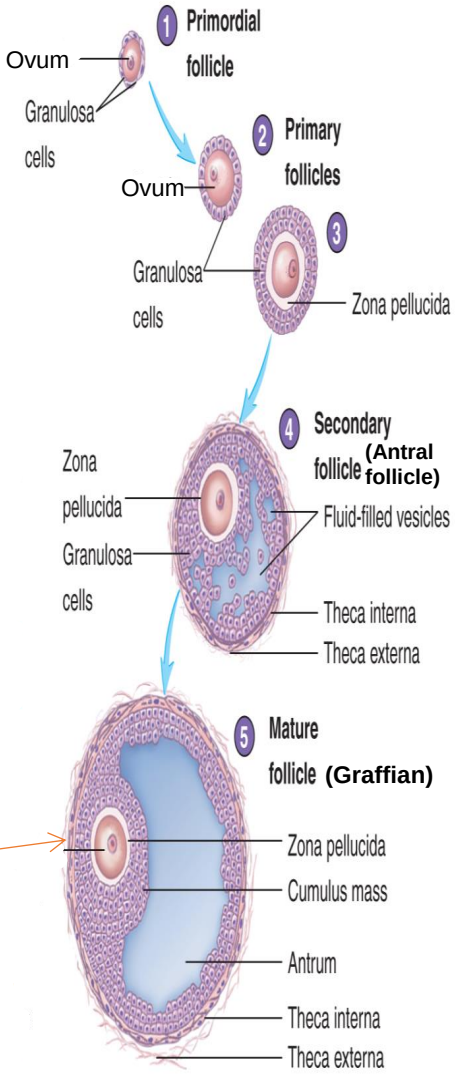
5

- Few days after proliferation & growth of the follicles, the granulosa cells secrete follicular fluids contain high concentration of estrogen.
- This fluid accumulate to form antrum(antrum is a fluid sac filled with estrogen) within the mass of the granulosa cells.
- The early growth of the follicle up to the antral is under FSH stimulation ALONE. عندما يتكون الانتروم في هذي المرحله لكي تستمر الفوليكل نموها لا يكفيها الفستش لكي تنمو أكثر بل تحتاج الى هرمون اضافي الي هو إل إتش لكي تزداد بالنمو

- Then there is accelerated growth of the follicle to larger follicle called **vesicular follicle (Graffian)** caused by:- كيف تحولت الانترال فوليكل إلى قرافين فوليكل ماهي المكانزم الي سببت هذا التحول**(مهمه جدا جدا جدا)**



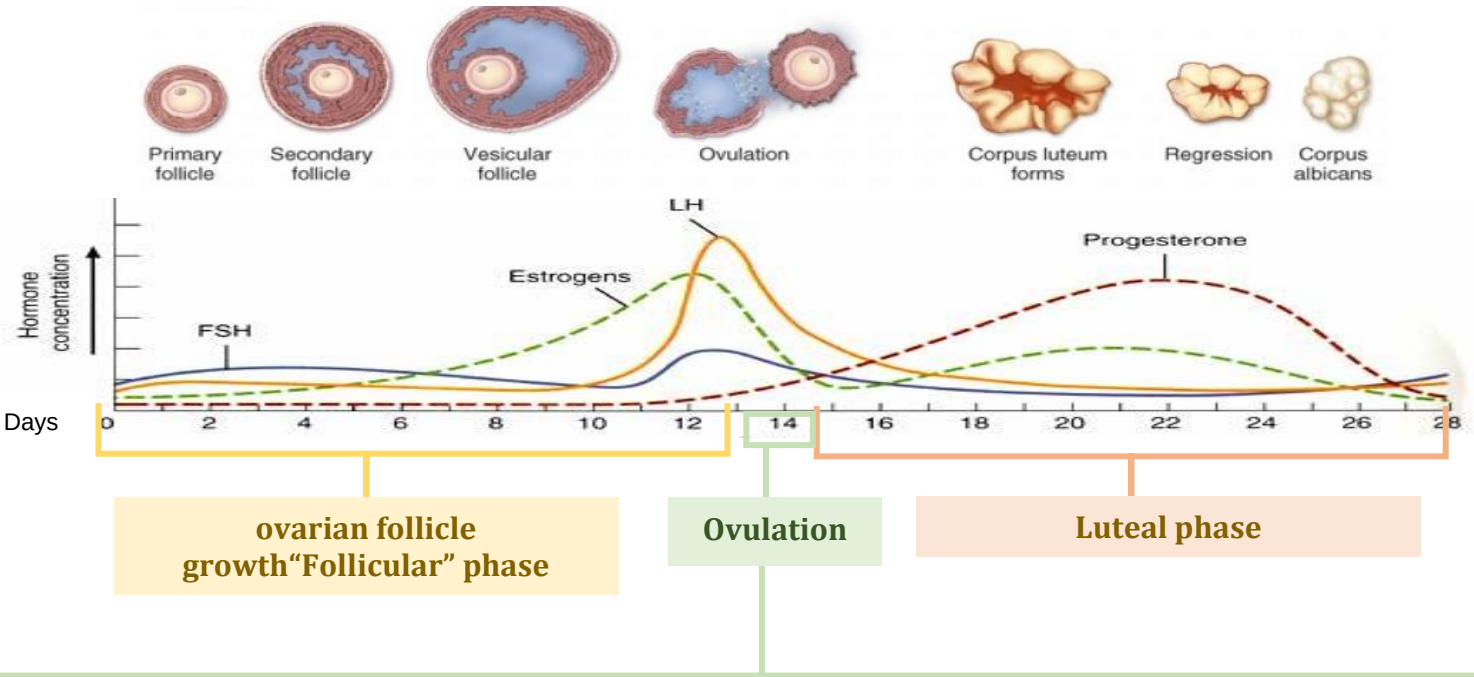
1)Estrogen secreted into the follicle causes the granulosa cells to form increasing number of FSH receptors which causes **positive feedback effect;**
2)Both estrogen & FSH combine to promote **LH receptors** on the granulosa cells, allowing more increase follicular secretion;
3)The increasing estrogen from the follicle plus increasing **LH** from the AP causes proliferation of the follicular theca cells & increase their secretion.



- The antral follicles begin to grow.
- The ovum enlarges & remain embedded at one pole of the granulosa cells of the follicle.

