بسم الله الرحمن الرحيم

PHYSIOLOGY OF THE MENSTRUAL CYCLE & BASICS OF FEMALE REPRODUCTIVE SYSTEM

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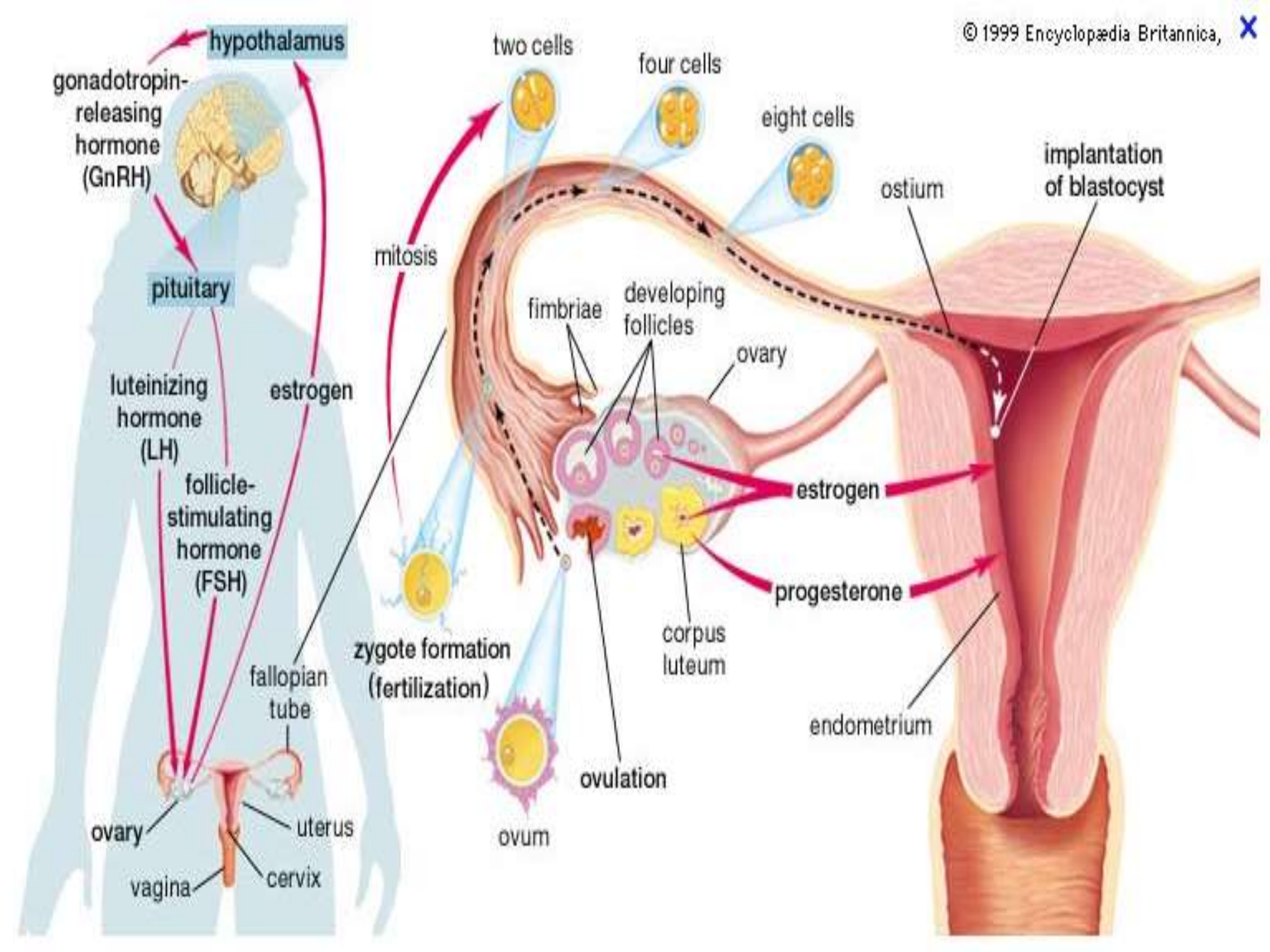
hypothalamus
gonadotropin-releasing hormone (GnRH)
pituitary
luteinizing hormone (LH)
follicle-stimulating hormone (FSH)
estrogen
fallopian tube
ovary
uterus
vagina
cervix
two cells
four cells
eight cells
mitosis
zygote formation (fertilization)
ovum
ovulation
fimbriae
developing follicles
ovary
corpus luteum
estrogen
progesterone
ostium
implantation of blastocyst
endometrium
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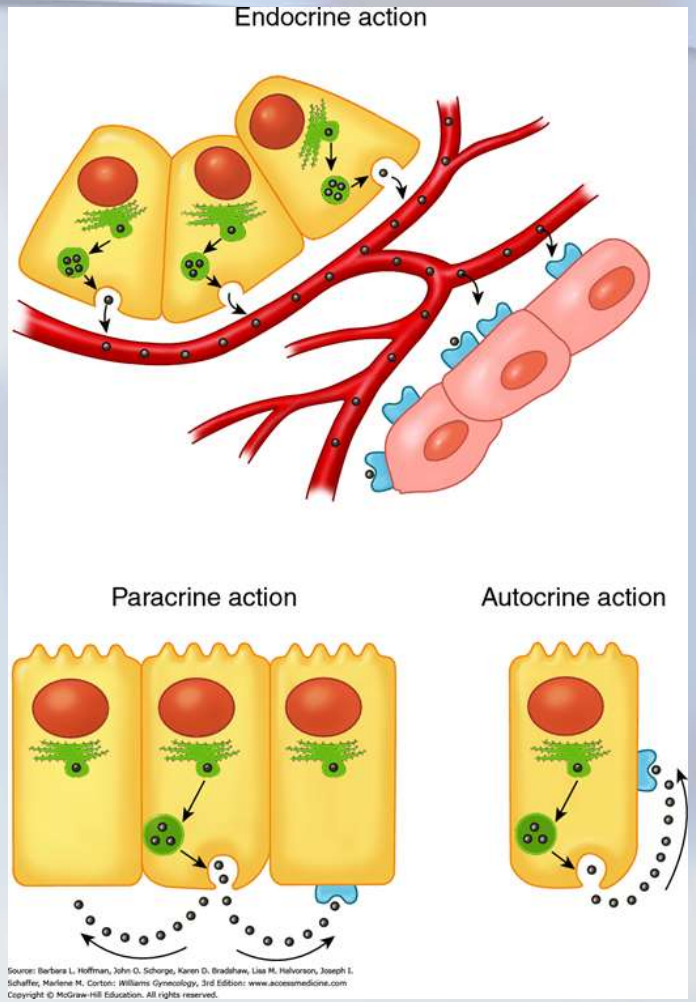
Different types of hormone communication

- Endocrine: hormones travel through the circulation to reach their target cells.
- Paracrine: hormones diffuse through the extracellular space to reach their target cells, which are neighboring cells.
- Autocrine: hormones feed back on the cell of origin, without entering the circulation



Source: Barbara L. Hoffman, John O. Schorge, Karen D. Bradshaw, Lisa M. Halvorson, Joseph I. Schaffer, Marlene M. Corton: Williams Gynecology, 3rd Edition: www.accessmedicine.com
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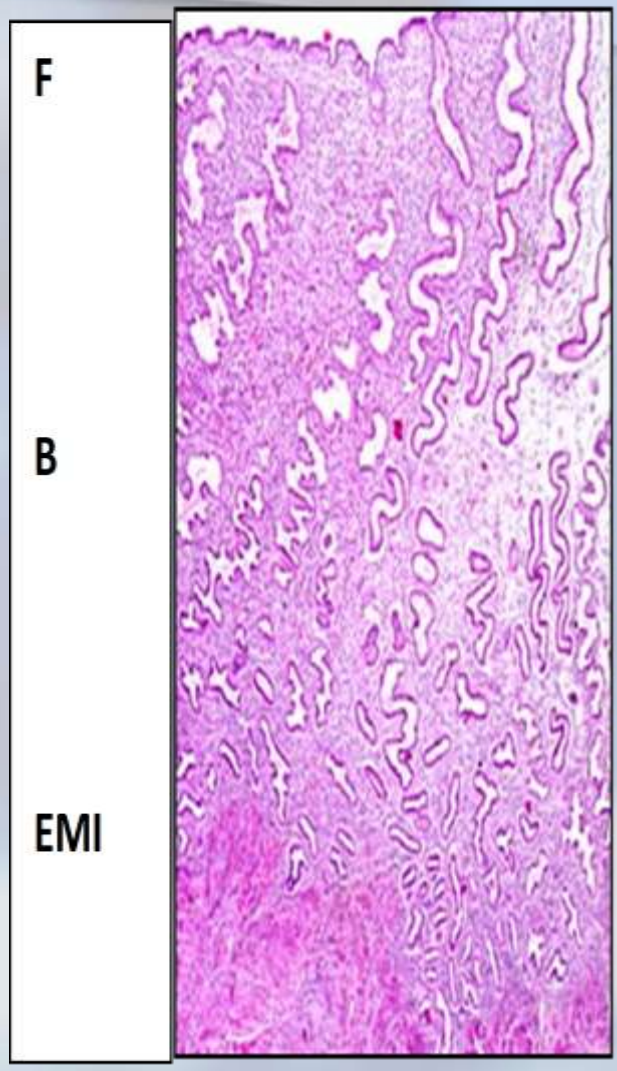
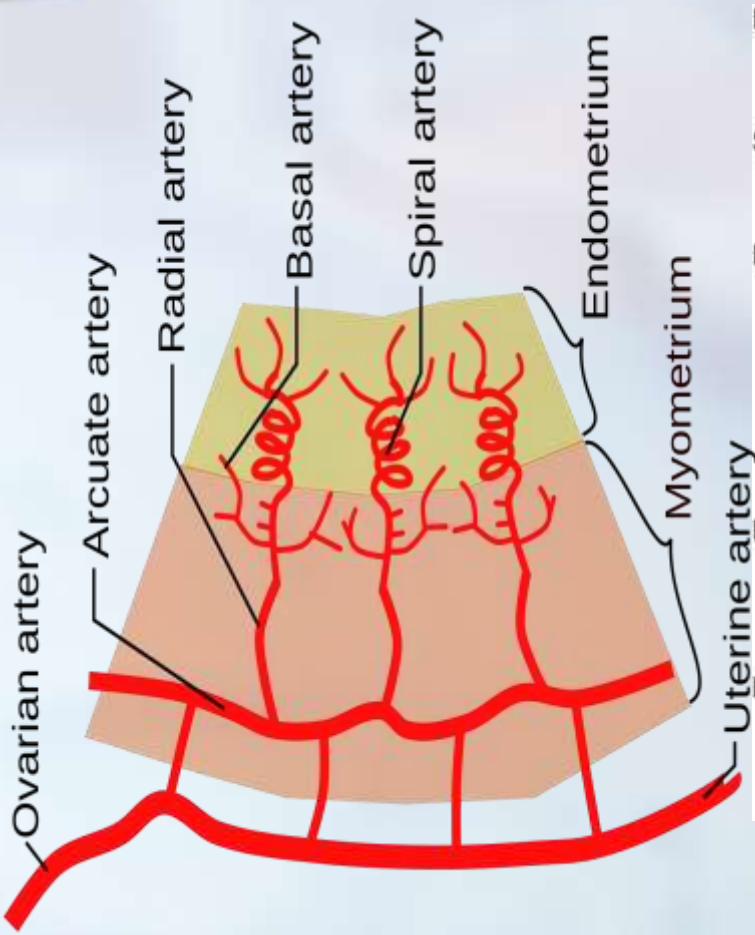
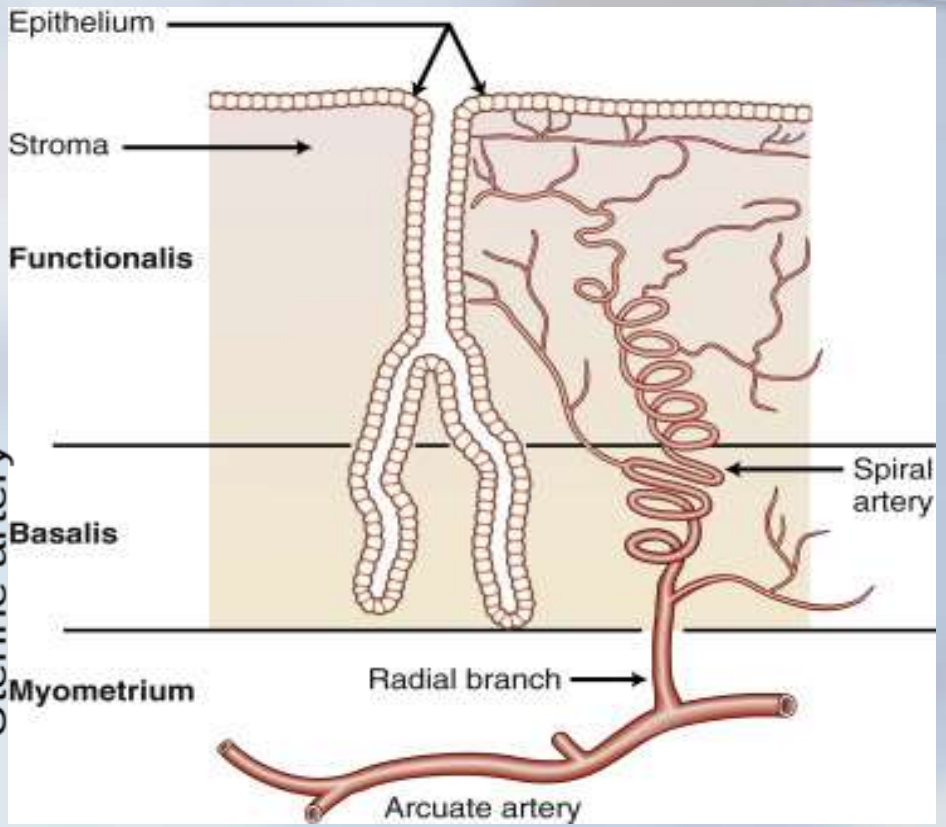
The endometrium

- (1) the stratum basale, which lies on top of the myometrium consists of primordial glands and densely cellular stroma, which change little during the menstrual cycle and do not desquamate at menstruation.
- (2) the stratum functionale, which lies between the basale and the lumen of the uterus:
  - The superficial layer (stratum compactum) consists of the neck of the glands and densely populated stromal cells.
  - The lower layer (stratum spongiosum) consists primarily of glands with less populated stroma and large amounts of interstitial tissue.
- Differences in structure in the two layers reflect different biologic functions: whereas the upper layer serves as the site of blastocyst implantation and provides the metabolic environment for it, the lower layer maintains the integrity of the mucosa

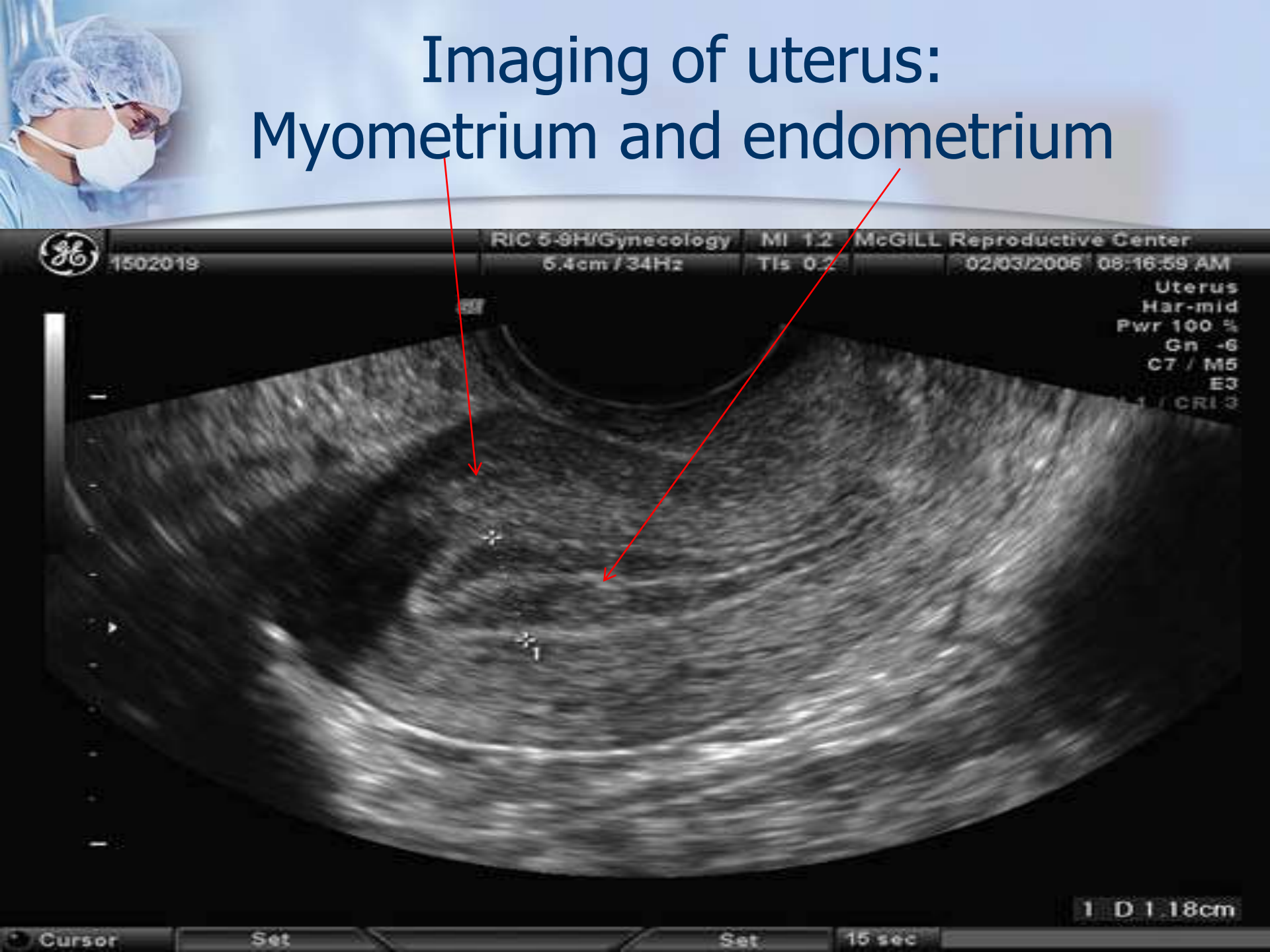


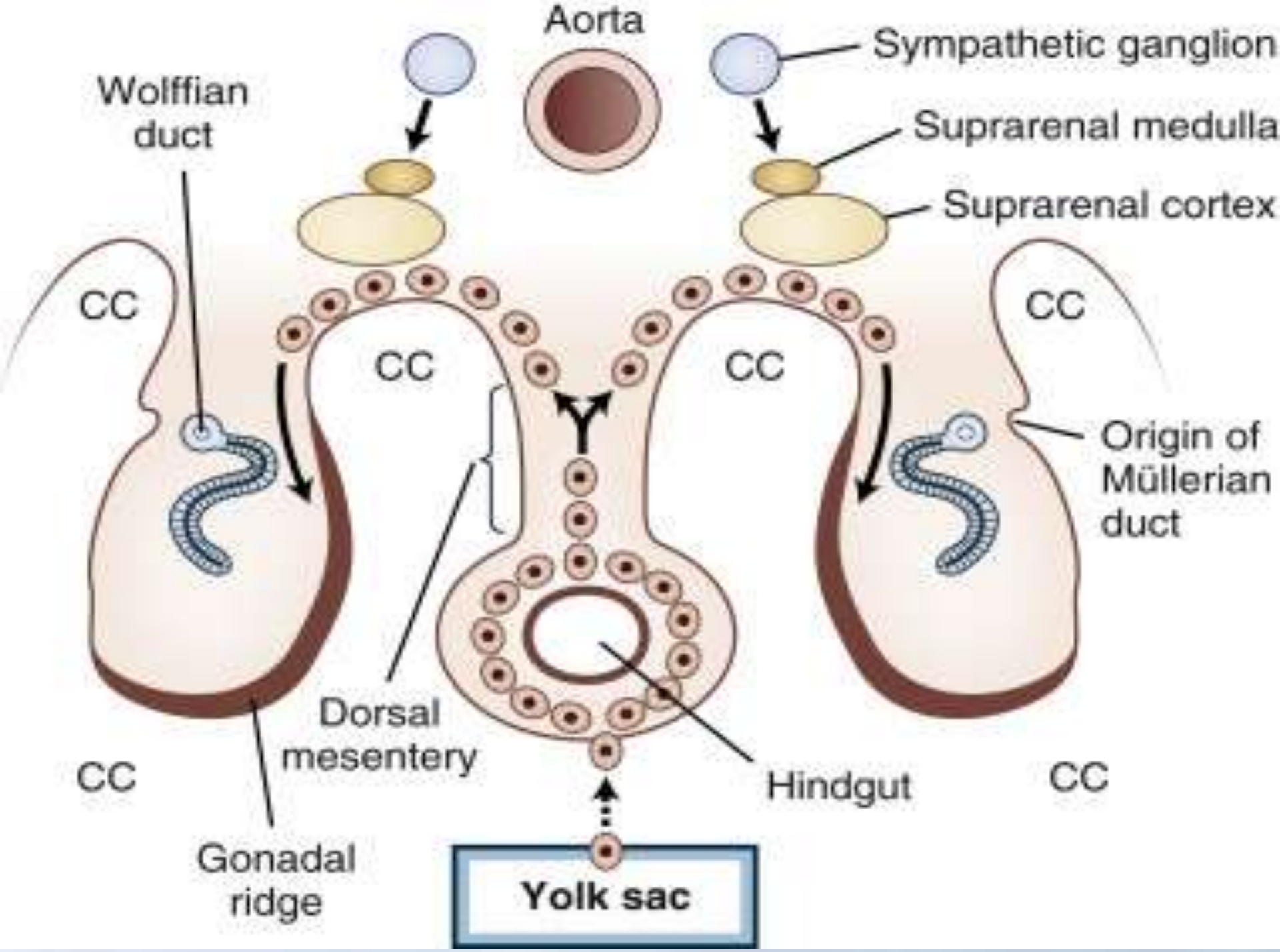
Uterine Blood supply





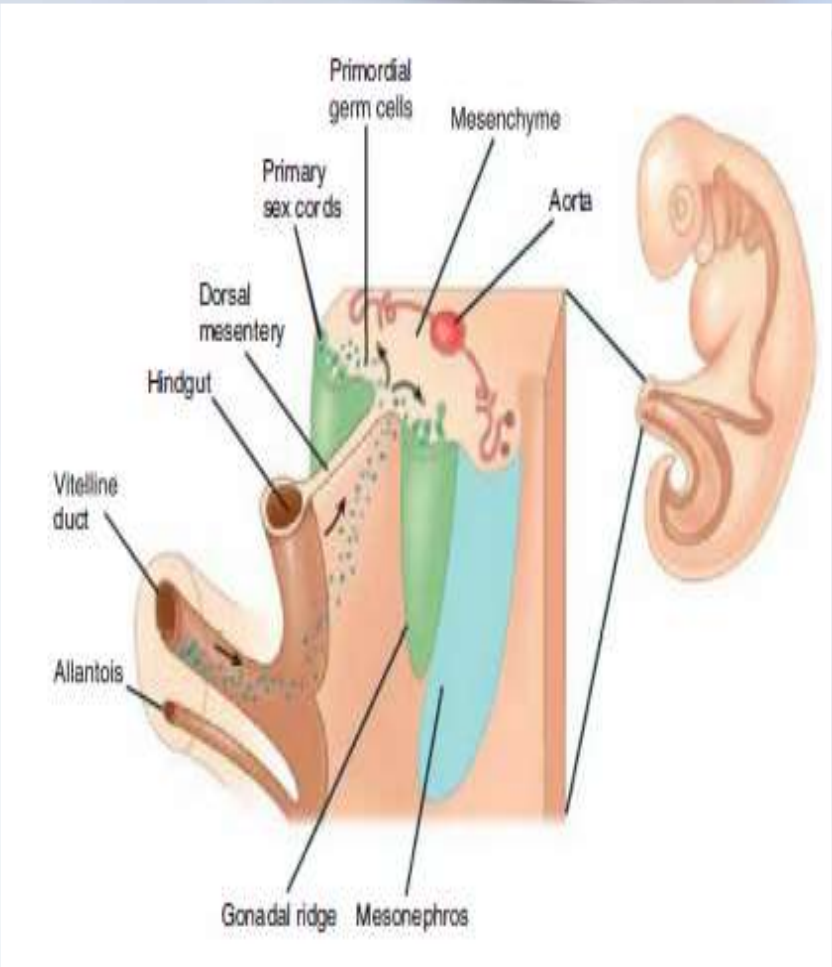
Imaging of uterus: Myometrium and endometrium

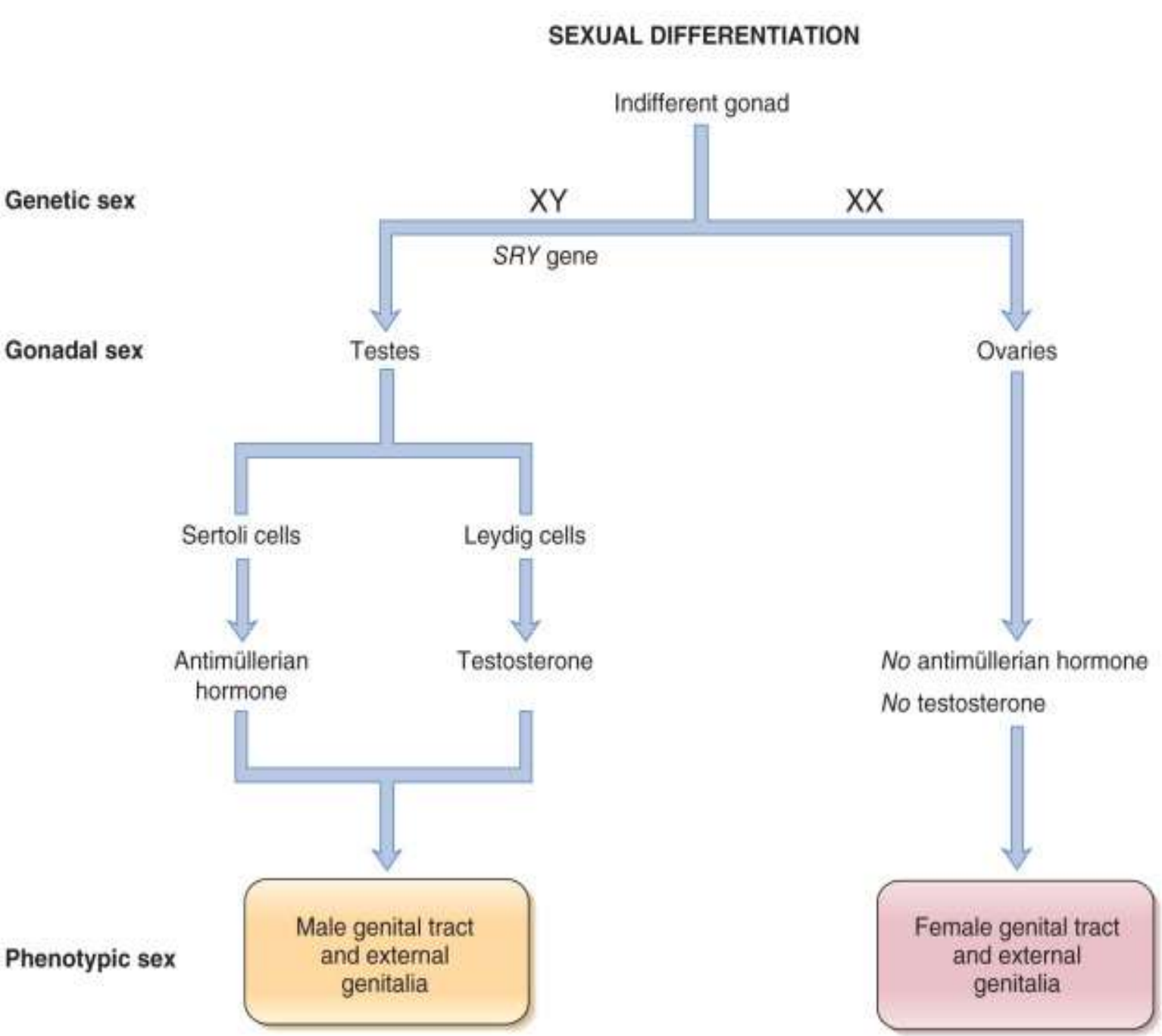



Aorta
Sympathetic ganglion
Wolffian duct
Suprarenal medulla
Suprarenal cortex
CC
CC
CC
CC
Origin of Müllerian duct
Dorsal mesentery
Hindgut
CC
CC
Gonadal ridge
Yolk sac

Primordial germ cell migration and gonadal ridge formation.

- Primordial germ cells, the precursor cells to the gametes, migrate out to the yolk sac wall during gastrulation.
- Between the fourth and sixth weeks, they return to the embryo through the GI tract, surrounding peritoneum, and dorsal mesentery while undergoing mitotic divisions
- The primordial germ cells (blue specs) migrate from the wall of the yolk sac to the gonadal ridge, where they settle into the primary sex cords.




SEXUAL DIFFERENTIATION
Indifferent gonad
Genetic sex
XY
XX
SRY gene
Gonadal sex
Testes
Ovaries
Sertoli cells
Leydig cells
Antimüllerian hormone
Testosterone
No antimüllerian hormone
No testosterone
Phenotypic sex
Male genital tract and external genitalia
Female genital tract and external genitalia

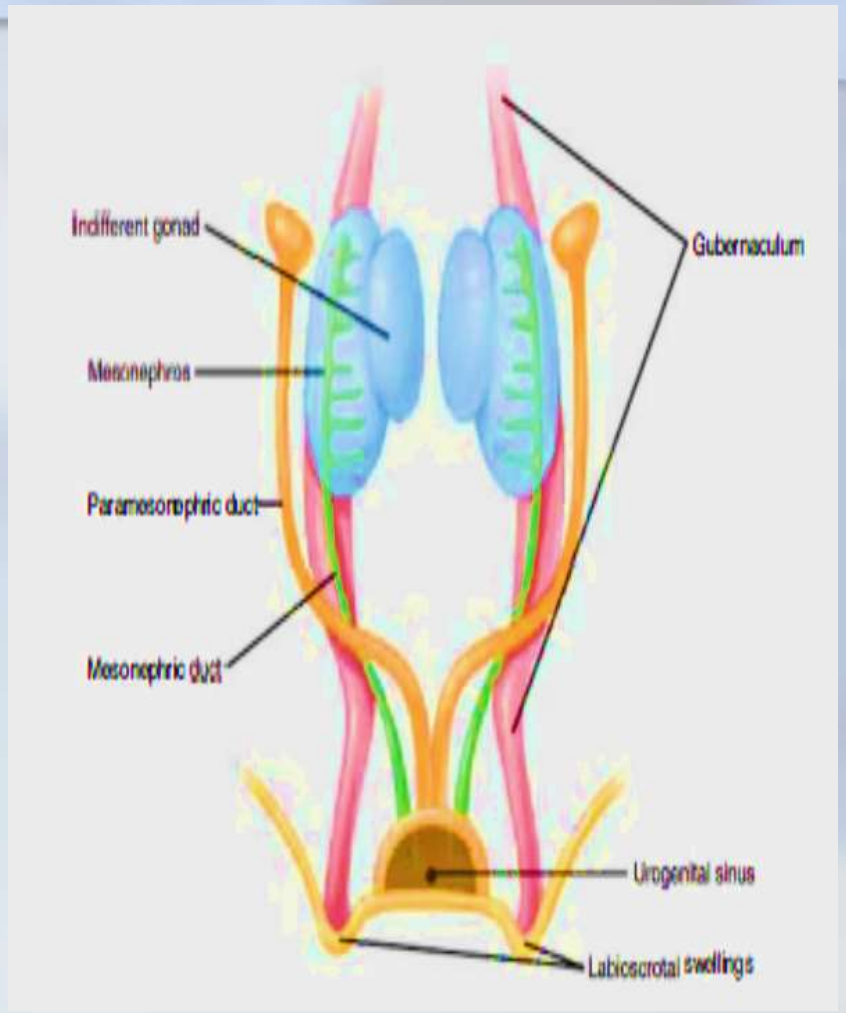
Three primary cell types develop in the gonadal ridge

- Mesenchymal cells,
- Mesothelial cells,
- Primordial germ cells

Cell Type	Fate
Mesenchymal cells	Gonadal ridge medulla: Male = Leydig cells; Female = ovarian support stroma.
Mesothelial cells	Gonadal ridge and primary sex cord cortex: Male = seminiferous tubules; Female = ovarian follicles.
Primordial germ cells	Enter primary sex cords as future gametes: Male = spermatogonia; Female = oogonia.

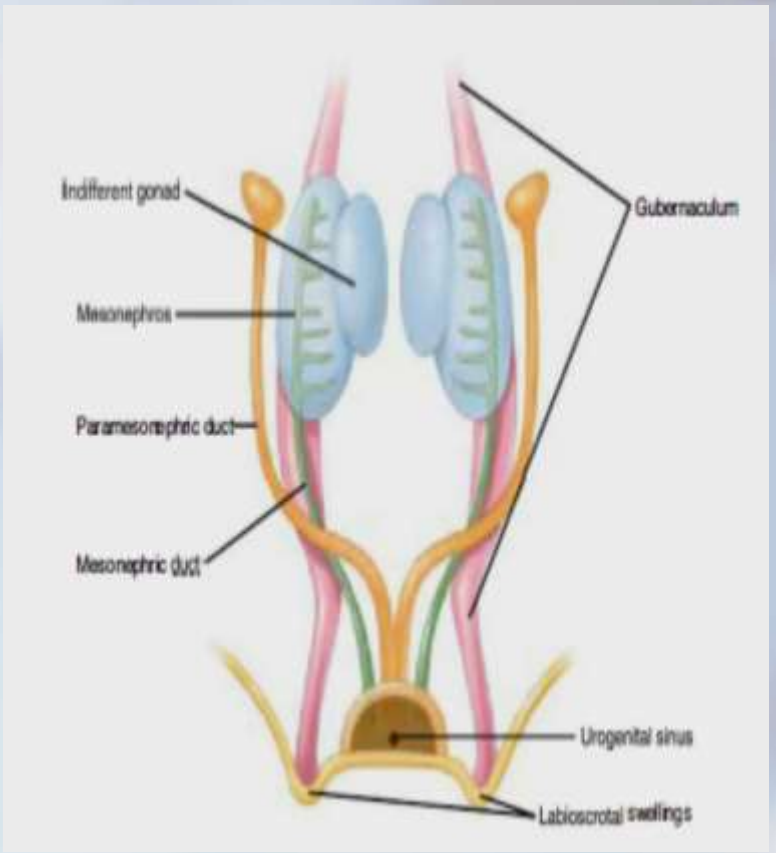
Gonadal ducts

- The mesonephric (Wolffian)
- The paramesonephric (Mullerian) ducts are mesodermal derivatives that form the male and female genital duct systems, respectively



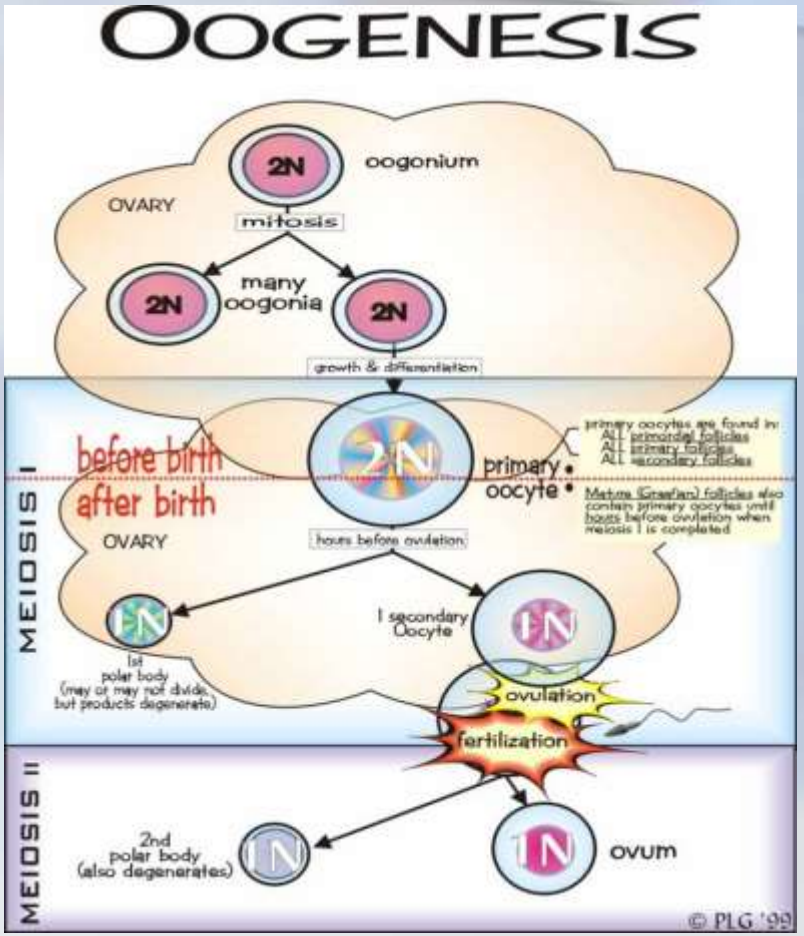
Indifferent genital duct formation

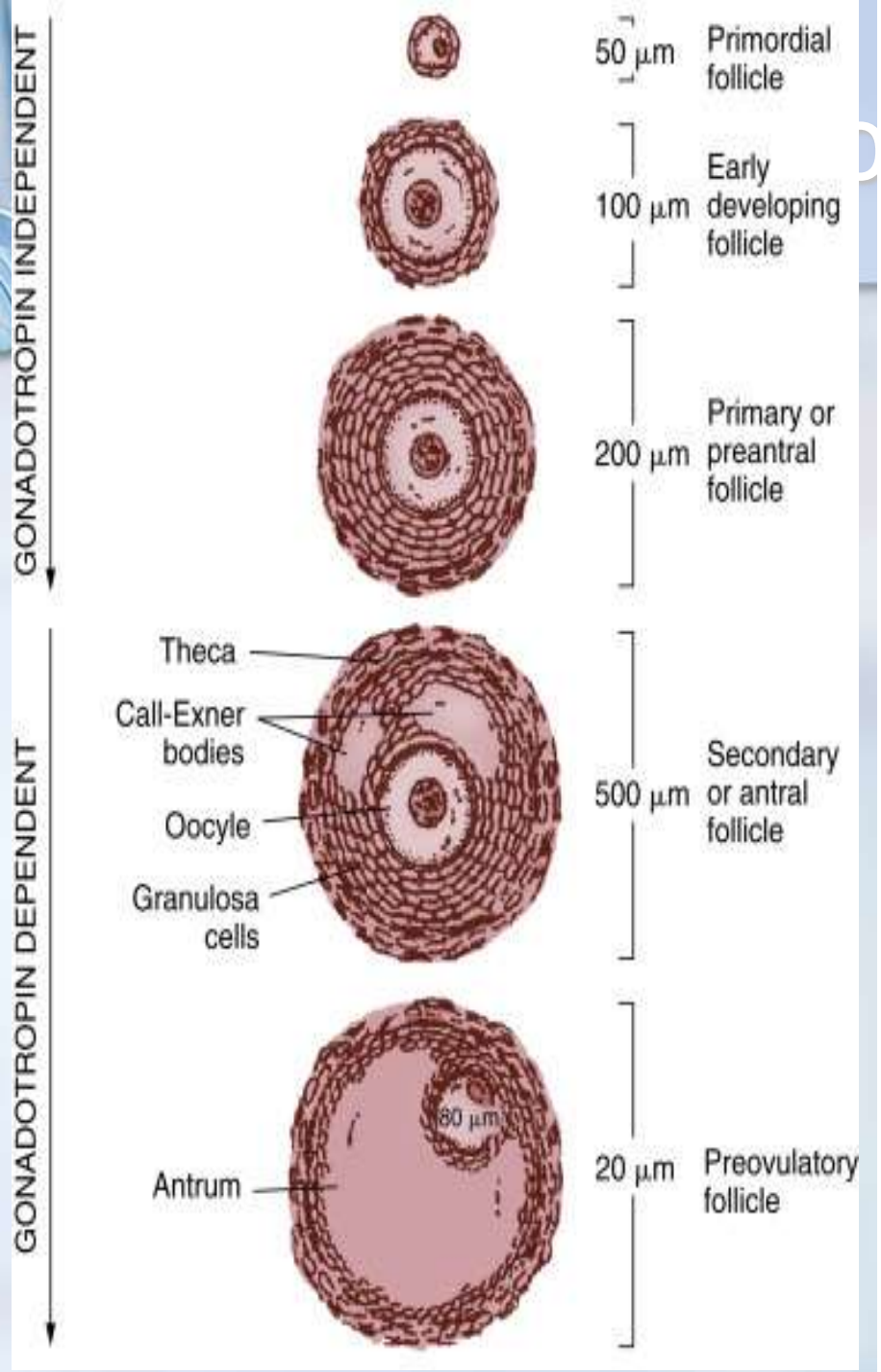
- Once it becomes hollow, the mesonephric duct drains urine for the mesonephros.
- The paramesonephric duct forms lateral to the mesonephric duct and fuses at the midline.
- This fused tip becomes the uterus.
- Failure to do so results in Uterus didelphys