- After a week or more of growth—but before ovulation occurs—one of the follicles begins to outgrow all the others, and the remaining 5 to 11 developing follicles involute (a process called atresia)

The cause of the atresia is unknown, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well developed follicles. Therefore, the largest follicle continues to grow because of its **intrinsic positive feedback** effects, while all the other follicles stop growing and actually involute because of **central negative feedback.**



When ovulation occur? Ovulation in a woman who has a normal **28-day** female sexual cycle occurs **14 days** after the onset of menstruation So it's occur in the half of the period time e.g if the cycle is 30 days the ovulation will be in the 15th day and so on

before ovulation:

- 2 days before ovulation → rate of LH secretion ↑ to 6-16 fold & peaks about 16 hrs before ovulation & FSH also ↑ 2 to 3 fold & acts synergistically with LH to cause swelling of the follicle before ovulation.

- (Without LH hormone, ovulation will not occur)LH surge is necessary for final follicular growth and ovulation: WHY????

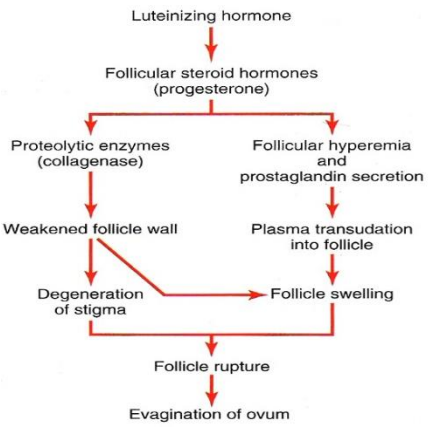
  LH has specific effect on the granulosa cells & theca cells converting them to *progesterone-secreting cells* → rate of estrogen secretion ↓ about 1 day **before ovulation** while progesterone secretion begin to increase تذكروا انه ببداية الفوليكيولر فيز ال اتش يحفز الثيكا انترنا والقرانيولوزا على افراز الاستروجين لكن بنهاية الفوليكيولر فيز وقبل الاوفيوليشن بيوم ال اتش بيخلي الثيكا انترنا والقرانيولوزا تفرز بروجسترون بكمية كبيرة..طيب ليش خلاها تفرز بروجسترون وبهذا الوقت بالذات وش فايدته؟؟ البروجسترون له دور مهم بالاوفيوليشن بأنه يخلي الخطوتين الي تحت تصير ومن ثم يحدث اوفيوليشن

  This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours 2 events occur which are necessary for ovulation:

  2 mechanisms cause rupture of the follicle:

  1) the **theca externa** begins to secrete proteolytic enzymes & causes weakening of the wall resulting in swelling of the follicle & degeneration of the stigma ستيقما هي بروز الاوفام على جدار الفوليكل

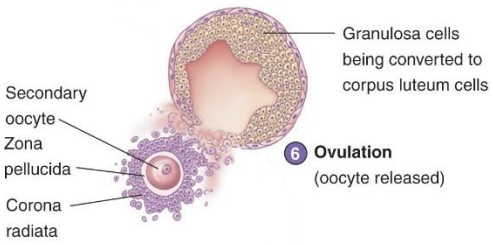
  2) rapid growth of **new blood vessels** into the follicle wall & prostaglandins are secreted into the follicular tissue.

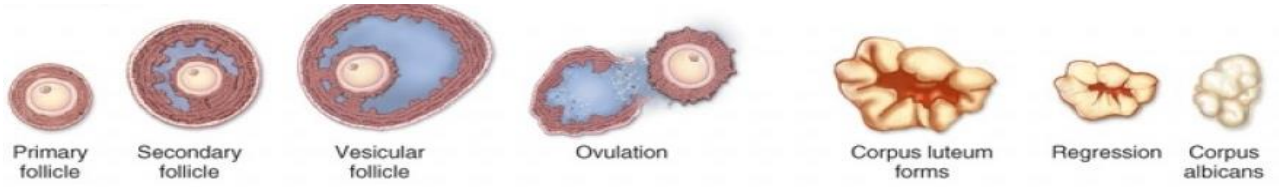


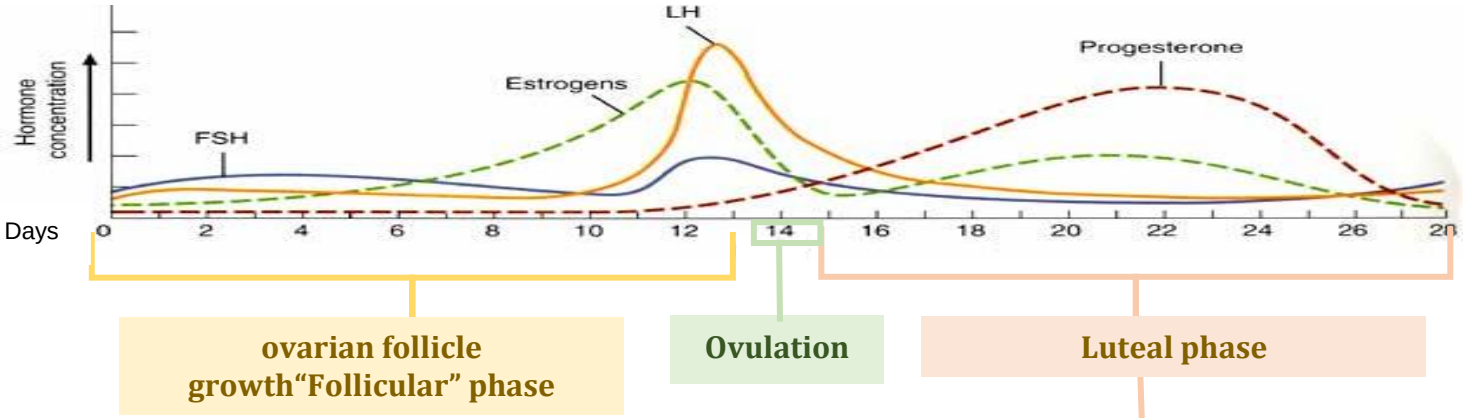
6 During ovulation:

stigma protrudes & fluids ooze from the follicle & the stigma ruptures allowing more viscous fluid outward carrying with it the ovum surrounded by mass of granulosa cells called corona radiata

when the ovulation occurs > after two weeks
bleeding must occur
, the problem is the duration of follicular phase it's not constant



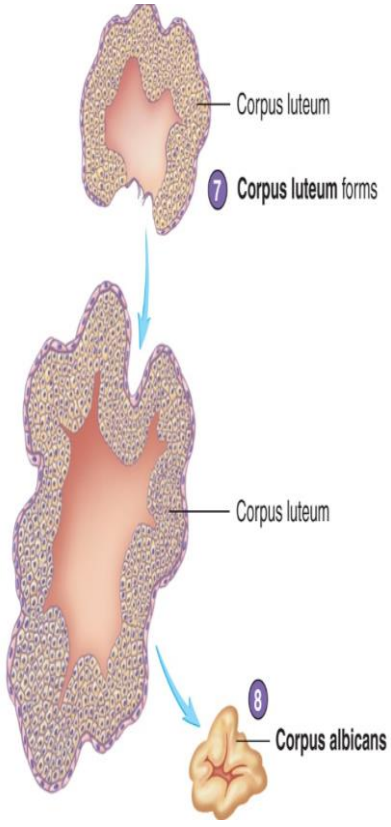




7 After expulsion of the ovum from the follicle, the remaining granulosa & theca interna cells change to **lutein cells** & become filled with lipid inclusions giving them yellowish appearance.(Under the influence of LH mainly)

The granulosa cells in corpus luteum secrete large amount of **progesterone** &small amount of estrogen& inhibin.