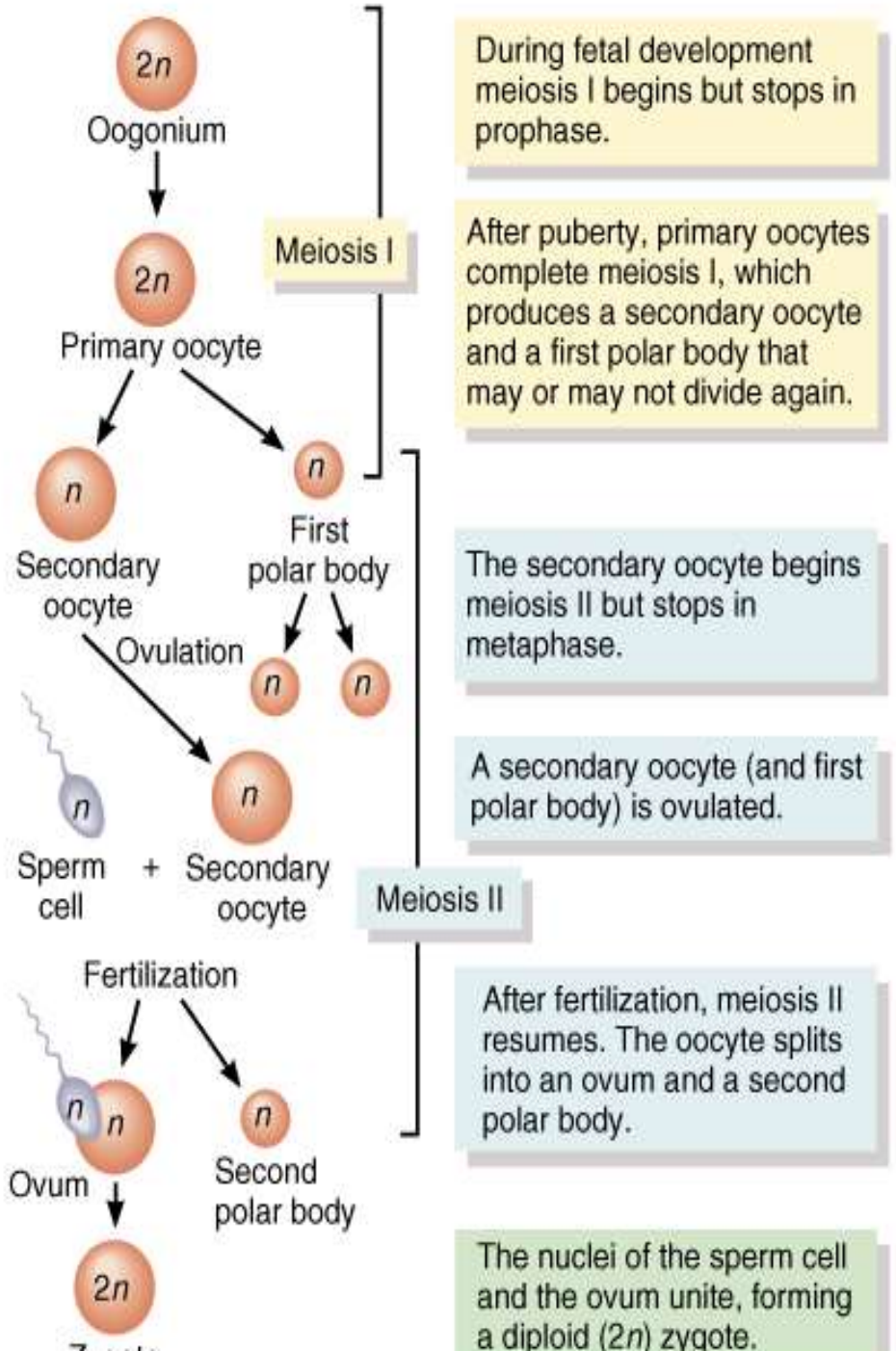


Oogenesis: Before birth

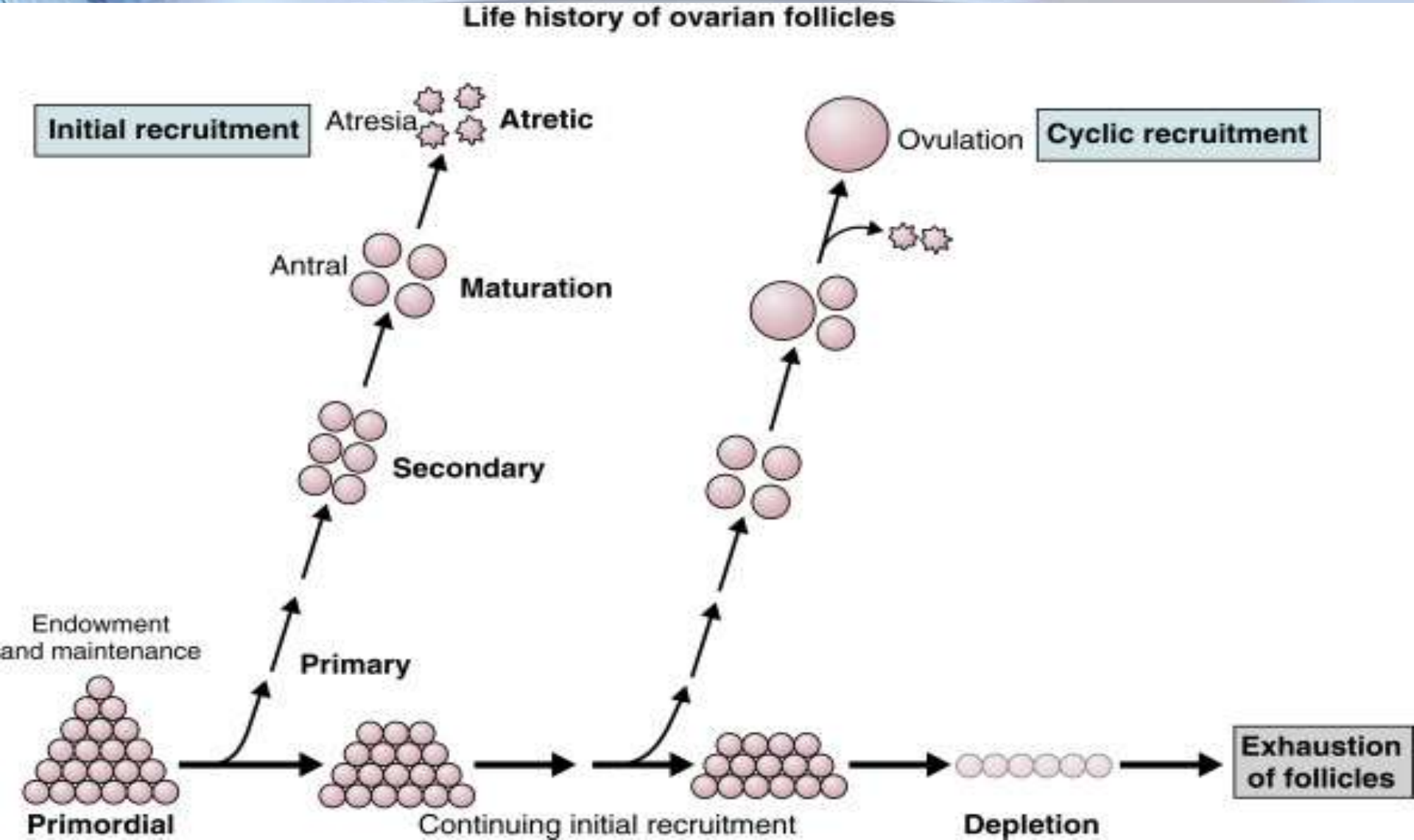
- During fetal development, oogonia (stem cells) divide by mitosis to make primary oocytes
- Primary oocytes begin meiosis and **stop in prophase I until puberty**
  - Primordial follicles: Support cells that surround the oocyte in the ovary
  - 2 million present at birth
  - 400,000 remain at puberty




GONADOTROPIN INDEPENDENT
GONADOTROPIN DEPENDENT
50 μm
Primordial follicle
100 μm
Early developing follicle
200 μm
Primary or preantral follicle
Theca
Call-Exner bodies
Oocyle
Granulosa cells
500 μm
Secondary or antral follicle
80 μm
Antrum
20 μm
Preovulatory follicle


2n
Oogonium
2n
Primary oocyte
Meiosis I
n
Secondary oocyte
n
First polar body
Ovulation
n
n
n
Sperm cell
+
n
Secondary oocyte
Meiosis II
Fertilization
n
n
Ovum
n
Second polar body
2n
During fetal development meiosis I begins but stops in prophase.
After puberty, primary oocytes complete meiosis I, which produces a secondary oocyte and a first polar body that may or may not divide again.
The secondary oocyte begins meiosis II but stops in metaphase.
A secondary oocyte (and first polar body) is ovulated.
After fertilization, meiosis II resumes. The oocyte splits into an ovum and a second polar body.
The nuclei of the sperm cell and the ovum unite, forming a diploid (2n) zygote.

Life history of ovarian follicles:



Folliculogenesis

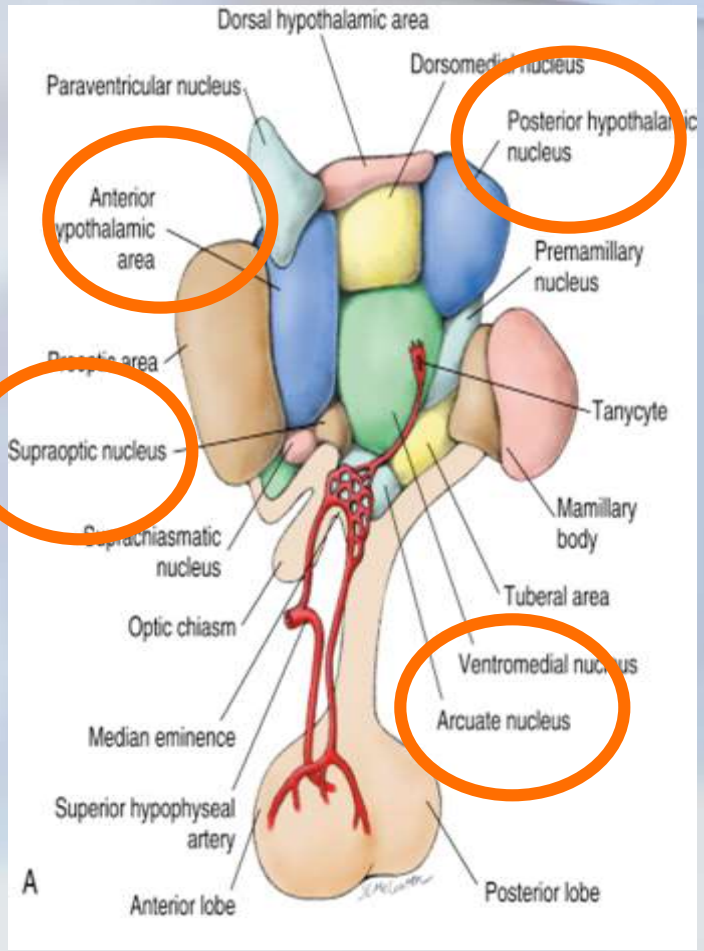
- It takes 1 year
- Folliculogenesis can be divided into two phases:
  - preantral growth (gonadotropin-independent phase)
  - antral growth (gonadotropin-dependent phase)
- preantral or gonadotropin-independent phase: interval from recruitment of a primordial follicle to the end of the secondary stage.
- The Graafian follicle grows progressively larger, predominantly through the accumulation of increasing amounts of fluid in the antrum.
- The fully developed Graafian follicle is termed a *preovulatory follicle.*
- Follicle maturation is inhibited by epidermal growth factor and AMH

Ovarian reserve measurement

- (1) by a measurement of **FSH** on day 2 to 3 of the cycle: higher FSH levels denote ovarian aging
- (2) by a sonographic **antral follicle count** ;
- (3) by the measurement of **inhibin B** on day 2 to 3 of the cycle, the recruitment of the follicle cohort being reflected by an increase in this hormone produced and secreted by these recruited follicles, thus inhibin B levels provide an early indicator of the number of recruited follicles and of their secretory activity
- (4) by the measurement of **anti-müllerian hormone (AMH)**

Hypothalamus and GnRH

- GnRH neurons derive from progenitor cells in the embryonic **olfactory** placode.
- Hypothalamic nuclei mainly **arcuate nucleus**
- GnRH neurons and the hypophyseal portal system that will transport GnRH to the anterior pituitary gland are established by about 16 weeks of fetal life.
- External zone of the **median eminence** (infundibulum) where GnRH is released.
- Has a short half-life of about 2 to 4 minutes and **pulsatile** mode of release



Factors affecting GnRH Pulsatility

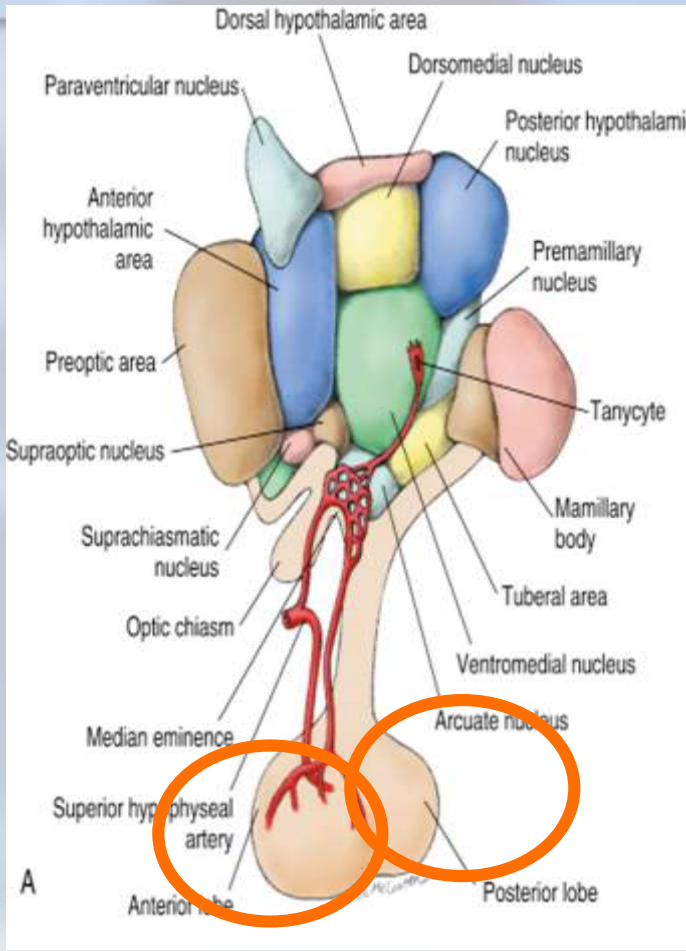
- Kisspeptin (KISS1) plays a key role in the regulation of GnRH release.
- Drugs (methyl dopa, reserpine, tricyclic antidepressants, SSRIs, ⟹ oligomenorrhea or galactorrhea.
- Hypothalamic prostaglandins may also modulate the release of GnRH; the midcycle surge of LH- inhibition of prostaglandin at midcycle may disrupt ovulation.
- CRH release negatively affects the GnRH pulse generator, which results in a decrease in GnRH pulse frequency
- Leptin also appears to function as one of the metabolic cues regulating the GnRH pulse generator
- Inhibitory effect of NPY on the GnRH pulse generator- undernutrition
- A low GnRH pulse frequency favors FSH synthesis, whereas a high GnRH pulse frequency favors LH synthesis.
- E2 is known to decrease GnRH pulse amplitude, whereas P4 decreases GnRH pulse frequency.

Factors affecting GnRH Pulsatility

- Dopamine: the effect on LH is mediated through GnRH - in hypothalamic amenorrhea there appears to be an excess of dopaminergic tone- dopamine blocker may return the LH pulse frequency to normal
- Sustained exposure of the GnRH-R to constant GnRH concentrations drastically reduces the response of the gonadotrope to subsequent stimulation with GnRH--- ***desensitization*** or ***downregulation.***
- **GnRH agonists** , there is an initial stimulation of gonadotropin release (flare), followed by the process of desensitization to induce a "medical castration" state
- **GnRH antagonists** act by competing with GnRH for receptor sites and thereby never activating a stimulatory signal

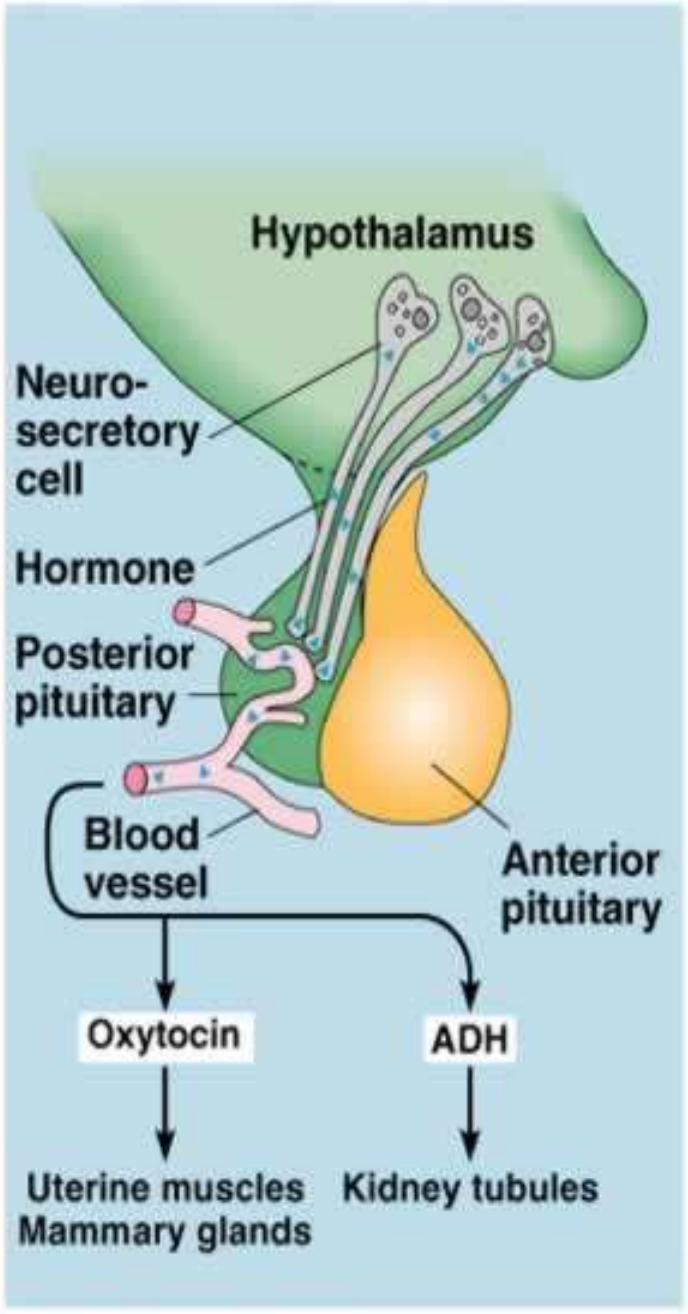
Pituitary Gland

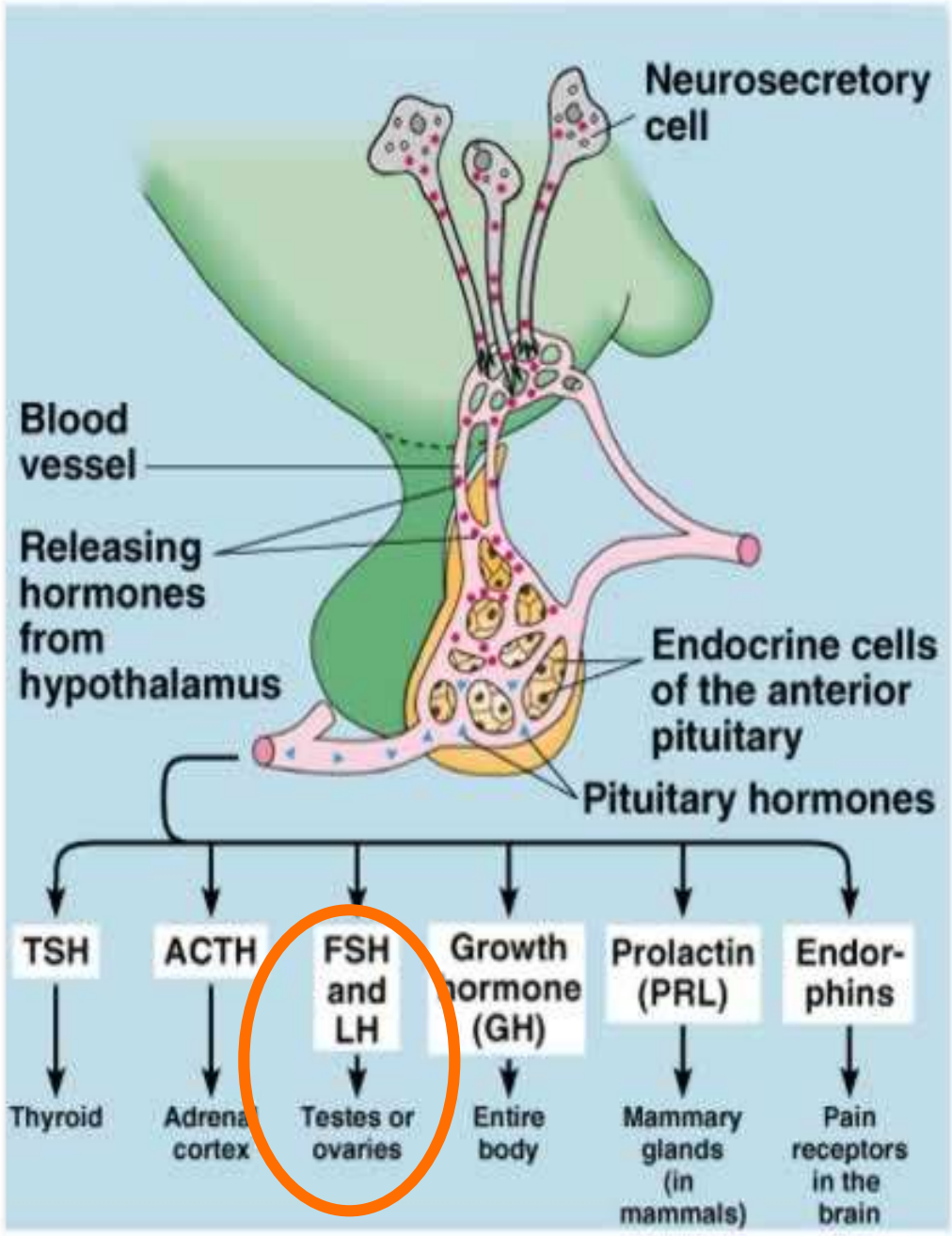
- The anterior pituitary (**adenohypophysis**) derives from the *Rathke pouch*- It originates at third week of life- the only vascularization is through the portal system
- The posterior pituitary (**neurohypophysis**) which develops as a direct extension of the brain-the neurohypophysis receives a direct arterial blood supply from the hypophyseal arteries.
- Gonadotropins: There are two distinct gonadotropins: **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH)** . (A third gonadotropin, chorionic gonadotropin [hCG], is produced by the placenta.)
- **<u>I believe they are Two separate glands!!!!</u>**



Gonadotropins & sex steroids

- Gonadotropin:
  - Gonad- ovary
  - trop- affect
- Estrogen- the feminizing hormone
- Progesterone-
  - Pro- before
  - Gesterone- from gestation- pregnancy





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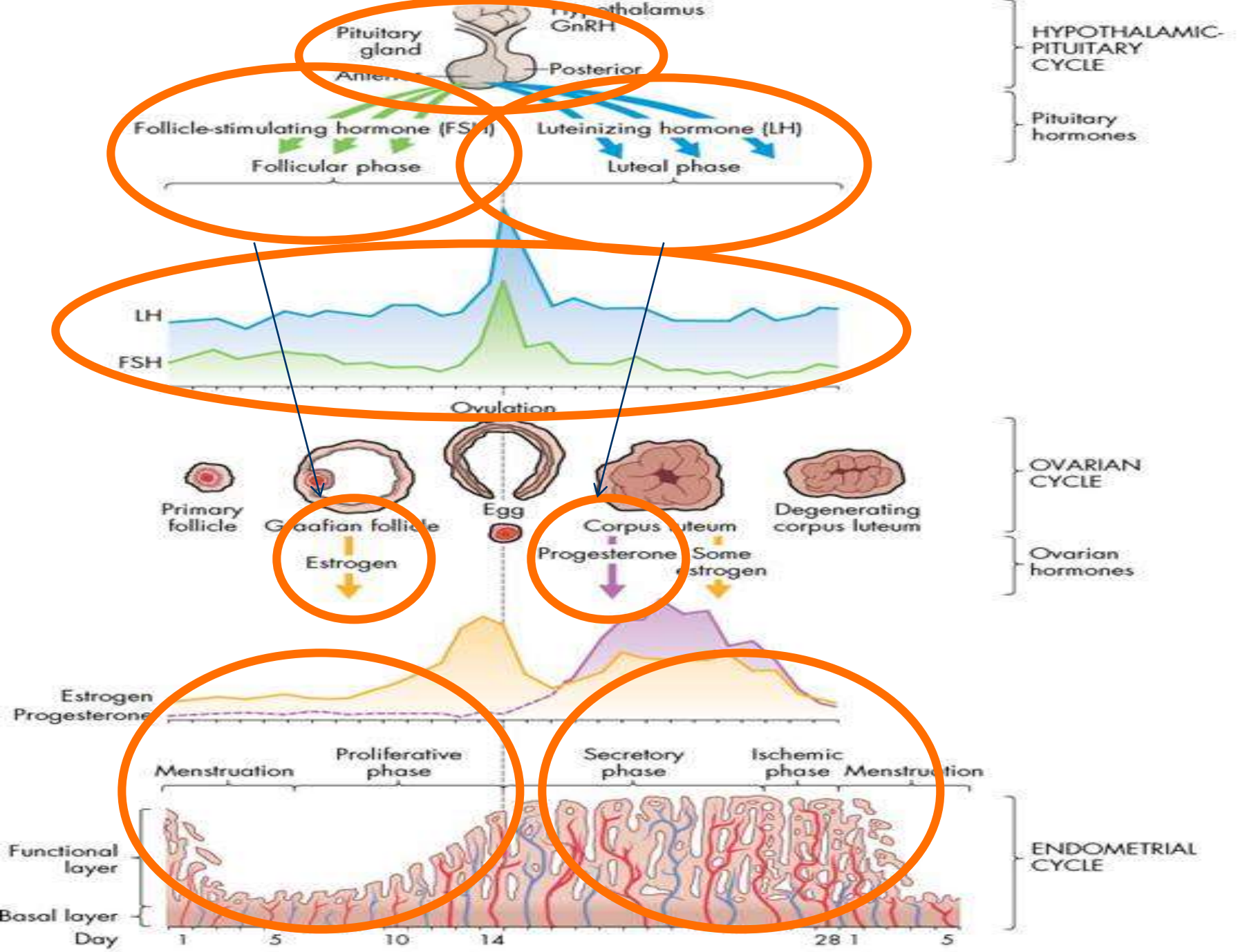
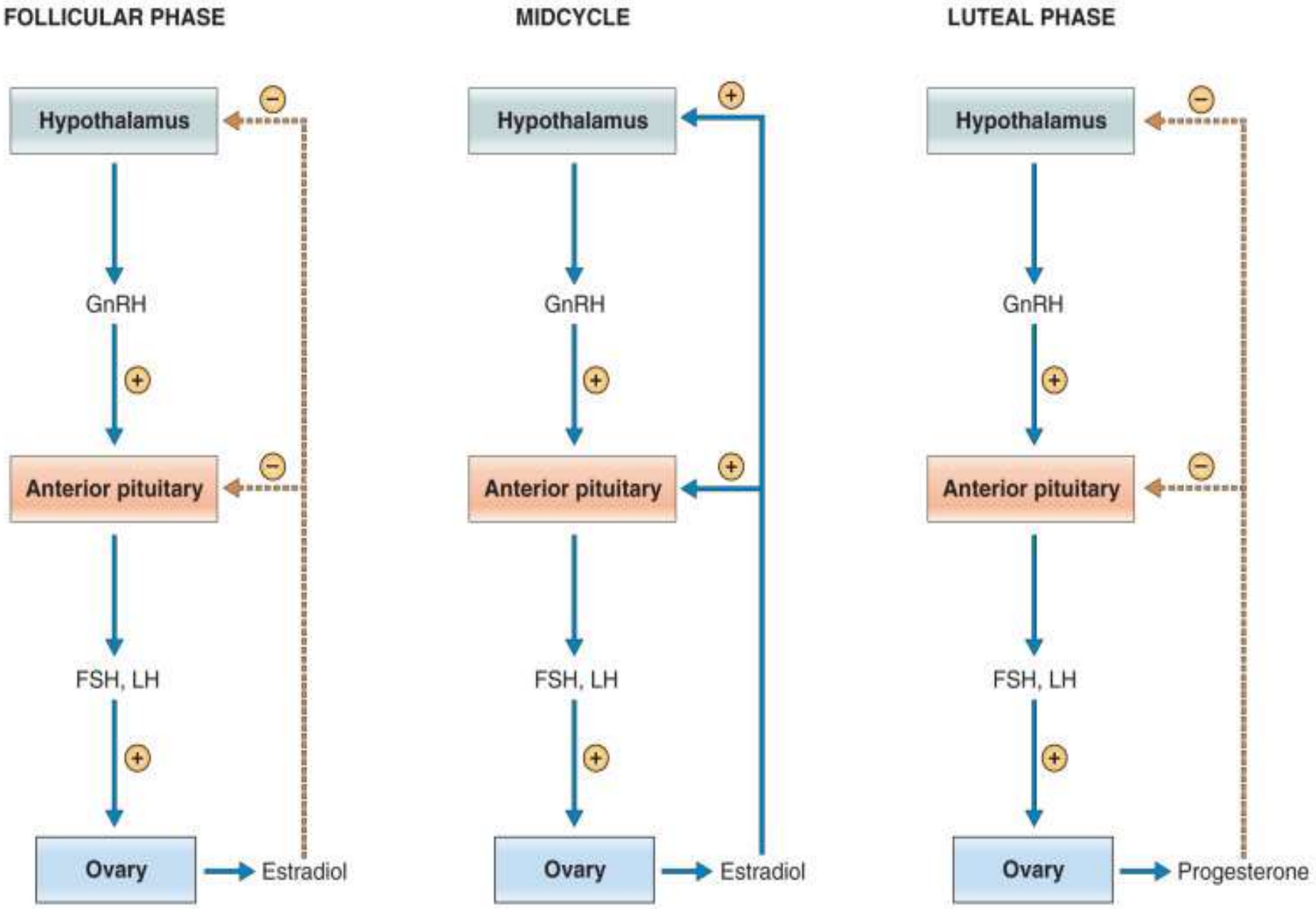

Pituitary gland
GnRH
Posterior
HYPOTHALAMIC-PITUITARY CYCLE
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Pituitary hormones
Follicular phase
Luteal phase
LH
FSH
Ovulation
Primary follicle
Egg
Degenerating corpus luteum
OVARIAN CYCLE
Estrogen
Progesterone
Some estrogen
Ovarian hormones
Estrogen
Progesterone
Menstruation
Proliferative phase
Secretory phase
Ischemic phase
Functional layer
Basal layer
Day
1
5
10
14
28
1
5
ENDOMETRIAL CYCLE

Inhibin, activin, and follistatin

- Inhibin, activin, and follistatin --- selective effects on FSH secretion.
- Although the primary source of inhibin remains the ovary, activin and follistatin are also produced in extragonadal tissues and can exert effects on FSH through an autocrine-paracrine mechanism.
- Inhibin-B is secreted by ovarian granulosa cells during the follicular phase (under the control of FSH) and inhibin-A by the corpus luteum in the luteal phase (under the control of LH).
- Inhibins act synergistically with estradiol to inhibit FSH secretion.
- Activin can directly stimulate FSH biosynthesis and release from the gonadotroph cells of the pituitary gland.
- Follistatin can negatively regulate biologic functions of activin via binding and prevent it from interacting with the activin receptor at the cell membrane.

Feed Back mechanisms

- **Follicular phase:** FSH and LH stimulate synthesis and secretion of estradiol by follicular cells. One action of estradiol is ***negative*** feedback on GnRH secretion by the hypothalamus and FSH and LH secretion by the anterior pituitary.
- **Midcycle,** the feedback pattern reverses. When a critical level of estradiol is reached (of at least 200 picograms per milliliter of plasma), estradiol has a ***positive*** feedback effect on GnRH secretion and on FSH and LH. This burst of hormone secretion by the anterior pituitary, called the **ovulatory surge of FSH and LH,** then triggers ovulation of the mature oocyte.
- **Luteal phase:** One of the actions of progesterone is ***negative*** feedback on GnRH secretion and FSH and LH secretion.
- **Inhibin inhibits** FSH secretion from the anterior pituitary.
- **Activin** is also produced by ovarian granulosa cells and **stimulates** FSH secretion from the anterior pituitary.

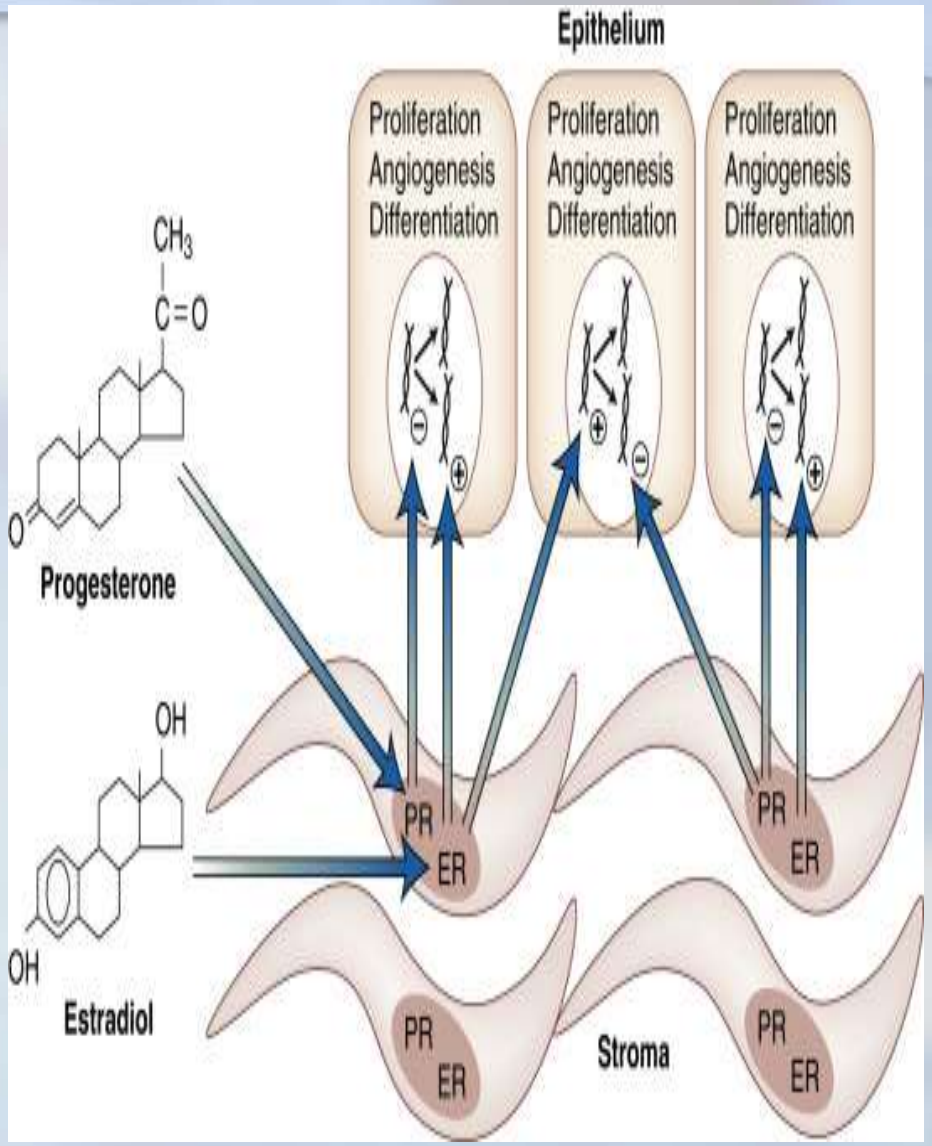

FOLLICULAR PHASE
MIDCYCLE
LUTEAL PHASE
Hypothalamus
GnRH
Anterior pituitary
FSH, LH
Ovary
Estradiol
Hypothalamus
GnRH
Anterior pituitary
FSH, LH
Ovary
Estradiol
Hypothalamus
GnRH
Anterior pituitary
FSH, LH
Ovary
Progesterone

Prostaglandins

- Prostaglandins are produced intracellularly shortly before they are released and generally act locally.
- Modulate the responses of endogenous stimulators and inhibitors, such as ovarian stimulation by LH, which is modulated by PGF2α.
- They help control early follicular growth by increasing blood supply to certain follicles
- Inducing FSH receptors in granulosa cells of preovulatory follicles.
- Both PGF2α and PGE2 are concentrated in follicular fluid of preovulatory follicles and assist follicular rupture by facilitating proteolytic enzyme activity in the follicular walls.
- Concentrations of PGE2 and PGF2α in endometrium increase progressively from the proliferative to the secretory phase of the cycle, with highest levels at menstruation.
- Help regulate myometrial contractility and regulate the process of menstruation.

Role of E2 & P4 on endometrium

- Critical epithelial effects of estrogen (i.e., DNA synthesis, proliferation, and gene expression) are mediated primarily by estrogen receptor-α (ER) in stromal cells in a paracrine manner in the endometrium.
- Antiestrogenic effects of progesterone on epithelial cells (e.g., decreased proliferation, enhanced differentiation) are mediated primarily by progesterone receptors (PRs) in stromal cells



NORMAL MENSTRUAL CYCLE

What is the mean duration of the MC?

Mean 28 days (only 15% of ♀)

Range 21-35

What is the average duration of menses?

3-8 days

What is the normal estimated blood loss?

Approximately 30 ml

When does ovulation occur?

Usually day 14

36 hrs after the onset of mid-cycle LH surge

NORMAL MENSTRUAL CYCLE

What regulate the phases of the MC & ovulation?

Interaction between hypothalamus, pituitary & ovaries

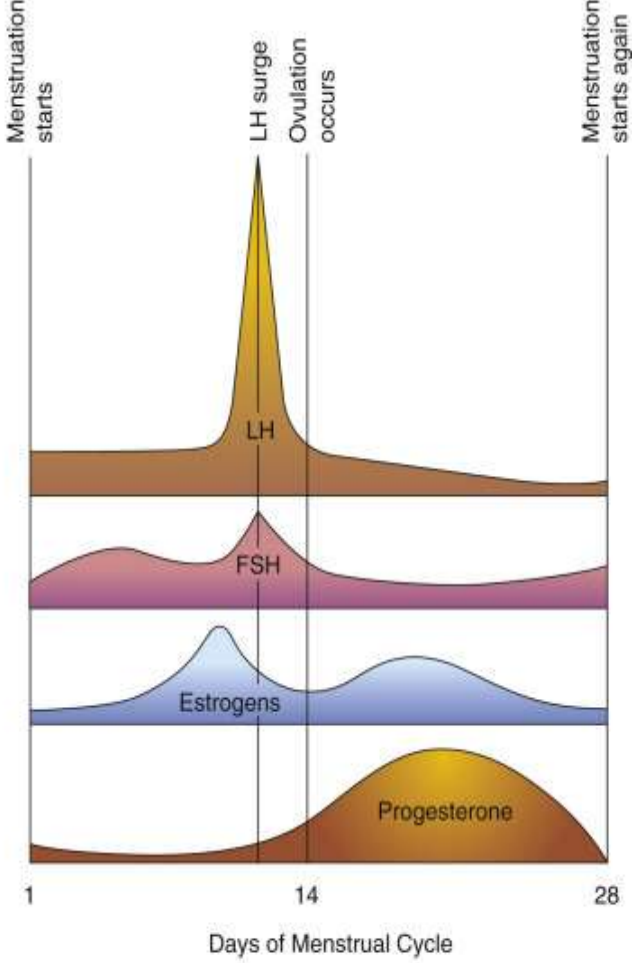
What is the mean age of menarche & menopause?