The theca cells secrete mainly androgens which are converted by granulosa cells into female hormones.



Function of LH:

1-Change of granulosa and theca interna cells into lutein cells.

2- Causes ovulation.

3- Maintains secretion of progesterone & estrogen from the corpus luteum

يساعد على تثبيت الحمل لان الاستروجين والبروجسترون تحفز نمو وثبات بطانة الرحم,بنرجع ناخذها بيتفاصيل اكثر بدرس الحمل دوونت ووري:)بس احفظوها الحين عشان اذا جينا للحمل تتذكرونها :))

If pregnancy occurs: the **chorionic gonadotropin** from the Trophoblast acts on the corpus luteum to prolong its life for 2 to 4 months of pregnancy بنرجع ناخذها بيتفاصيل اكثر بدرس الحمل دوونت ووري

8 Involution of the corpus luteum and onset of the next ovarian cycle:

1- corpus luteum secrete both progesterone & estrogen & inhibin which all together cause negative feedback effect on Ant.pituitary to inhibit both FSH & LH . تثبط هورموني الغدة النخامية التي يحتاجها الكوربوس ليتيوم لنمو والحفاظ على نفسه فتبدأ مستويات هومروني (ال اتش+اف اس اتش)بالانخفاض ممايؤدي الى ضمور واضمحالال الكوبروس ليتيوم فالبتالي الهورمونات التثبيطية التي تفرزها الكوربوس لوتيوم ستقل اذا قلت هذي الهرمونات المثبطة للانتيريور بيتيوتري سيأخذ افراز هرموني الغده النخاميه بالزيادة معلنا نهاية الدورة الشهرية وبداية دورة جديدة

2- Around 26th days of normal sexual cycle & after involution of corpus luteum, sudden cessation of estrogen, progesterone & inhibin removes the negative feedback inhibition of the AP & allowing ↑ secretion of FSH & LH again. FSH & LH initiate the growth of new follicles, beginning a new ovarian cycle.

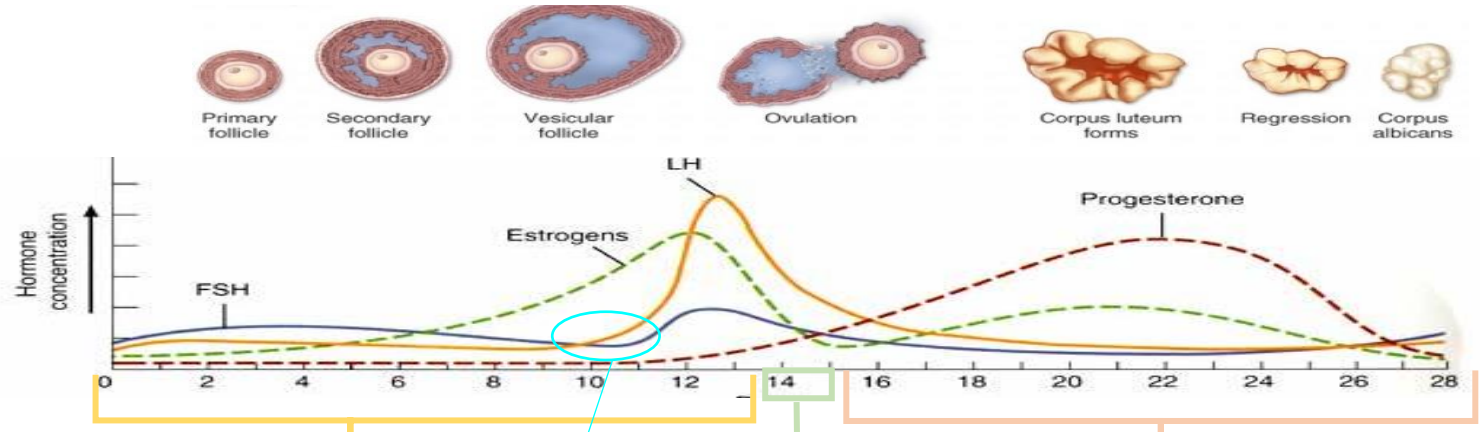
Feedback oscillation of the hypothalamic-pituitary-ovarian system

-To make ur life easy, keep in mind:

- Estrogen & progesterone have a POSITIVE feedback on LH &FSH secretion(during days 12 through 14)
- Estrogen & progesterone have a NEGATIVE feedback on LH &FSH secretion(occurs throughout most of the cycle)

-I advise u to read (pic below) The luteal phase first >then the follicular phase>then the ovulation

-Now, after discussing much of the known information about the interrelations of the different components of the female hormonal system, we can explain the feedback oscillation that controls the rhythm of the female sexual cycle. It seems to operate in approximately the following sequence of three events:



Follicular phase

2

Follicular growth phase :

- 2 to 3 days before menstruation, corpus luteum regress & secretion of estrogen, progesterone & inhibin decrease.
- This decrease remove the negative feedback effect on AP hormones. Therefore a day after menstruation FSH secretion begins to increase (2 folds) while LH secretion is slightly because inhibin inhibit the secretion of FSH & **to lesser extent LH**.
- These hormones (FSH & LH) causes growth of the follicle.
- During the first 11 to 12 days of this follicle growth the rate of secretion of FSH & LH **decrease slightly** because of the negative feedback effect of estrogen on the AP.

Ovulation

3

Pre ovulatory surge of LH & FSH causes ovulation:

- About 12 days of the monthly cycle, the high secretion of FSH & LH start to increase due to high level of estrogens causes positive feedback on the anterior pituitary which leads to pre-ovulatory LH surge & FSH surge.