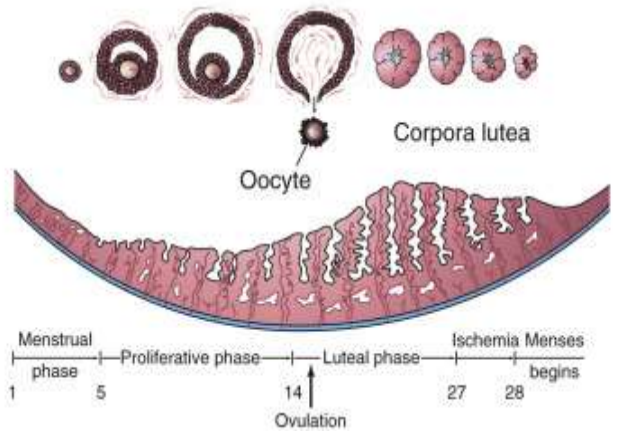
Menarche 12.7

Menopause 51.4

Phases of MC

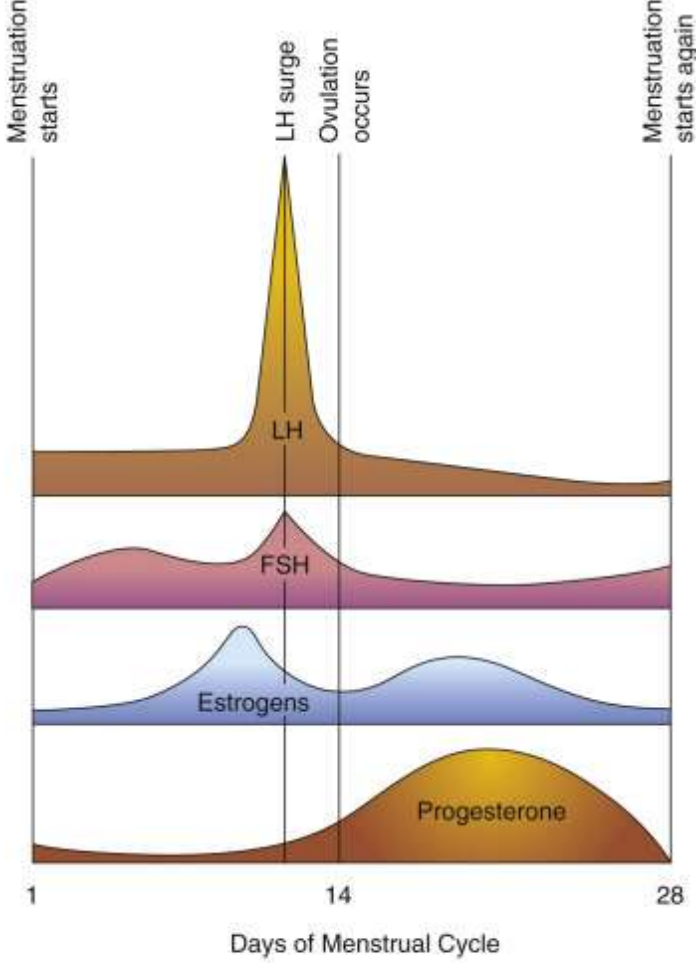
Cycle day	1–5	6–14	15–28
Ovarian phase	Early follicular	Follicular	Luteal
Endometrial phase	Menstrual	Proliferati	Secretory
Estrogen/progesterone	Low levels	Estrogen	Progestere

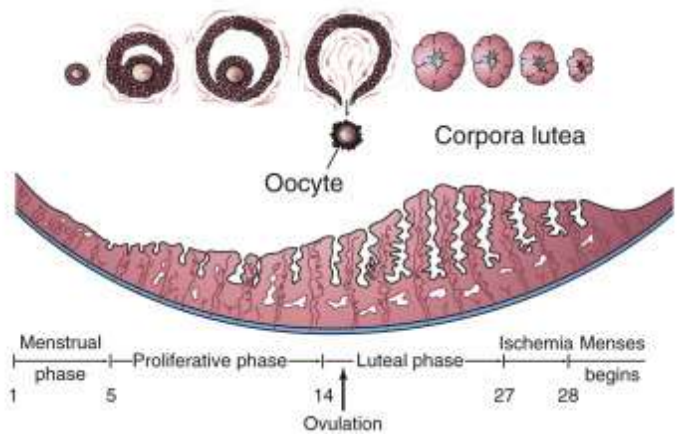




PREOVULATORY PERIOD

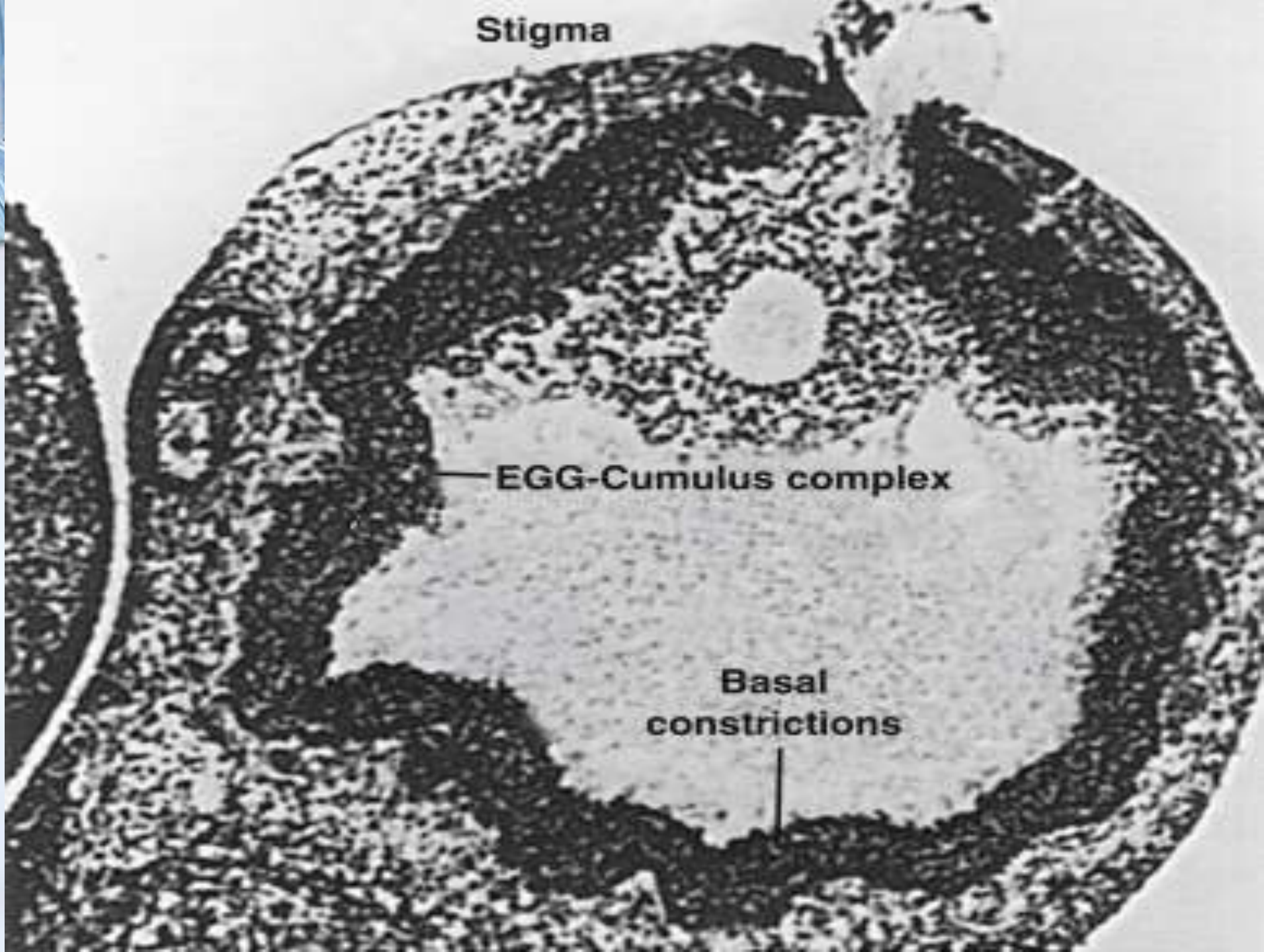
- Ovulation occurs about 24 hours after the estradiol peak, as well as 32 hours after the initial rise in LH, and about 12 to 16 hours after the peak of LH levels in serum.
- Lasts for 48 hrs
- Ovulation occurs after 36 hrs of LH SURGE and about 16 hours after LH PEAK
- Accompanied by rapid fall in estradiol level
- Triggers the resumption of meiosis
- Affects follicular wall ⇨ follicular rupture
- Granulosa cells ⇨ lutenization ⇨ progestrone synthesis

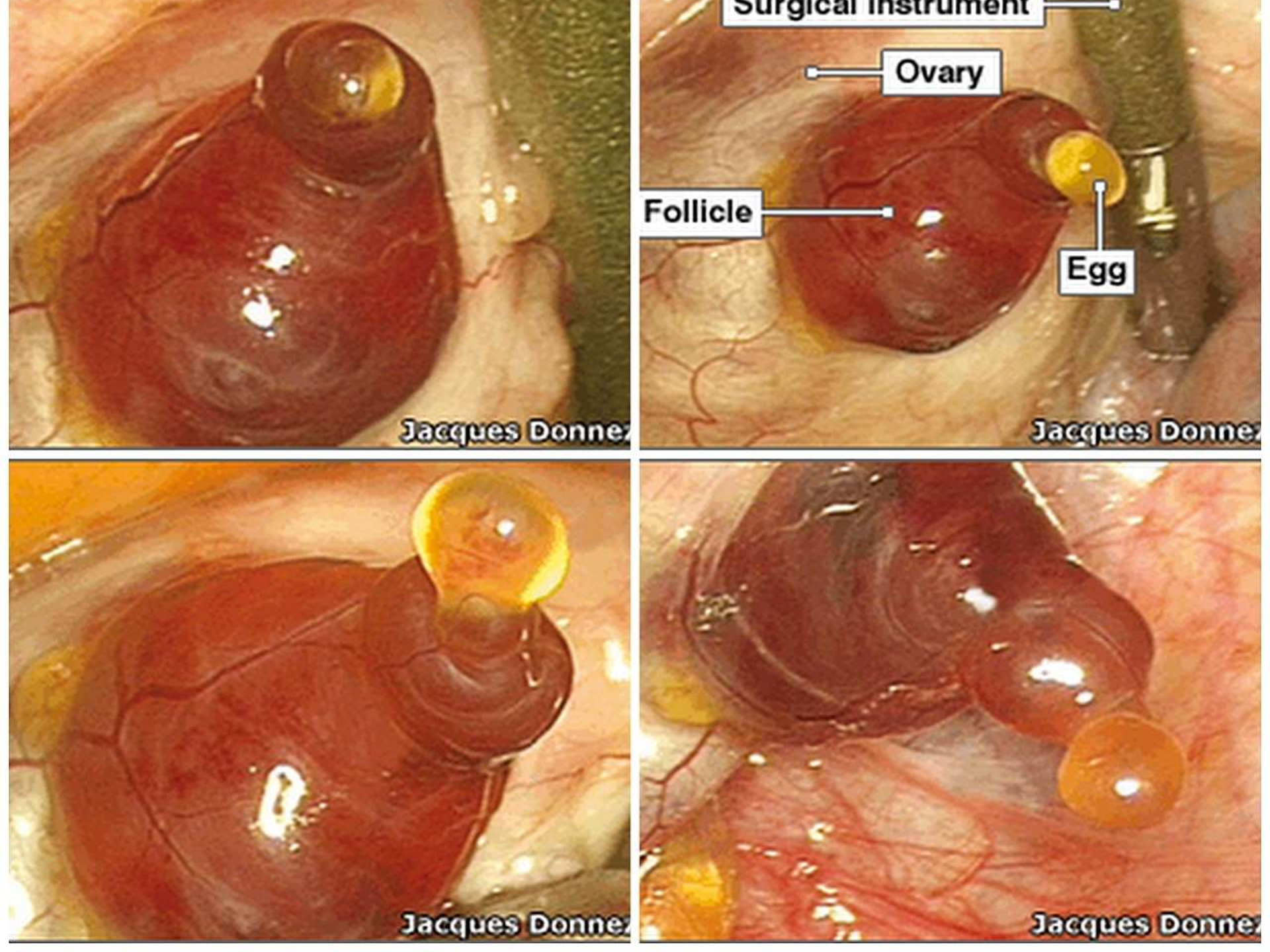




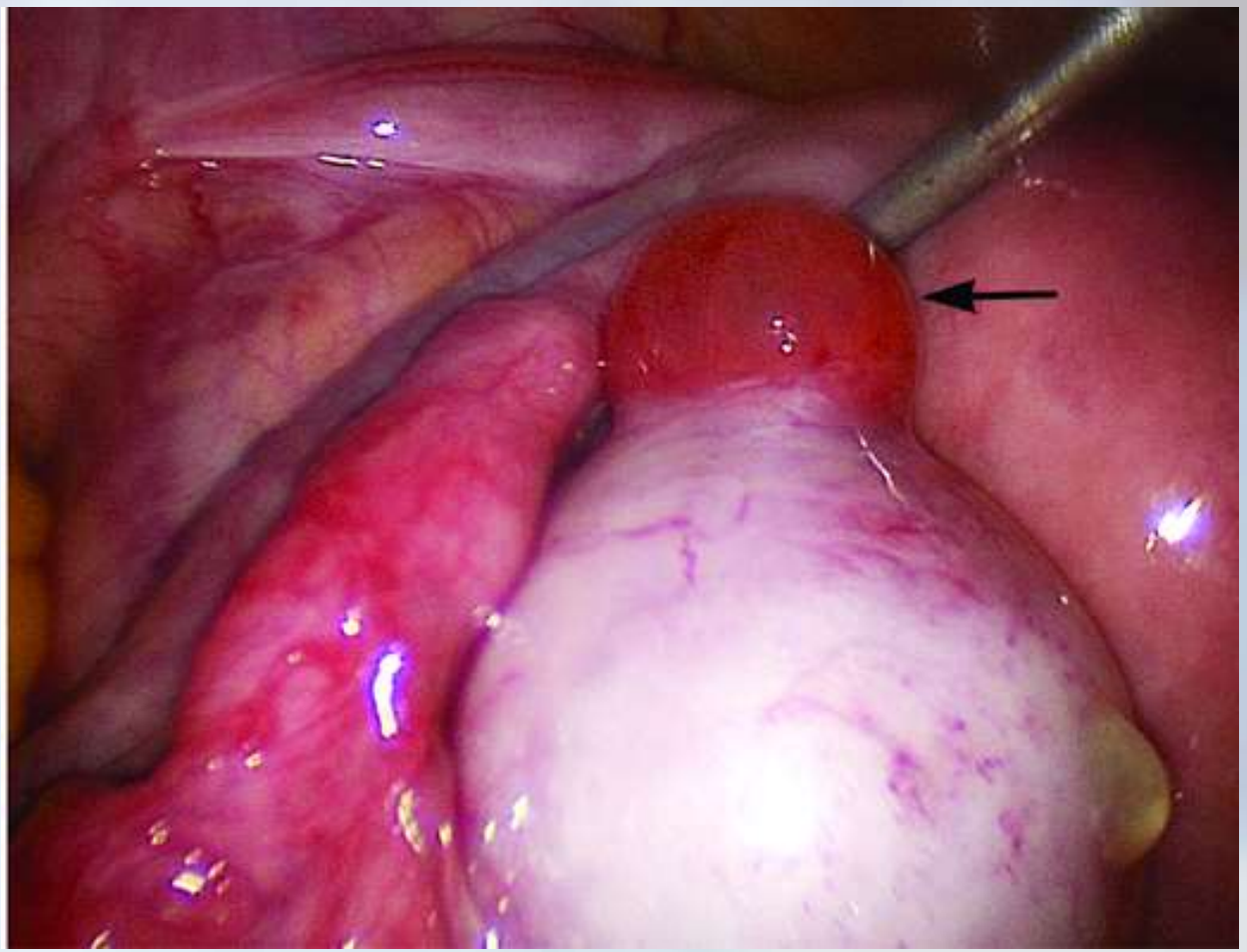
Summary of the Key Ovulatory Events

- The LH surge initiates the continuation of meiosis in the oocyte, luteinization of the granulosa, and synthesis of progesterone and prostaglandins within the follicle.
- Progesterone enhances the activity of proteolytic enzymes responsible, together with prostaglandins, for digestion and rupture of the follicular wall.
- The progesterone-influenced midcycle rise in FSH serves to free the oocyte from follicular attachments, to convert plasminogen to the proteolytic enzyme, plasmin, and to ensure that sufficient LH receptors are present to allow an adequate normal luteal phase.
- Progesterone levels in serum are less than 1 ng/mL before ovulation and reach midluteal levels of 10 to 20 ng/mL.


Stigma
EGG-Cumulus complex
Basal
constrictions

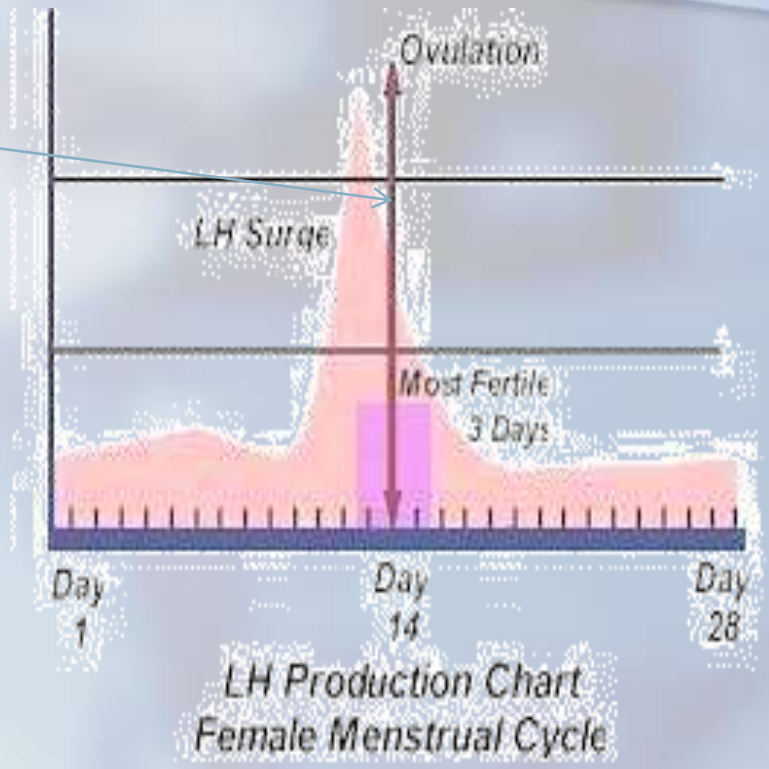

Surgical instrument
Ovary
Follicle
Egg
Jacques Donnez
Jacques Donnez
Jacques Donnez
Jacques Donnez

During laparoscopy, a stigma on the ovarian surface (*arrow*) prior to ovulation is seen.



Ovulation

- Ovulation occurs about 24 hours after the estradiol peak, as well as 32 hours after the initial rise in LH, and about 12 to 16 hours after the peak of LH levels in serum.
- A history of regular, predictable menses strongly suggests ovulatory cycles.
- Additionally to:
  - pelvic discomfort (mittelschmerz),
  - fullness and tenderness of the breasts

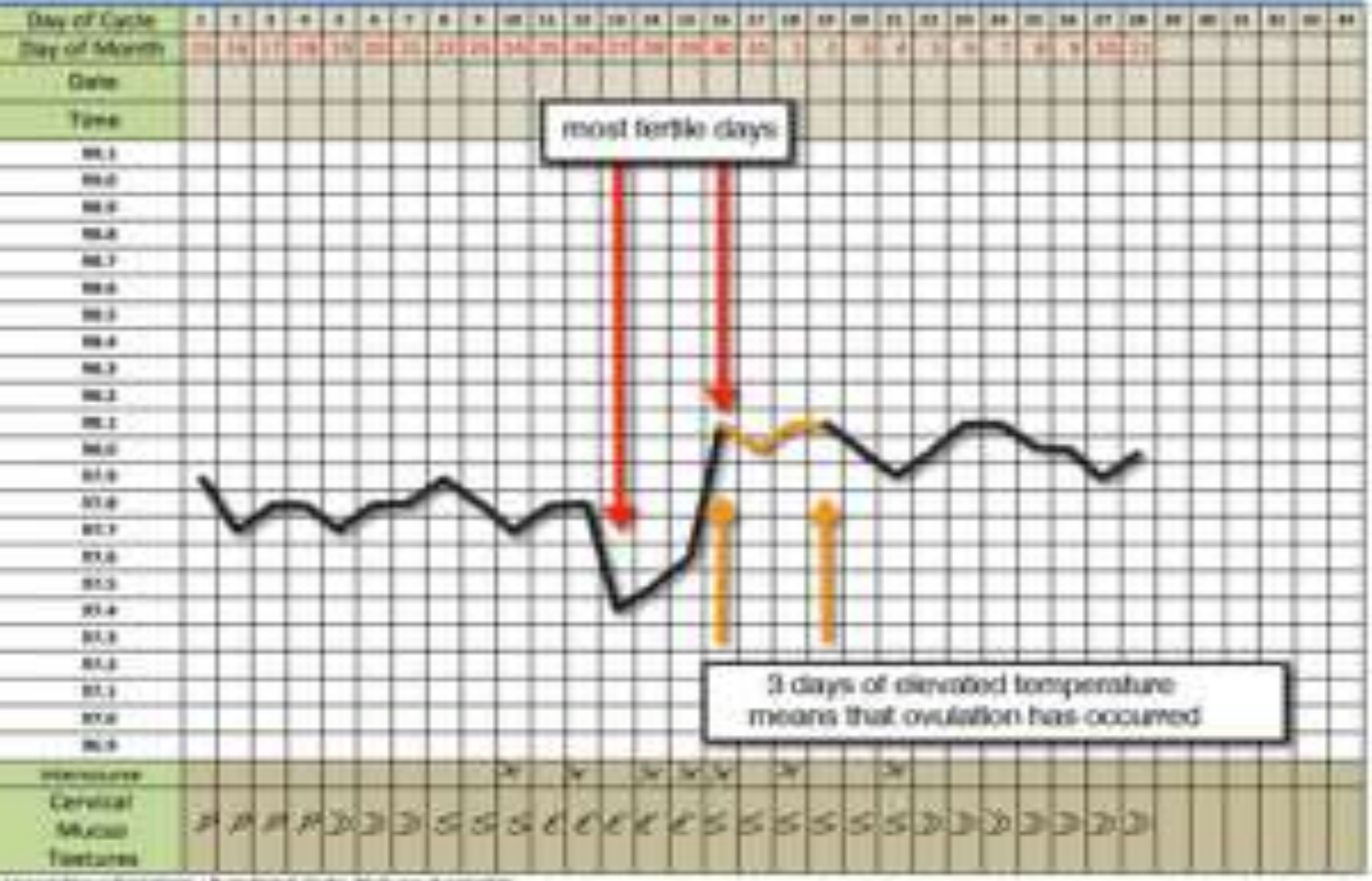


How to test for ovulation?

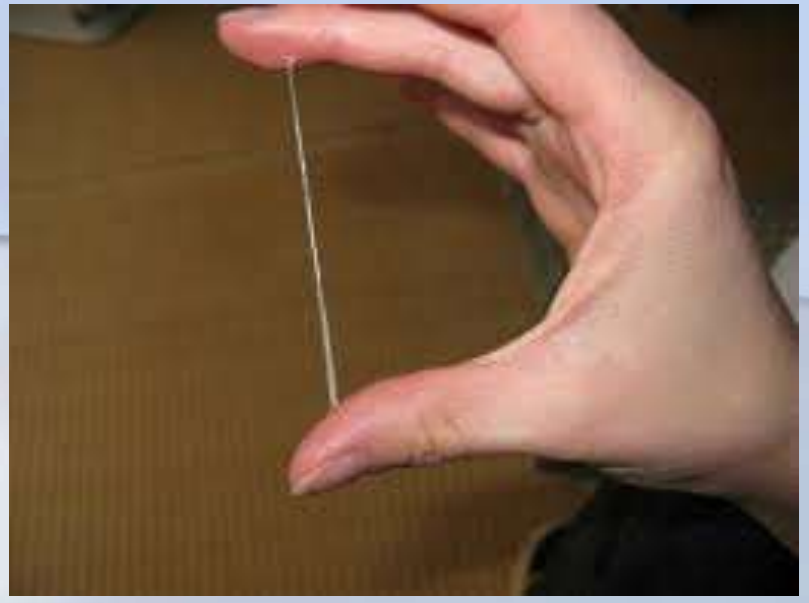
- Day 21 P4:
  - a luteal phase progesterone value of >28 nmol/L
  - a serum progesterone level at any time above 3 to 5 nmol/L suggests some ovulatory function, but it cannot indicate the adequacy of normal ovulation
- BBT chart
- **LH Kit- the best initial step**
- Cervical mucus changes

Basal Body Temperature (BBT) and Cervical Mucus Chart

Month: May / June



DHgate.com
Fast Trading Marketplace



spinnbarkeit

fern

Dry/Tacky/Thick CM
{Not Fertile}

Creamy/Sticky CM
{Not Fertile}

Cloudy/Stretchy CM
{Semi-Fertile}

Watery/Stretchy
Egg White CM
{Most Fertile}

Progressive Cervical Mucus Chart

© Like A Mustard Seed

Variations in cycle length and ovulation

- Women who have a 25-day cycle ovulate on or about cycle day 10–12, and those with a 35-day cycle ovulate approximately 10 days later.
- The prevalence of anovulatory cycles is highest in women under age 20 and over age 40

ENDOMETRIAL CHANGES DURING THE MENSTRUAL CYCLE

1-Follicular /proliferative phase

Estrogen ⇨ mitotic activity in the glands & stroma ⇨

↑ enometrial thickness from 2 to 8 mm

(from basalis to opposed basalis layer)

2-Luteal /secretory phase

Progestrone ⇨- Mitotic activity is severely restricted

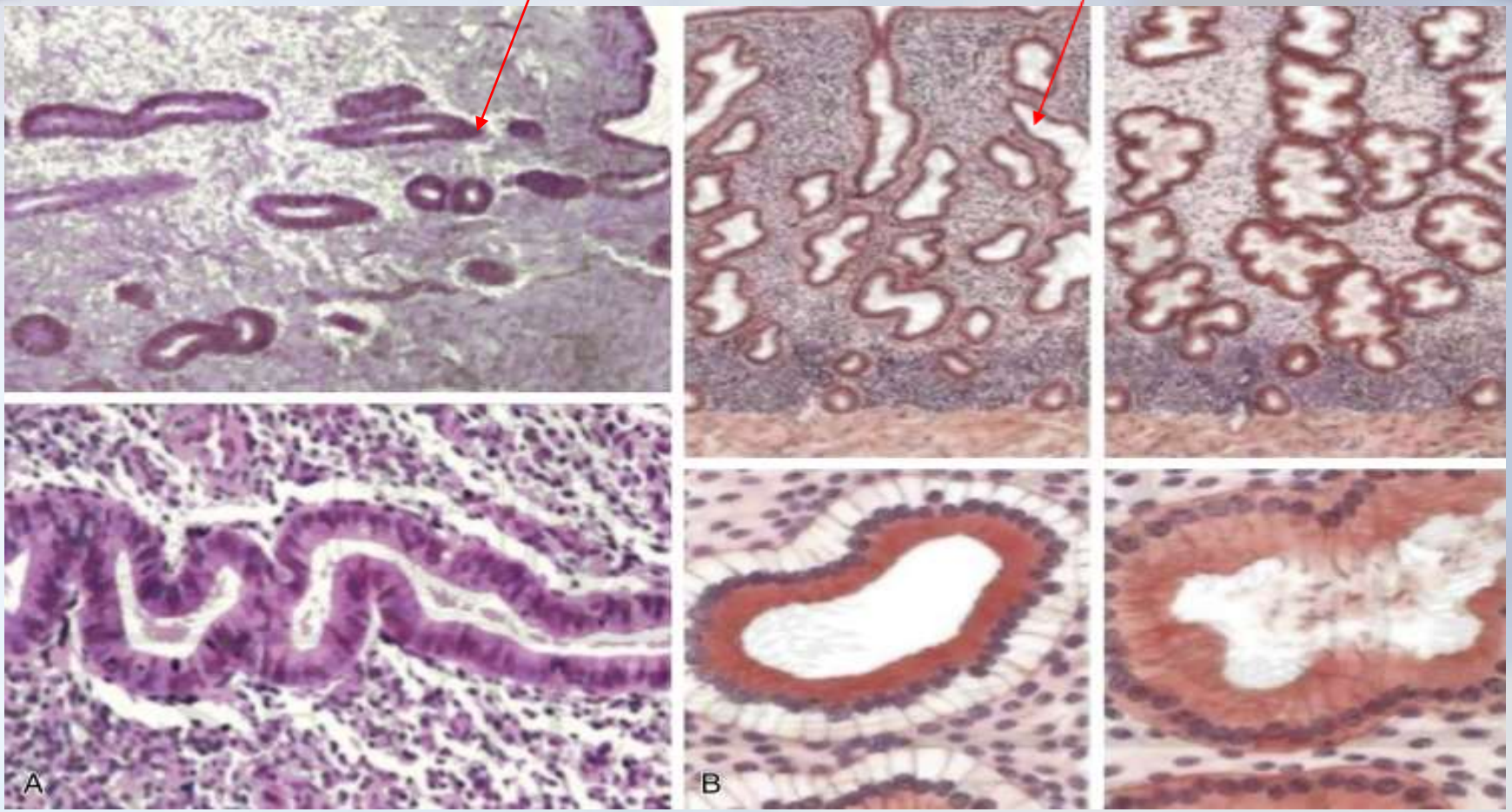
-Endometrial glands produce then secrete glycogen rich vacules

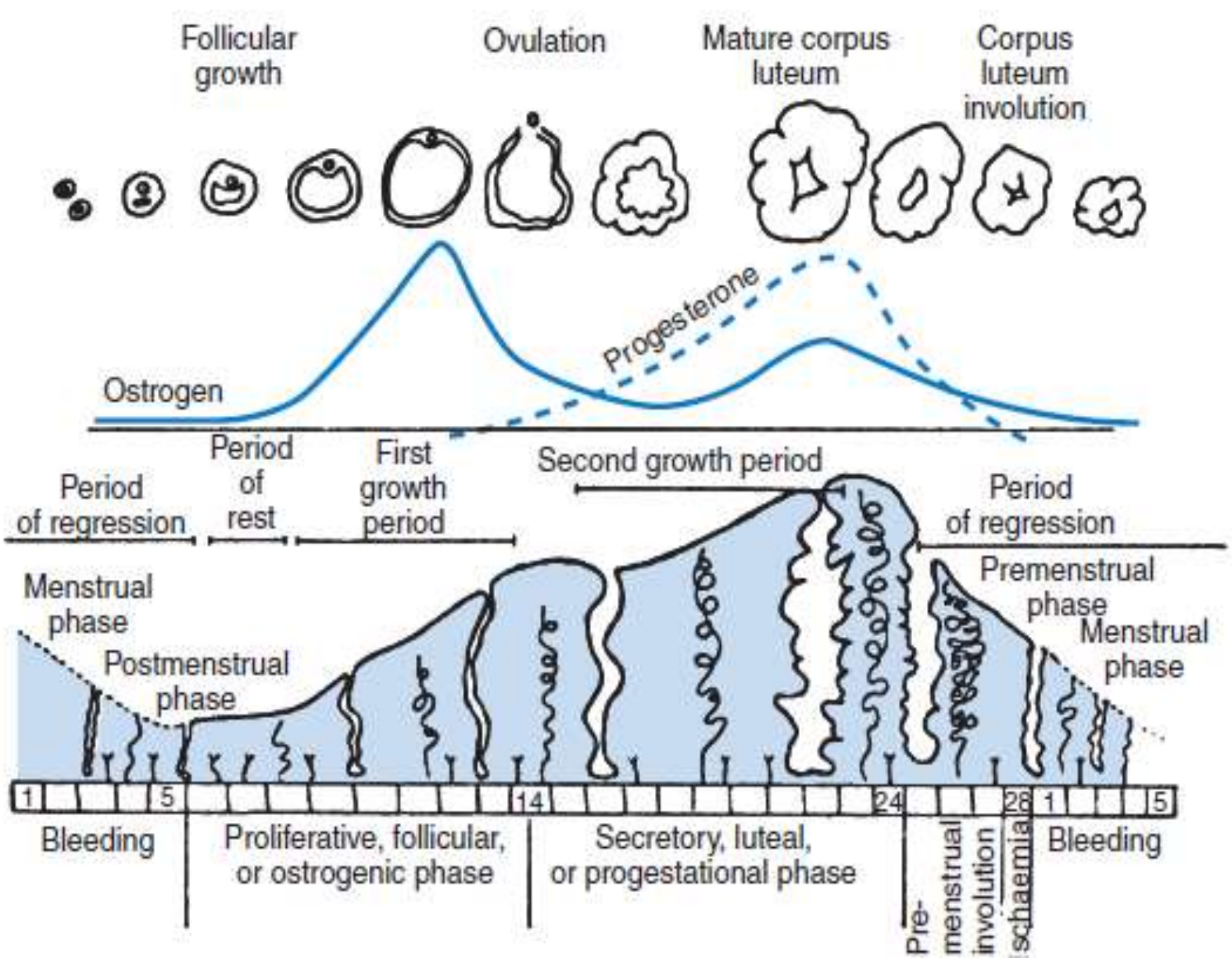
-Stromal edema

-Stromal cells enlargement

-Spiral arterioles develop, lengthen & coil

Histology of proliferative (**A**) and secretory (**B**) endometrial tissue.



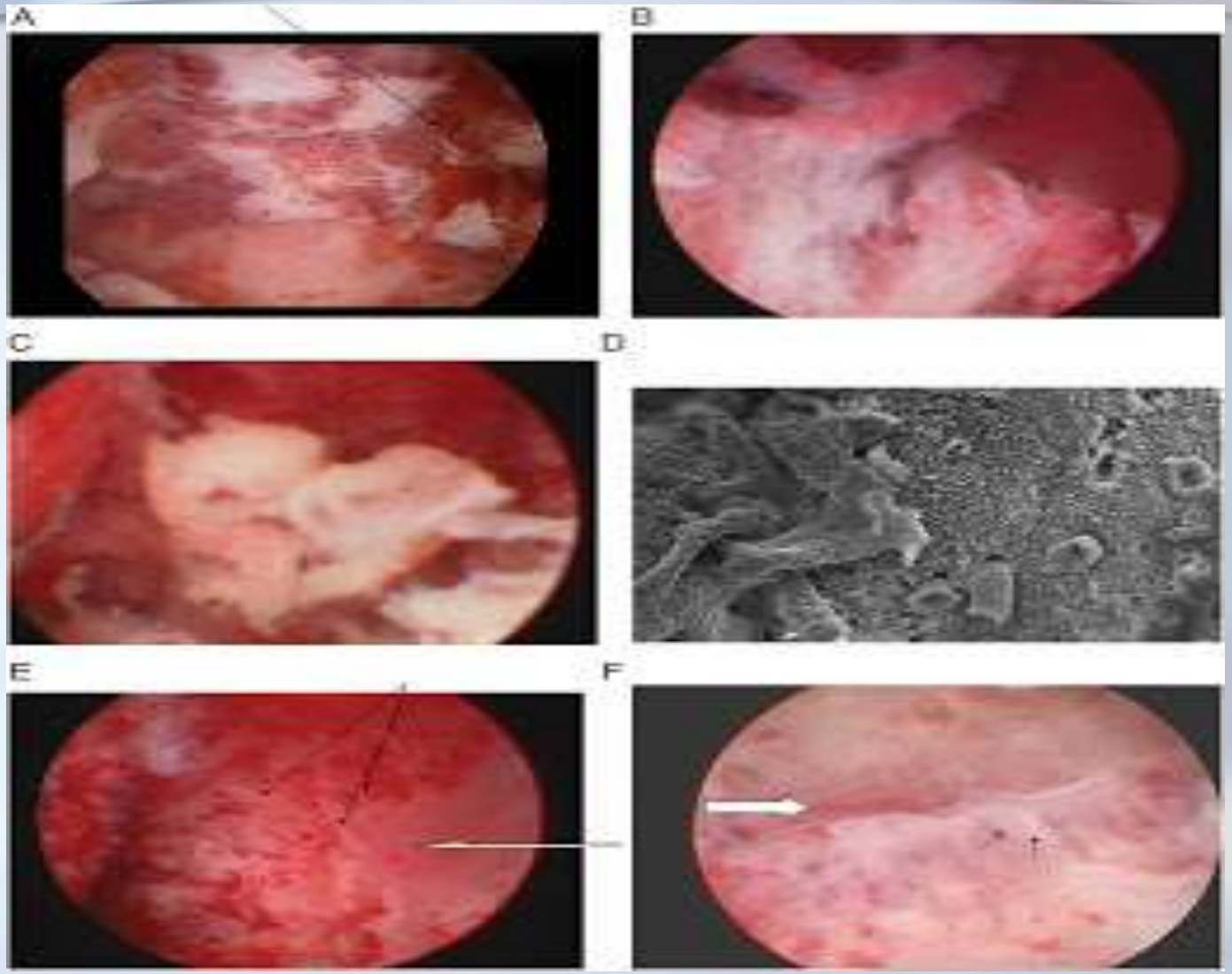

Follicular growth
Ovulation
Mature corpus luteum
Corpus luteum involution
Progesterone
Ostrogen
Period of regression
Period of rest
First growth period
Second growth period
Period of regression
Menstrual phase
Postmenstrual phase
Premenstrual phase
Menstrual phase
1
5
14
24
28
1
5
Bleeding
Proliferative, follicular, or ostrogenic phase
Secretory, luteal, or progestational phase
Pre-menstrual involution
Ischaemia
Bleeding

MENSTRUATION

- Periodic desquamation of the endometrium
- The external hallmark of the menstrual cycle
- Intense tissue breakdown by proteolytic enzymes, mainly members of the matrix metalloproteinase family (MMPs)
- Just before menses the endometrium is infiltrated with leucocytes
- Prostaglandins are maximal in the endometrium just before menses
- Prostaglandins ⇨ constriction of the spiral arterioles ⇨ischemia & desquamation

  Followed by arteriolar relaxation, bleeding & tissue breakdown
- **After menstruation, regeneration of the endometrium comes from cells in the spongiosum that were previously a portion of the secretory endometrium and not from the stratum basale as previously believed.**

Hysteroscopic view of endometrium during menses

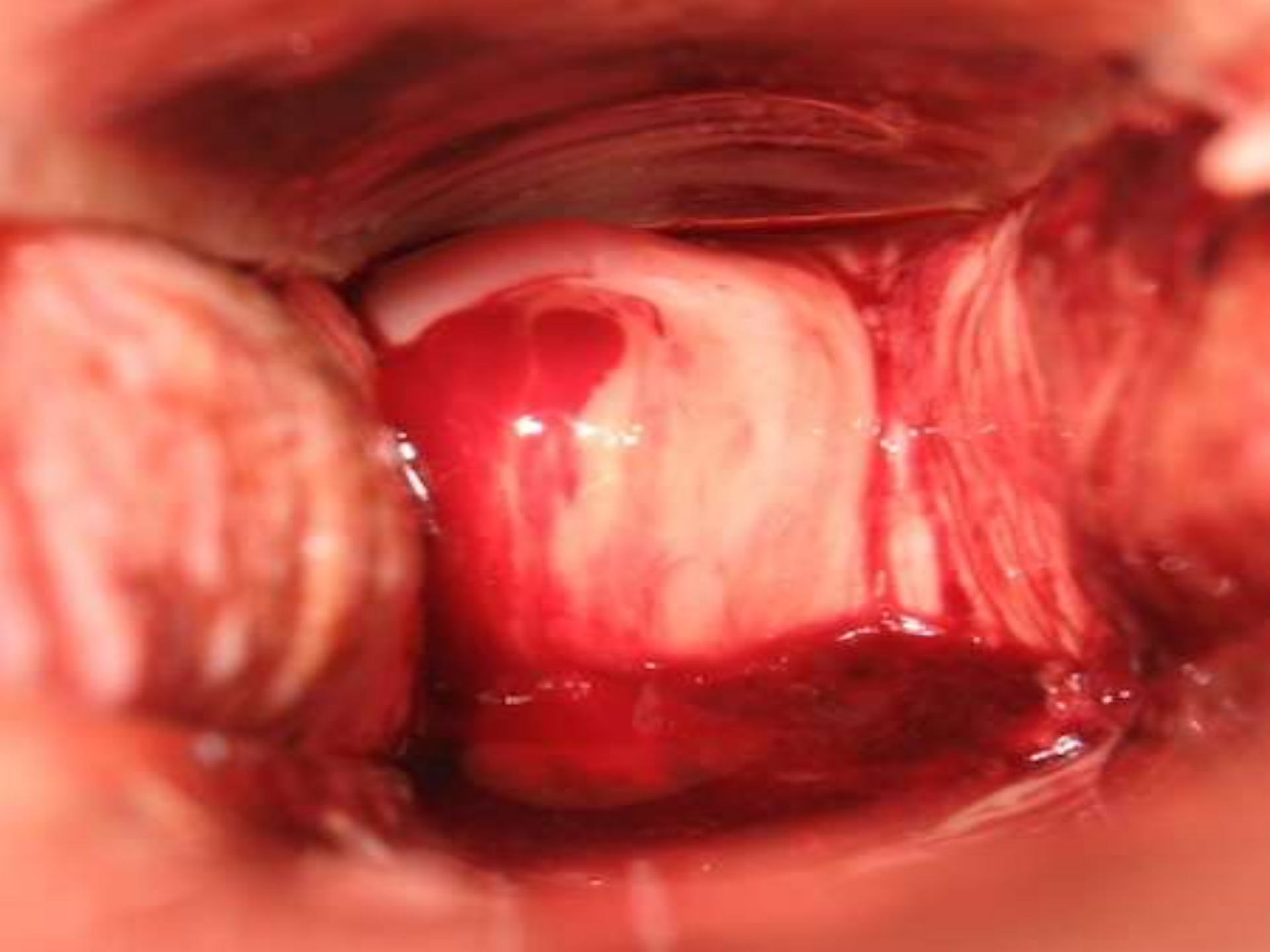


The cervix during menstrual cycle

- Changes in the production and property of mucus secreted by the cervical glands are closely correlated to changes in estradiol and progesterone
- Enhanced production of cervical mucus and the presence of crypts within the endocervix serve to facilitate the transport and storage of spermatozoa around midcycle.
- Cervical mucus is produced in copious amounts in response to high estradiol levels at the end of the follicular phase:
  - it has a clear, water-like appearance, which is acellular, takes the aspect of a "fern" when it dries as viewed under the microscope, and is "stringy," referred to as "spinnbarkeit" (i.e., cervical mucus that can stretch on a slide at least 6 cm).
- So characteristic are these findings that the appearance of this type of mucus signifies the "fertile period"