يقولك ان قبل الاوفيوليشن بيومين بيرتفع
FSH & LH ارتفاع كبيرر وهذا الارتفاع سيؤدي الى خروج البيضه من البويضه (الاوفيوليشن)
كمان قبل الاوفيولشن بيومين لاحظو ان إل إتش مرتفعه اكثر من إف اس اتش,طيب ليش وش معنى
إل إتش يرتفع اكثر من إف اس اتش؟؟؟؟؟؟؟؟بتعرفو السبب اذا قريتو تحت :))

AP secretes increased amount of LH for 1 to 2 days before ovulation. -FSH surge is much smaller in the pre-ovulatory than LH surge, why? The possible causes of LH secretion could be??.

- estrogen has special positive feedback effect of stimulating pituitary secretion of LH & to a lesser extent FSH.
- the granulosa cells of the follicle begin to secrete small increasing amount of progesterone about 1 day before ovulation which stimulate LH secretion

Luteal phase

1

During the postovulatory phase (between ovulation & beginning of menstruation) the corpus luteum secrete large quantities of both progesterone & estrogen & inhibin which **all together cause negative feedback** effect on Ant.pituitary & hypothalamus to inhibit both FSH & LH secretion.

- Estrogen in small amounts has strong effect to inhibit the production of LH & FSH. This inhibitory effect of estrogen is increased when progesterone is available. This inhibitory effects more on the AP directly & to lesser extent on the hypothalamus to inhibit the secretion of GnRH.
- The hormone inhibin secreted by the granulosa cells of the ovarian corpus luteum inhibit the secretion of FSH & to **lesser extent LH.**

(lowest level 3-4 days before the onset of menstruation لأنه بنهاية اللوتيال فيز تبدأ الكوربوس ليتيوم تضمحل فالبتالي الهورمونات التثبيطية التي تفرزها ستقل اذا قلت هذي الهرمونات المثبطة للانتيريور بيتيوتري سيأخذ افراز هرموني LH& FSH بالزيادة
زيادة افراز هذي الهورمونين تؤدي الى تكوين فوليكل جديده مؤديا الى ظهور الفوليكيوار فيز واستمرار هذه المنسترول سايكل)

What is the predominant hormone in the follicular phase??estrogen

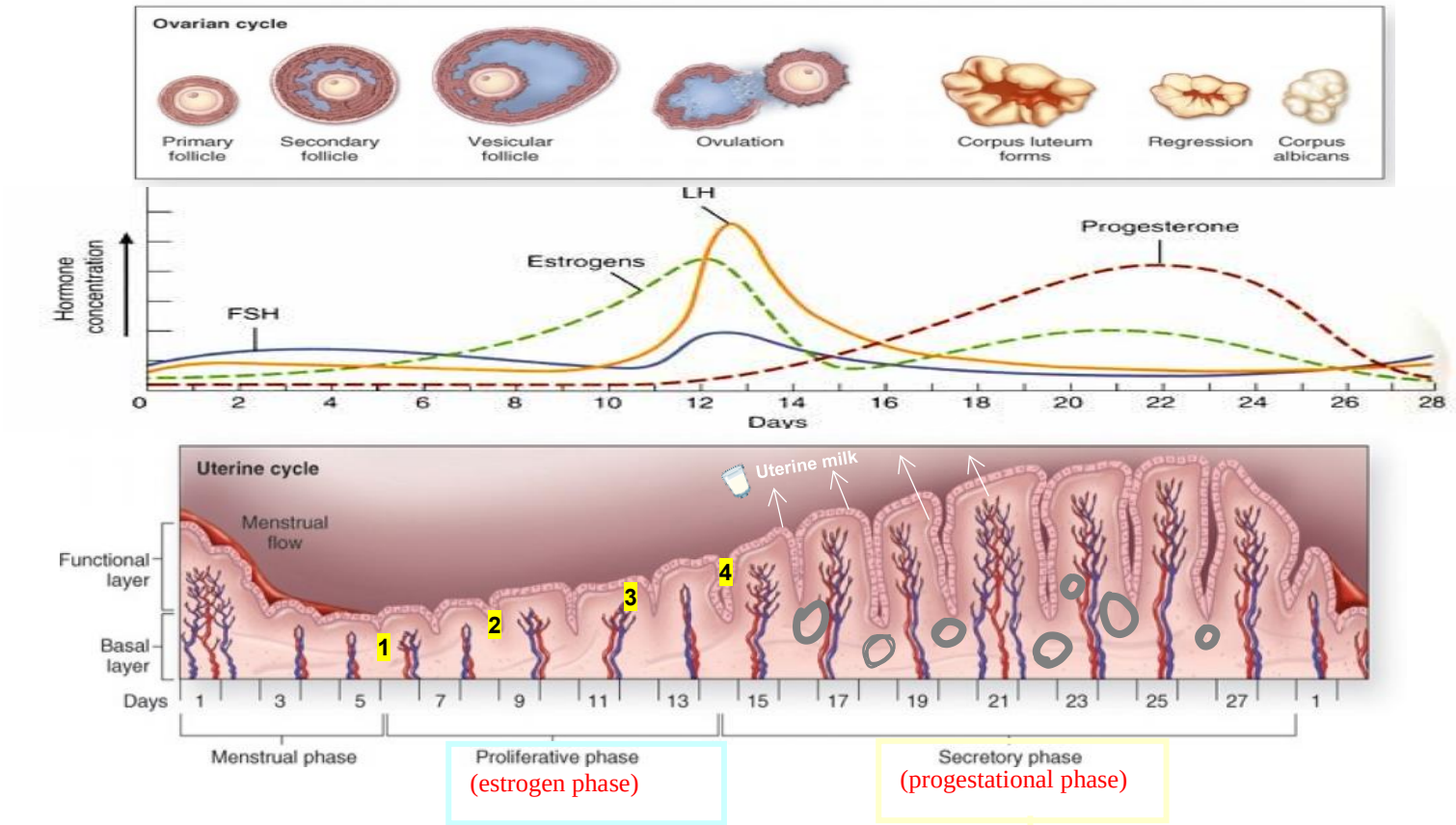
What is the predominant hormone in the luteal phase??progesterone

The principle of Oral Contraceptive ? the combination of small amount of estrogen with progesterone

The rate limiting step in the estrogen synthesis is the desmolase enzyme

Physiology of Uterine (Endometrial) Cycle

It is associated with the monthly cyclical production of estrogens & progesterone by the ovaries in the lining of the uterus pass through the following stages:



قبل مانبدأ مهم تعرفون ان الاستروجين والبروجوسترون تعمل على الحفاظ وزيادة نمو بطانة الرحم لكن مين الي تأثيره اقوى في البرولوفريشن والي بدونه بيموت الاندوميتريوم؟البروجسترون

-على كل نهاية و بداية سايكل بتصير عندي نسبة الاستروجين والبروجسترون مرره قليلية لان ماعندي فوليكل المتنجه لهما فاكيد الاندوميتروبم بيصير له انسلاخ وسمكه سيقل..فأول مايفرز الاستروجين ستأخذ الاندوميتريوم بالنمو شيئا فشيئا وتزداد سماكة جداره الداخلي، وتكثر أوعيته الدموية وخلايه الإفرازية

1) At the beginning of each cycle, most of the endometrium has been lost during menstruation, and only a thin layer of basal endometrial stroma remains. The only remaining epithelial cells are located in the crypts of the endometrium and in the deep portions of the endometrial glands.

2)Estrogen secreted from developing follicles during the early portion of the cycle stimulates rapid proliferation of stromal and epithelial cells.

3)The entire endometrial surface is re-epithelialized within 4 to 7 days of the beginning of menstruation(The endometrium thickness increases, due to increase numbers of stromal cells &progressive growth of the glands & new blood vessels).

4)At the time of ovulation, the endometrium is **3-5 mm thick**. The endometrial glands of the cervical region secrete a thin, stringy mucus which helps to guide sperm in the proper direction from the vagina into the uterus.

- After ovulation, the corpus luteum secretes **large amounts of progesterone** and small amount estrogen.

The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory development of the endometrium

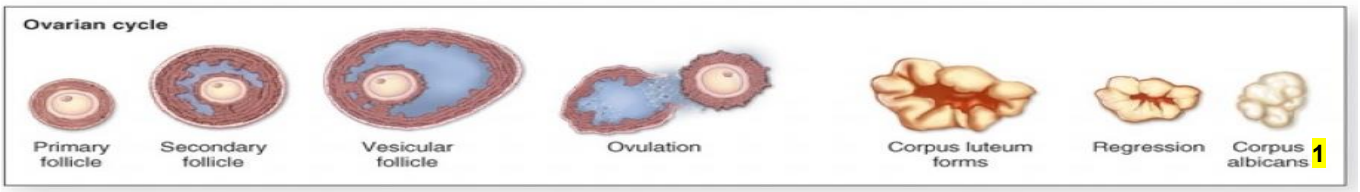
- **What are The effects of progesterone??** يعمل على الحفاظ على بطانة الرحم وتهيئتها للانغراس

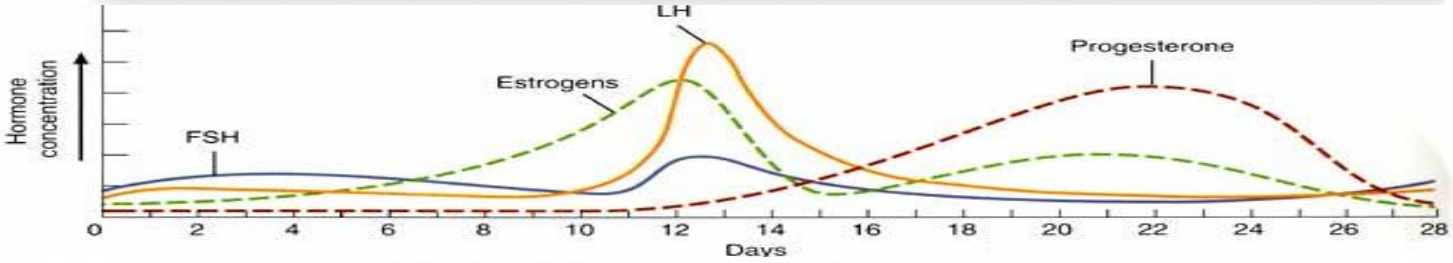
-cause MARKED swelling of the endometrium
-↑the blood supply & the blood vessels becoming highly tortuous
- The glands increase in tortuosity.
-Cause secretory development of the endometriumand* .
-endometrial cells accumulate lipids and glycogen in their cytoplasm**.

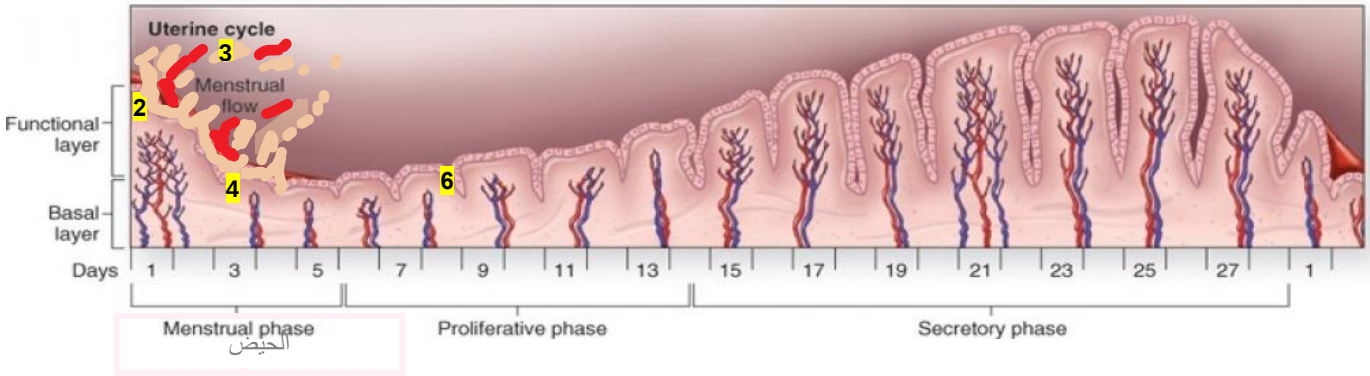
- 1 week after ovulation, endometrium thickness is 5-6 mm .

*Uterine secretions called "uterine milk" 🥛 provide nutrition for the dividing ovum)

**The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a *fertilized* ovum Then, once the ovum implants in the endometrium, the trophoblastic cells on the surface of the implanting ovum begin to digest the endometrium and absorb the endometrial stored substances







الحيض هو أول أطوار الدورة الرحميةإليه يرجع القصد عند القول أن المرأة في دورتها، وخروج دم الحيض علامة على أن المرأة لم تحمل في دورتها السابقة تستمر فترة الحيض عادة ثلاثة إلى خمسة أيام، ولكن استمرارها ليومين وحتى سبعة أيام يظل طبيعياً

How does the menstruation occur? Or events trigger the menstruation?