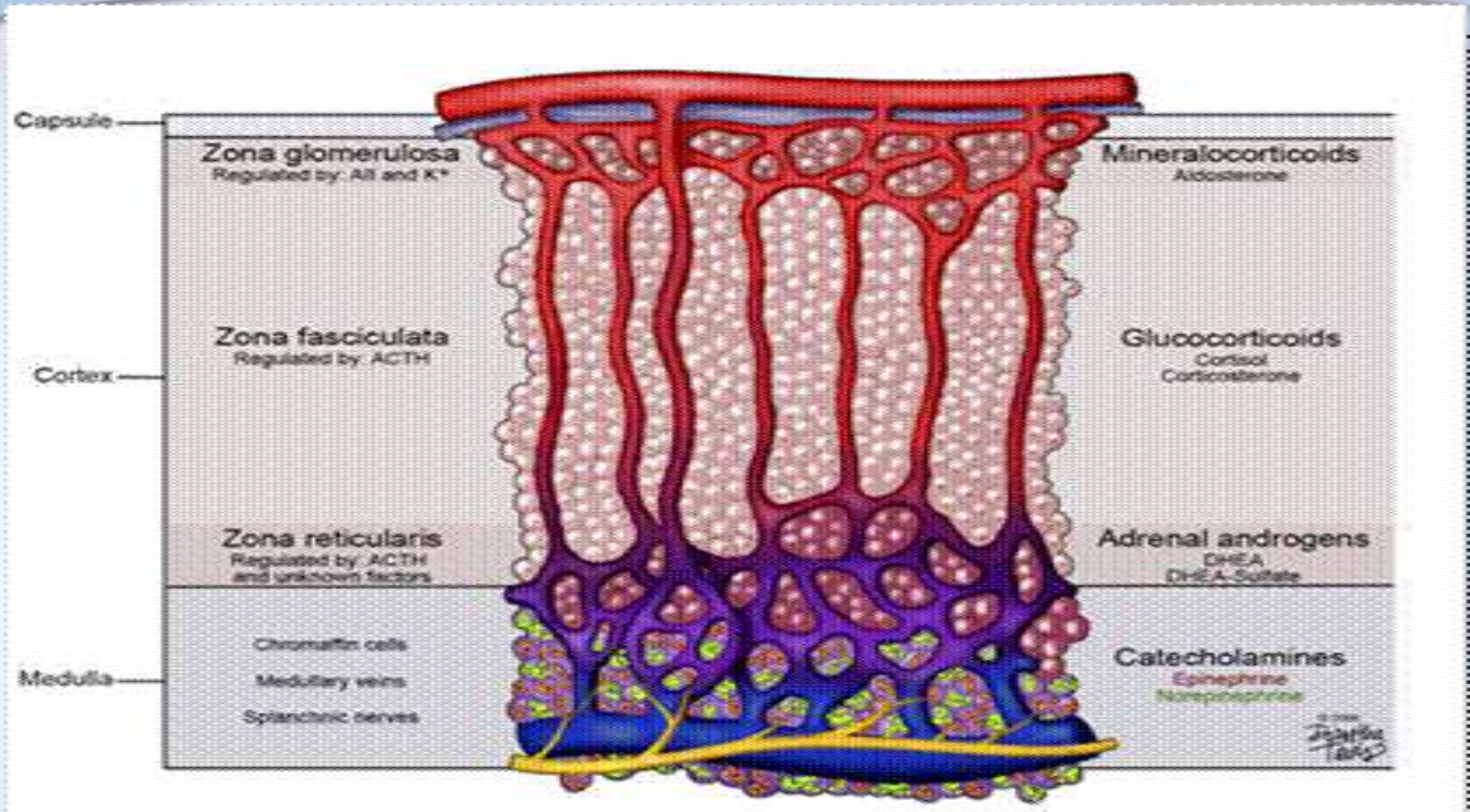
Day 11

Day 20

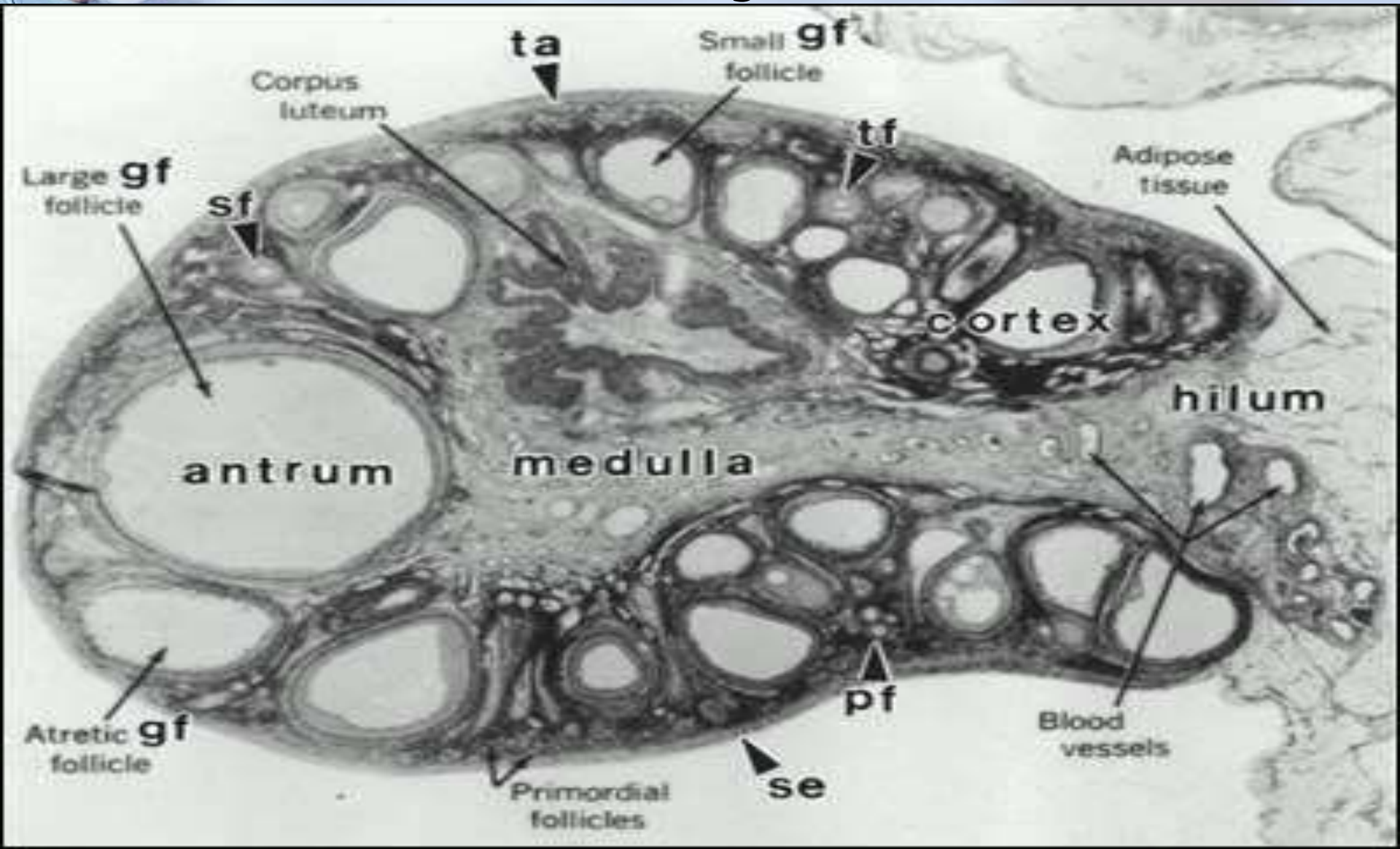


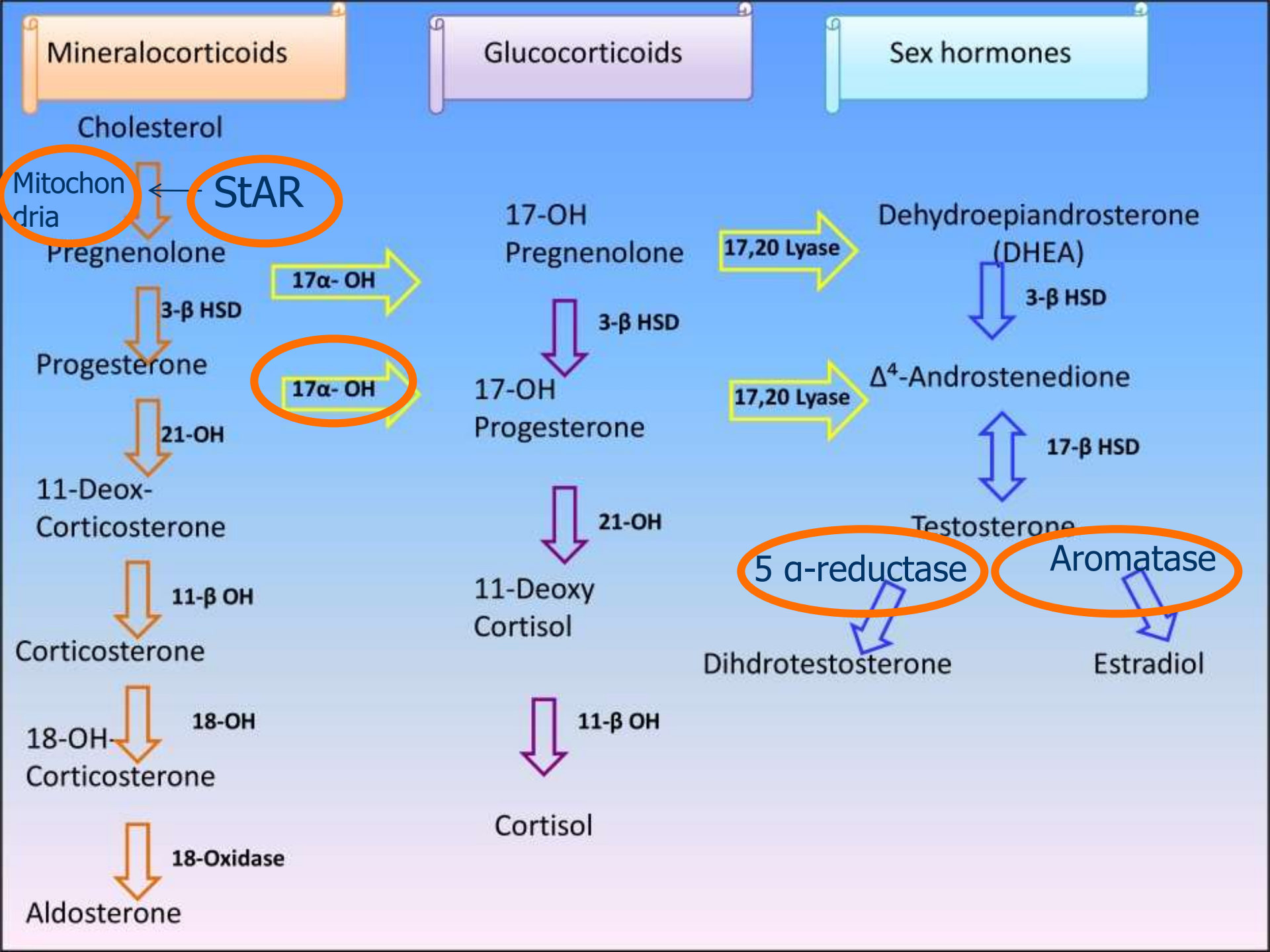
Steroidogensis: you need it even if you are not planning to be a gynecologist!

Schematic presentation of the adrenal zones and the main product

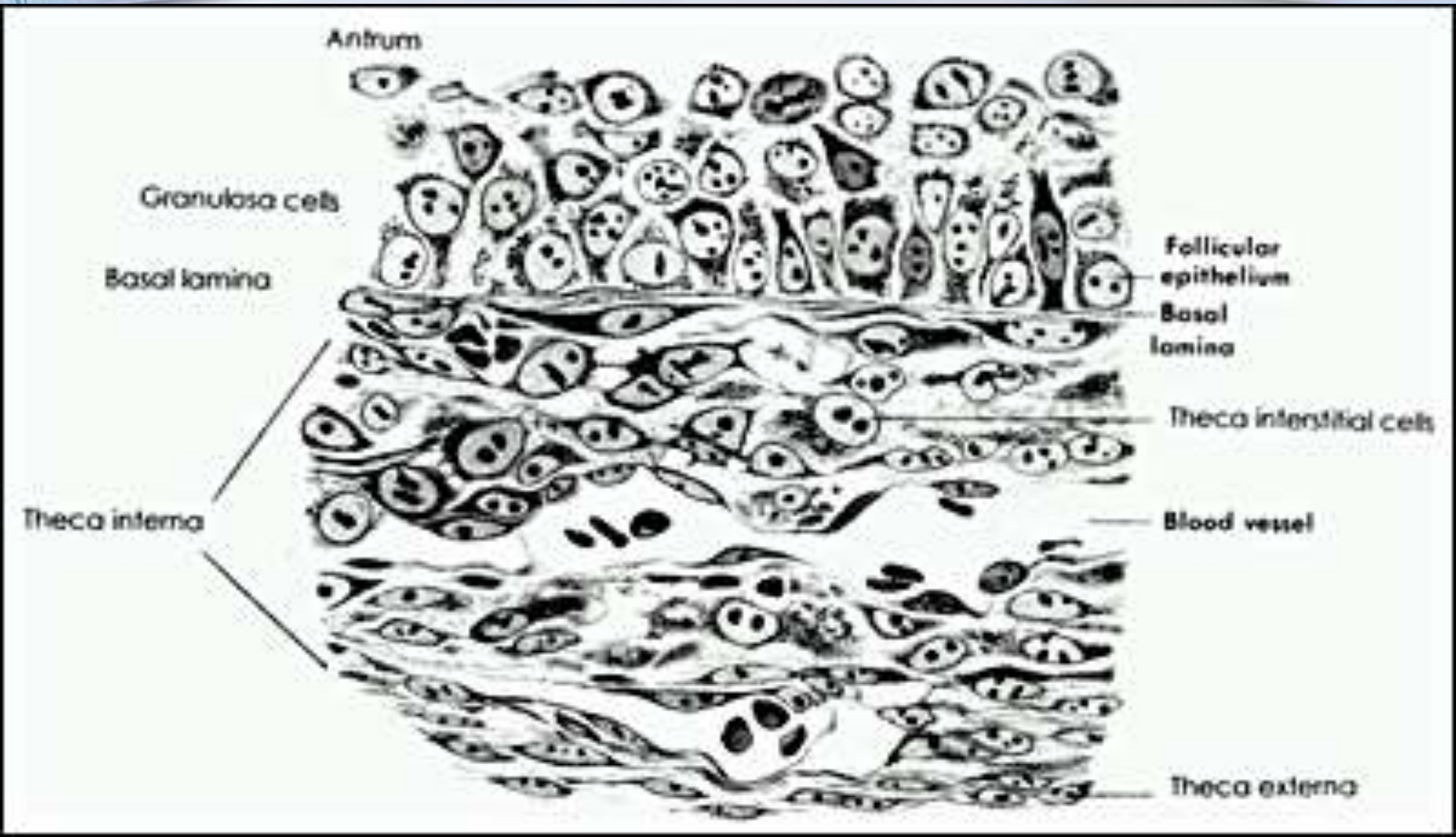


The adult ovary can be subdivided into three regions: the cortex, medulla, and hilum regions

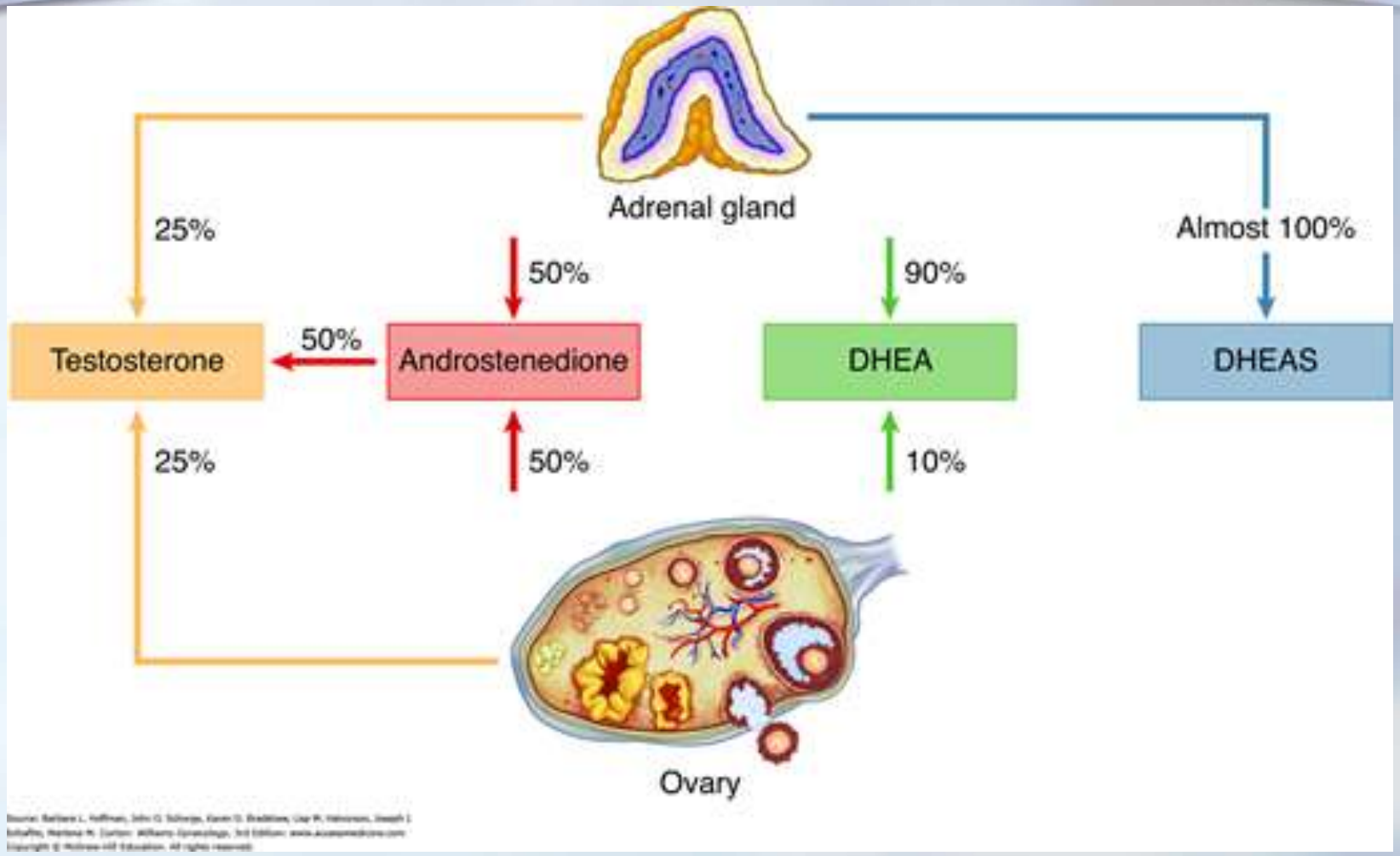



Mineralocorticoids
Glucocorticoids
Sex hormones
Cholesterol
Mitochon dria
StAR
Pregnenolone
3-β HSD
Progesterone
21-OH
11-Deox-Corticosterone
11-β OH
Corticosterone
18-OH
18-OH-Corticosterone
18-Oxidase
Aldosterone
17α- OH
17-OH Pregnenolone
3-β HSD
17-OH Progesterone
17α- OH
21-OH
11-Deoxy Cortisol
11-β OH
Cortisol
17,20 Lyase
Dehydroepiandrosterone (DHEA)
3-β HSD
Δ4-Androstenedione
17,20 Lyase
17-β HSD
Testosterone
5 α-reductase
Aromatase
Dihdrotestosterone
Estradiol