1)If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum involutes & estrogens & progesterone decrease to low levels.

2)Due to decrease estrogen & progesterone there is decrease stimulation of the endometrium, followed by involution of the endometrium to about 65% of its previous thickness.

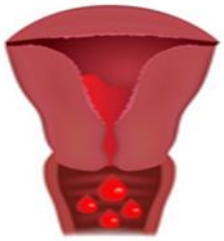
- During the 24 hrs preceding the menstruation,There are:

  1-Loss of hormonal stimulation(estrogen &progesterone)

  2-Vasospasm :due to release of vasoconstrictor (prostaglandins)*.البروستاقلاندين لما يشتغل على الرحم يسبب فازوكونستركشن

  3-Decrease nutrients to the endometrium

  "All initiate necrosis in the endometrial blood vessels".



-كيف يحدث المنسترال بليدينق ؟؟

اذا ماعندي بروجيسترون واستروجين بطانة الرحم ستفقد المحفز الي يحفزها على البقاء بعدها بتضعف وبتتقطع , واذا تقطعت طبقة وش يصير بتتقطع الارتريز الي جواها وبيصير بلييدنق(mensuration)

What happen during this phase?

3)Gradual necrosis of the outer layer of the endometrium leads to separation from the uterus at the site of the hemorrhages

4)Within 48 hrs, all the superficial layers of the endometrium desquamated in the uterine cavity.

5)The mass of desquamated tissue & blood plus the contractile effects of prostaglandins initiate contractions which expel the uterine contents. ايش فايدة الكونتراكشن الي يسويه البروستاقلاندين؟يعمل على تفريغ الرحم من الدم والانسجة المنسلخة

Why do women feel -menstrual pain??*

فكروا فيها ياشباب اذا تقطعت طبقة الاندوميتريوم وش بيصير بصير بليدنق ,هذا الدم الي طلع من اليوتراين ارتريز غني جدا بالبروستاقلندين فيذهب لى المايو ميترويم (حيث ان فيها ريسورز كثيرة للبروستاقلاند فيرتبط بهذه الريسبترز)مسببا very strong contraction which lead to vasospasm of the uterine arteries to prevent further bleeding..

What happen after this phase?

6)Within 4 to 7 days after menstruation, the loss of blood ceases & the endometrium become re-epithelialized.

Facts about menstrual blood:

- In normal menstruation, about 40 ml of blood + 35 ml of serous fluid are lost.
- The menstrual blood is normally non-clotting due to the presence of fibrinolysin. If excessive bleeding occurs from the uterine surface, the quantity of fibrinolysin may not be sufficient to prevent clotting. The presence of clots during menstruation is often clinical evidence of uterine pathology
- **Leukorrhea during menstruation:** During menstruation, leukocytes are released with the necrotic material & blood so the uterus is highly resistant to infection (protective mechanism).

Estrogen vs progesterone (boy's slides only)

Functions of estrogen	Functions of progesterone
• Estrogens increase the size of ovaries, fallopian tubes, uterus, and external genitalia. • Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands. • Estrogens cause: (1) development of the stromal tissues of the breasts (2) growth of an extensive ductile system (3) deposition of fat in the breasts. • Estrogens stimulate bone growth and slightly increase protein deposition. • Estrogens increase body metabolism and fat deposition. • Estrogens cause sodium and water retention by the kidney tubules.	• Progesterone promotes the secretory changes in the uterine endometrium. • Progesterone promotes increased secretion by the mucosal lining of the fallopian tubes. • Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory. • Progesterone decreases the frequency and intensity of uterine contractions.

Menopause

women who has a lot of pregnancies will have a delayed menopause

Why menopause occur??

- With advanced age(At the age of 40 to 50 years) the ovaries become unresponsive to gonadotropins (due decline in the number of primodial follicles), and their function declines so that reproductive cycles disappear (menopause).

what happen during menopause?

- The ovaries no longer secrete estrogen and progesterone→The uterus and vagina atrophy.
- When estrogens production falls below the critical value, estrogens no longer inhibit the production of gonadotropins (FSH & LH)Due to removal of the negative feedback effect there is increased secretion of FSH and LH..

Physiological changes due to loss of estrogens:

- "hot flushes" characterized by extreme flushing of the skin, psychic sensations and dyspnea, Irritability, fatigue, anxiety, occasionally various psychotic states, decreased strength and calcification of bones throughout the body.

Abnormalities of menstrual cycle

Amenorrhea
(Is absence of menstrual period either:

- **Primary Amenorrhea** (which menstrual bleeding has never occurred)
- **secondary Amenorrhea** (cessation of cycles in a woman with previously normal periods)

كانت تجيها قبل بس فجأه وقفت بالرغم انها مش عجوز لسا في سن الانجاب

Causes of secondary amenorrhea:

- Pregnancy (is the most common cause)
- Emotional stimuli and changes in the environment.
- Hypothalamic diseases (↓ GnRH pulses)
- Pituitary disorders
- Primary ovarian disorders and various systemic disease.

Hypomenorrhea
(Refer to scanty flow)

Menorrhagia
(Refer to abnormally profuse flow during regular periods)

Dysmenorrhea
(Painful menstruation)

(cramps due to accumulation of prostaglandins in the uterus can be treated with inhibitors of prostaglandin synthesis).

SUMMARY

Regulation of Male Reproduction

Control of male sexual functions by GnRH

- A peptide secreted intermittently by the arcuate nuclei of the hypothalamus
- Stimulate anterior pituitary gland to release gonadotropins (LH and FSH)

Testosterone production:

Regulation of Testosterone production by LH:

- Testosterone is secreted by Leydig cells, in the interstitium of the testis, by LH stimulation from the Anterior Pituitary.
- Mature leydig cells are found in a child's testis few weeks after birth & then disappear until puberty

Negative feedback control of testosterone:

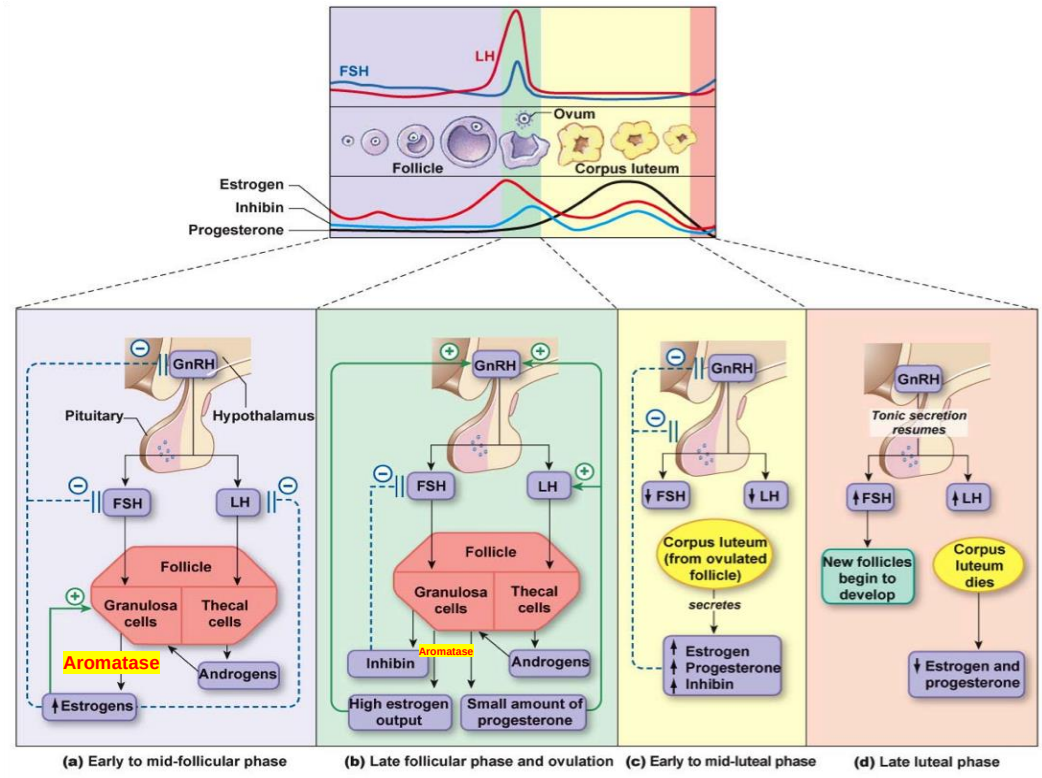
- LH stimulate Testosterone secretion by the testis
- Testosterone inhibit the secretion of LH.

Inhibition of GnRH leads to decrease secretion of both LH & FSH.

Spermatogenesis:

- FSH binds with specific FSH receptors attached to the sertoli cell in the seminiferous tubules, which causes these cells to grow & secrete spermatogenic substances.
- testosterone & dihydrotestosterone diffuses into the seminiferous tubules from the leydig cells affect the spermatogenesis

- **Positive feedback control:** When the seminiferous tubules fail to produce sperm the secretion of FSH from the AP increases.
- **Negative feedback control:** the secretion of inhibin hormone from the sertoli cells which strongly inhibit the Ant.Pituitary- FSH



Follicular growth

Childhood	• Each ovum is surrounded by single granulosa cell sheath called primordial follicle. • The granulosa cells: ○ Provide nourishment for the ovum ○ Secrete oocyte maturation inhibiting factor which keeps the ovum suspended in its primordial state.
After puberty	• AP secrete FSH and LH which Stimulate the ovaries and result in growth of some follicles. • Growth of the follicle begins with increase in size of the ovum to & growth of additional layers of granulosa cells of some follicles (At this stage, it is known as primary follicles). • The ovary interstitium collect in several layers outside the granulosa cells to form theca cells. • This theca is divided into 2 layers: 1) Theca interna, the cells have epithelioid characteristics and like the granulosa cells and secrete sex hormones **(ANDROGENS)**then androgens go to granulosa cells to convert into estrogen by aromatase enzyme • LH stimulates theca interna to produce androgen. 2) Theca externa, the outer layer, develops into a highly vascular connective tissue capsule of the developing follicle

Ovarian Cycle	Endometrial Cycle
Follicular phase	**Menstruation**
• **FSH** begin to increase, LH slightly increase • The early growth of the follicle up to the antral is under FSH stimulation ALONE • Accelerated growth to vesicular follicle (Graffian) caused by: 1) Estrogen → Granulosa cells → Increasing number of FSH receptors (positive feedback effect) 2) Estrogen & FSH → Granulosa cells → promote LH receptors → increase follicular secretion 3) Estrogen & LH → Proliferation of the follicular theca cells & increase their secretion. • Antral follicles begin to grow. • Ovum enlarges & remain embedded at one pole. • Atresia occur to all the others follicles • FSH & LH slightly decrease during 11-12 days because of estrogen **negative feedback**	If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum involutes & estrogens & progesterone decrease to low levels this will cause a decrease in the endometrium stimulation followed by involution of the endometrium to about 65% of its previous thickness > gradual necrosis > all the superficial layers of the endometrium desquamated in the uterine cavity and will cause contractile effect on the uterus to expel its content
	Proliferative(Estrogen phase) Occurring Before Ovulation
	• Most of the endometrium has been lost • Only a thin layer of basal endometrial stroma remains • Epithelial cells are only in the crypts of the endometrium and in the deep portions of the endometrial glands • Estrogen stimulates rapid proliferation of stromal and epithelial cells. • The entire endometrial surface is re-epithelialized within 4 to 7 days of the beginning of last menstruation
Ovulation phase(at the mid of the cycle)(at days 14)	
• 2 days before ovulation → Surge of FSH&LH. Both acts synergistically to cause swelling of the follicle. • Surge is caused by high level of estrogens causes positive feedback • 1 day before ovulation → Rate of estrogen secretion ↓ while progesterone secretion begins to increase • LH is more than FSH, because of estrogen positive feedback & small amount of progesterone • This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, 2 events occur which are necessary for ovulation: 1)Theca externa secrete proteolytic enzymes & causes weakening of the wall resulting in swelling of the follicle & degeneration of the stigma 2)rapid growth of new blood vessels into the follicle wall & prostaglandins are secreted into the follicular tissue	• The endometrium is 3-5 mm thick • The endometrial glands of the cervical region secrete a thin, stringy mucus which helps to guide sperm in the proper direction from the vagina into the uterus
Luteal phase	**Secretory (Progestational phase)** Occurring after Ovulation
• Remaining granulosa cells (secrete progesterone, estrogen & inhibin) & theca interna cells (secrete androgens) change to lutein cells by LH mainly • Function of LH: 1-Change of granulosa and theca interna cells into lutein cells. 2-Causes ovulation. 3-Maintains secretion of progesterone & estrogen from the corpus luteum • Progesterone, estrogen and inhibin (cause negative feedback on pituitary and hypothalamus). Lowest level is 3-4 days before the onset of menstruation • If pregnancy: hCG from the Trophoblast acts on the corpus luteum to prolong its life for 2 to 4 months of pregnancy	After ovulation, the corpus luteum secretes large amounts of progesterone • Effects of progesterone: -Swelling of the endometrium -Development of secretory endometrium - ↑ the blood vessels tortuosity -The glands increase in tortuosity -Endometrial cells accumulate lipids and glycogen in their cytoplasm. • Uterine secretions called "uterine milk" provide nutrition for the dividing ovum