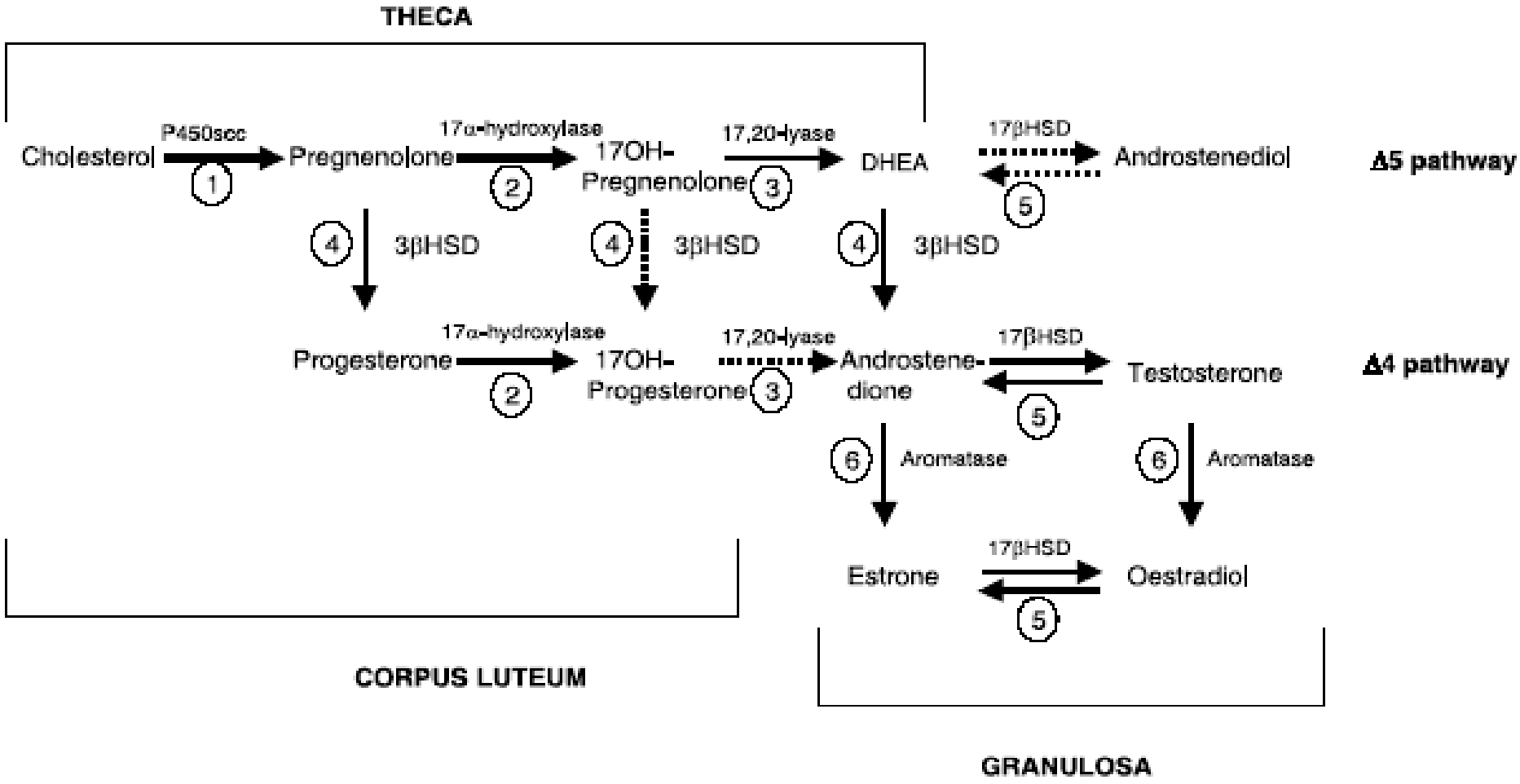
Cross section through the ovarian tissue



Contribution of the adrenal glands and ovaries to levels of androgens, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS).



Ovarian steroidogenesis

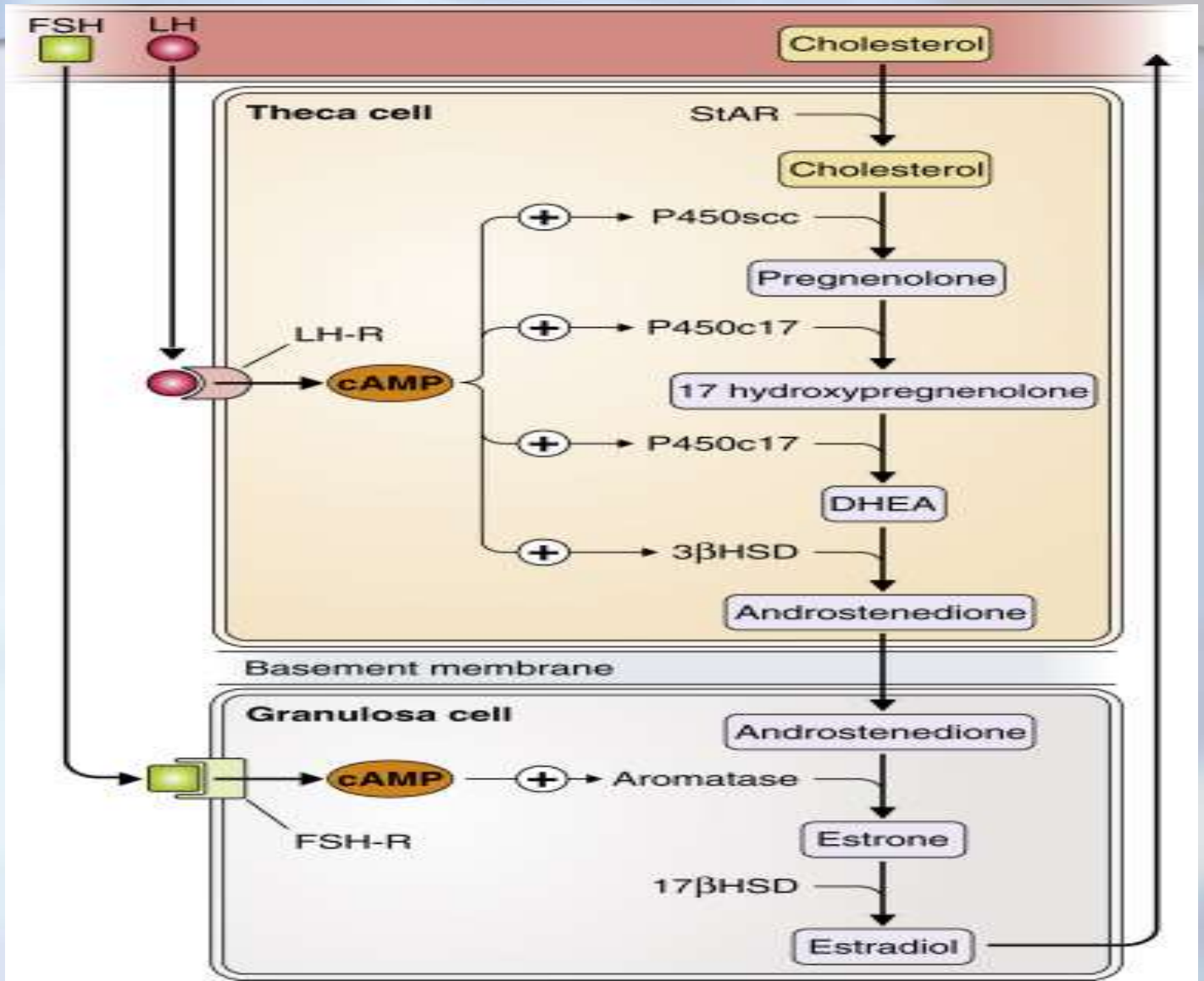


Source: Clin Endocrinol © 2004 Blackwell Publishing

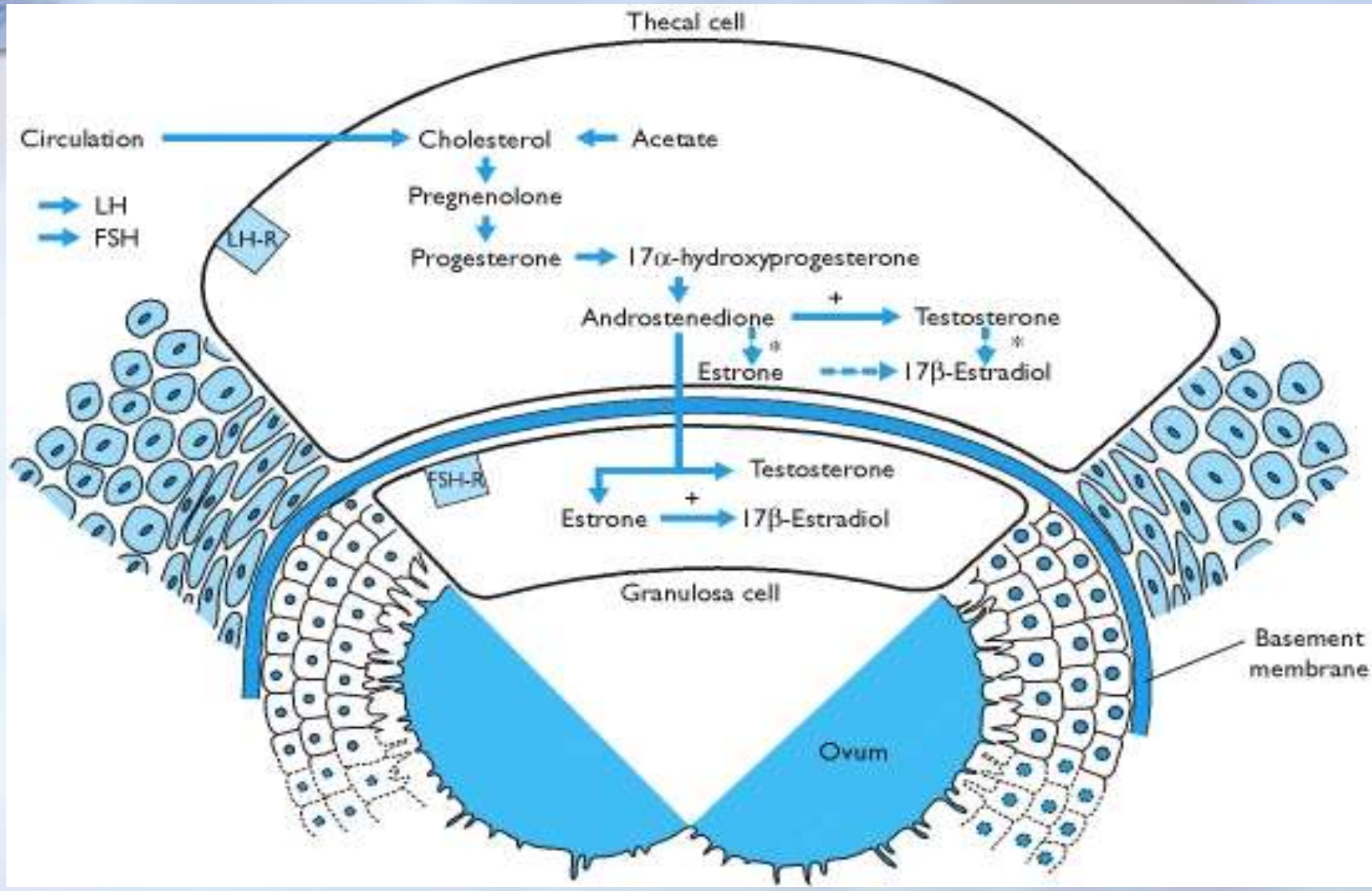
Ovarian Vs Adrenal steroidogenesis

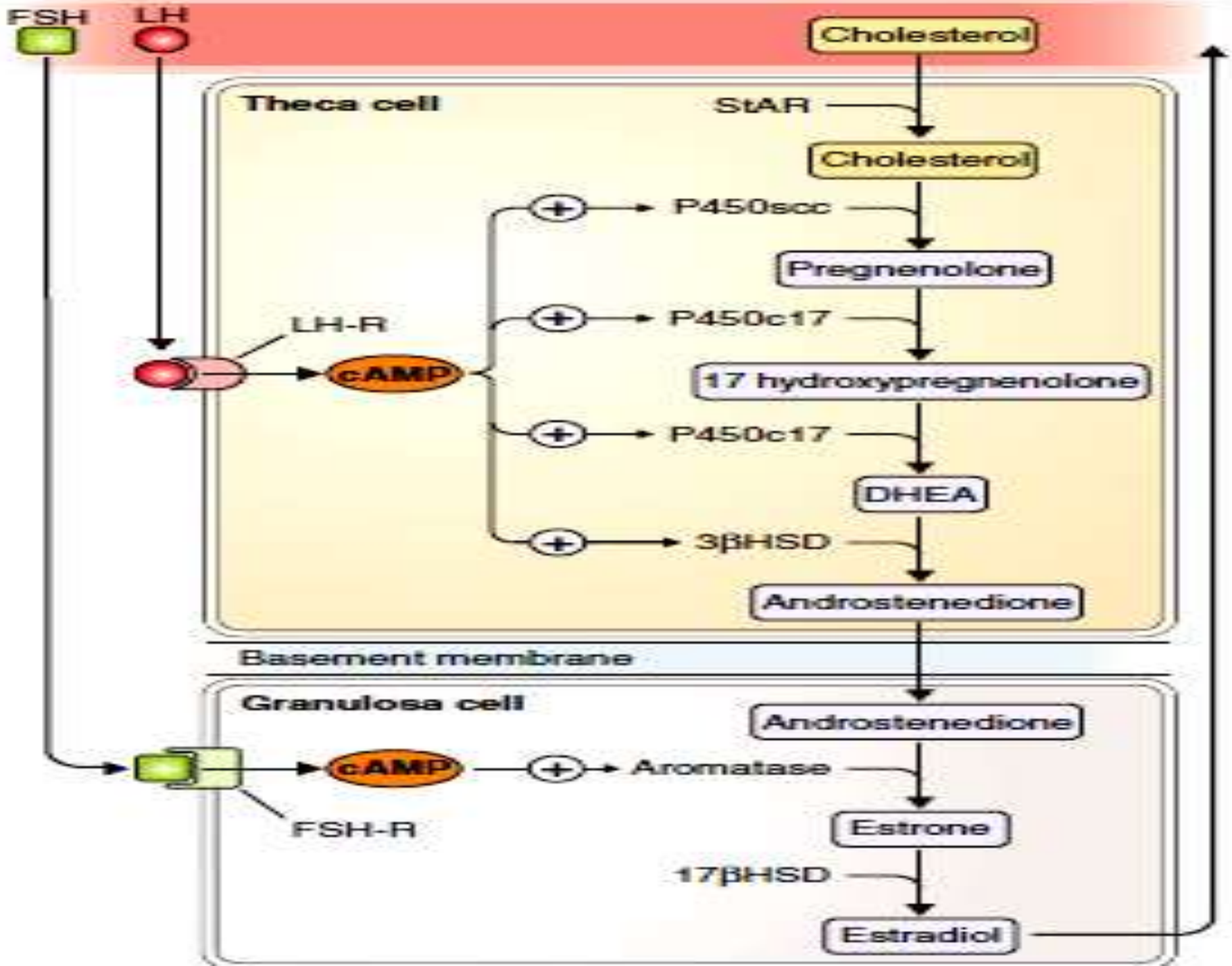
- The ovary lacks the 21-hydroxylase and B-hydroxylase reactions.
- Hence, no glucocorticoids and mineralocorticoids in the ovary

Two gonadotropin-two cell theory



Two gonadotropin-two cell theory




FSH
LH
Cholesterol
Theca cell
StAR
Cholesterol
P450scc
Pregnenolone
LH-R
cAMP
P450c17
17 hydroxypregnenolone
P450c17
DHEA
3βHSD
Androstenedione
Basement membrane
Granulosa cell
Androstenedione
cAMP
Aromatase
Estrone
FSH-R
17βHSD
Estradiol

Key points

- LH and FSH have the same α subunit of TSH and HCG). The β subunits of all these hormones have **different** amino acids and carbohydrates, which provide specific biologic activity.
- LH acts on the theca cells to produce androgens, which are then transported to the granulosa cells, where they are aromatized to estrogens.
- Pregnenolone, 17-hydroxypregnenolone, progesterone, 17-hydroxyprogesterone, and corticosteroids have 21 carbon atoms; androgens (testosterone and androstenedione) have 19 carbon atoms; estrogens have 18 carbon atoms and a phenolic ring A.
- Kisspeptin (KISS1) plays a key role in the regulation of GnRH release.
- Because the ovaries lack 21-hydroxylase, 11-β-hydroxylase, and 18-hydroxylase reductase activity, they are unable to synthesize mineralocorticoids or glucocorticoids.
- After menstruation, regeneration of the endometrium comes from cells in the spongiosum that were previously a portion of the secretory endometrium and not from the stratum basale as previously believed.

Key points

- SHBG primarily binds dihydrotestosterone, testosterone, and estradiol.

About 65% of circulating testosterone is bound to SHBG and 30% to albumin. Approximately 2% remains unbound or free.

- Estrogen stimulates the synthesis of both estrogen and progesterone receptors in target tissues, and progestins inhibit the synthesis of both estrogen and progesterone receptors.
- With ultrasound it has been found that there is a steady increase in follicular diameter and volume that parallels the rise in estradiol. The dominant follicle has a maximal mean diameter of about 19.5 mm, with a range of 18 to 25 m just before ovulation.
- Ovulation occurs about 24 hours after the estradiol peak, as well as 32 hours after the initial rise in LH, and about 12 to 16 hours after the peak of LH levels in serum.
- Progesterone levels in serum are less than 1 ng/mL before ovulation and reach midluteal levels of 10 to 20 ng/mL.
- After menstruation, regeneration of the endometrium comes from cells

- Cases for your discussion tomorrow
- Please take a snap shot

Case # I

- A 23-year-old G0P0 woman presents to the office with complaints of irregular cycles since menarche. Upon further questioning, she has also noticed an increase in facial hair and acne for many years. She denies any history of medical problems and has a strong family medical history of diabetes. On examination, she is noted to have a normal blood pressure (BP), pulse, respiratory rate, and temperature. She is obese with a body mass index (BMI) of 34 kg/m2, WC- 91 cm. She is noted to have mFG >12, Ludwig-II and acanthosis nigricans ++ (of neck and inner thighs). Her pelvic examination is limited by her obesity but normal. She does not desire pregnancy at this time. Her pregnancy test is negative.
- What is the most likely diagnosis?
- What complications is the patient at risk for?
- What is your next diagnostic step?
- What is your therapeutic plan for this patient?

Case # II

- A 42-year-old parous woman has noticed increasing hair growth on her face and abdomen over the past 6 months. She denies the use of steroid medications, weight changes, or a family history of hirsutism. Her menses previously had been monthly, and now occur every 35 to 70 days. Her past medical and surgical histories are unremarkable. On examination, her thyroid is normal to palpation. She has excess facial hair and male-pattern hair on her abdomen. Acne is also noted on the face. The cardiac and pulmonary examinations are normal. The abdominal examination reveals no masses or tenderness. Examination of the external genitalia reveals possible clitoromegaly. Pelvic examination shows a normal uterus and cervix and an 8-cm, right adnexal mass.
- What is the most likely diagnosis?
- What is the probable management?