Menopause	When the women become advanced in age the ovaries become unresponsive to gonadotropins and their function declines so this will lead to menopause
Abnormalities of menstrual cycle	**Menorrhagia** (Refer to abnormally profuse flow during regular periods) **Hypomenorrhea** (Refer to scanty flow) **Dysmenorrhea** (Painful menstruation) **Amenorrhea** (Is absence of menstrual period either: primary or secondary

MCQs (Lecture 1)

1. Most of the testosterone inhibitory effect results from:
a- Direct inhibition of leydig cells
b-Direct inhibition of GnRH release
c-Direct inhibition of anterior pituitary
d-Indirect inhibition of GnRH release

2. From where the GnRH get released: a-Paraventricular nuclei
b-Supraoptic nuclei
c-Optic chiasma
d-Arcuate nuclei

3. Spermatogenesis can be induced by:
a-LH
b-Testosterone
c-FSH
d-All of them

4. During first 11 to 12 days of the follicular growth the rate FSH&LH:
a- Only FSH decrease
b- Only LH decrease
c- Both FSH&LH decrease
d- Both FSH&LH increase

5.Inhibitory effect of inhibin mainly on:
a-FSH
b-LH
c-GnRH
d-All of them

6. pulsatile release of GnRH caused by which mechanism:
a-Hormonal
b-Neuronal
c-Vascular
d-Osmotic

7. regarding female sexual cycle at pre-ovulation which of the following is NOT true:
a-FSH will increase
b-LH will increase
c-FSH level is higher than LH
d-Estrogen & progesterone are equal

8. Mechanism of action for FSH&LH receptors is:
a-Adenyl cyclase
b-Phopholipid
c-Guanylate Cyclase
d-Tyrosine kinase

9. Which of the following cells is the main target for FSH in females:
a- Sertoli cells
b- Lyeding cells
c- Granulosa cells
d- Theca cells

10. Which of the following hormones related to the HPG axis in males:
a-TSH
b-Cortisol
c-Estrogen
d-LH

Answer key:

1 (b) | 2 (d) | 3 (d) | 4 (c) | 5 (a) | 6 (b) | 7 (c) | 8 (a) | 9 (c) | 10 (d)

MCQs (Lecture 2,3)

1-Which one of the following is true regarding follicular phase:

a- LH increase slightly more earlier than FSH
b- Theca interna is a vascular connective tissue secrete estrogen and progesterone
c- During each cycle (5-11) follicle continue to grow reaching the maturity
d- The ova enlarge and become embedded at one pole of the follicle

2- To initiate ovulation:

a- Rapid growth of blood vessels and prostaglandin secretion
b- Large quantity of LH inhibit progesterone secretion
c- Proteolytic enzymes secreted by theca interna

3- The ovarian changes during the sexual cycle depend on:

a- FSH
b- LH
c- Estrogen
d- A&b

4- 9 years old Female will have which of the following follicles in her ovary:

a- Primordial follicles
b- Primary follicles
c- Secondary follicles
d- Antral follicles

5- A 35 years old of two females with differenent menstrual cycle (27 , 30 days) which of the following periods mostly will be the same for both of them:

a- Follicular phase
b- Luteal phase
c- Menstrual period
d- Proliferative phase

6-The growth of the primary follicle up to the antral stage is under which stimulation:

a- FSH
b- LH
c- Estrogen
d- Progesterone

7- a woman who has a 32-day female sexual cycle, ovulation will occur at:

a- 14 day after menstrual onset
b- 16 day after menstrual onset**
c- 14 day after last day of menstrual
d- 16 day after last day of menstrual

8- which of the following has specific effect on the granulosa cells & theca cells by converting them to progesterone-secreting cells:

a- LH
b- FSH
c- Estrogen
d- Progesterone

9- increase of which one of the following is not true regarding 24h before ovulation:

a- LH 6-16 fold
b- FSH
c- Progesterone
d- Estrogen

10-During ovulation fluids ooze from the follicle will contain which of the following hormone:

a- Estrogen
b- Progesterone
c- Follicular steroid hormone
d- Follicular stimulating hormone

Answer key:

1 (d) | 2 (a) | 3 (d) | 4 (a) | 5 (b) | 6 (a) | 7 (b) | 8 (a) | 9 (d) | 10 (a)

MCQs (Lecture 2,3)

11- Corpus luteum composed of:

a- Oocyte
b- Granulosa cells
c- Corona radiata
d- Zona pellucida

12-What is the predominate hormone secreted by corpus luteum:

a- Estrogen
b- Progesterone
c- Inhibin

13- What type of granulosa secretions are true mostly for follicular and luteual phases respectively:

a- Estrogen ,
b- progesterone
c- Progesterone
d- estrogen

14- What is the amenorrhea:

a- painful menstruation
b- scanty flow of blood
c- abnormally profuse flow
d- absence of menstrual period

15-At which stage in the uterine cycle does the proliferative phase occur:

a- 1-5 days
b- 5-14 days
c- 15-28days

16-Which of the following are effects of increased levels of estrogen in the follicular phase of the menstrual cycle:

a- Thickening of cervical mucous
b- Thinning of cervical mucous
c- Thickening of the endometrium
d- B&C

17-Menstruation occure as a result of :

a- Very high estrogen
b- Very high progesterone
c- Involution of the corpus luteum
d- Fertilized ovum

18- The most important cause of physiological changes in menopausal women is due to low level of:

a- Estrogen
b- Progesterone
c- GnRH
d- Androgens

19-Dysmenorrhea occurs due to accumulation of:

a- Leukotrienes
b- Prostacyclin
c- Nitric oxide
d- Prostaglandins

20- which of the following is responsible for development of the lobules and alveoli of the breasts:

a- Estrogen
b- Progesterone
c- Prostaglandins

21- During menstraual period which of the following is true:

a- the premordial follicles are being recruited and begining to develop
b- corpus luteum is well formed
c- grafian follicles prepare to ovulating
d- estrogen & progesterone levels are very high

Answer key:

11 (b) | 12 (b) | 13 (b) | 14 (d) | 15 (b) | 16 (d) | 17 (c) | 18 (a) | 19 (d) | 20 (b) | 21 (a)

Physiology 435 team

Thanks to this amazing team!

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