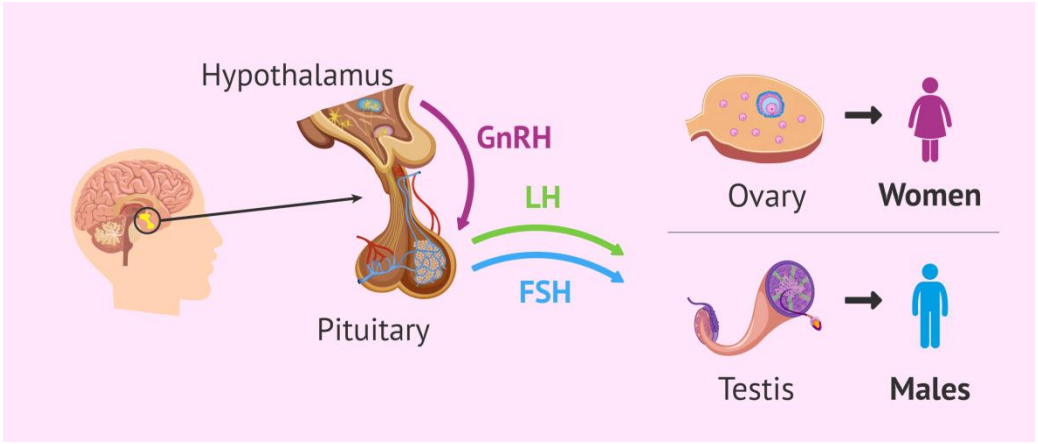
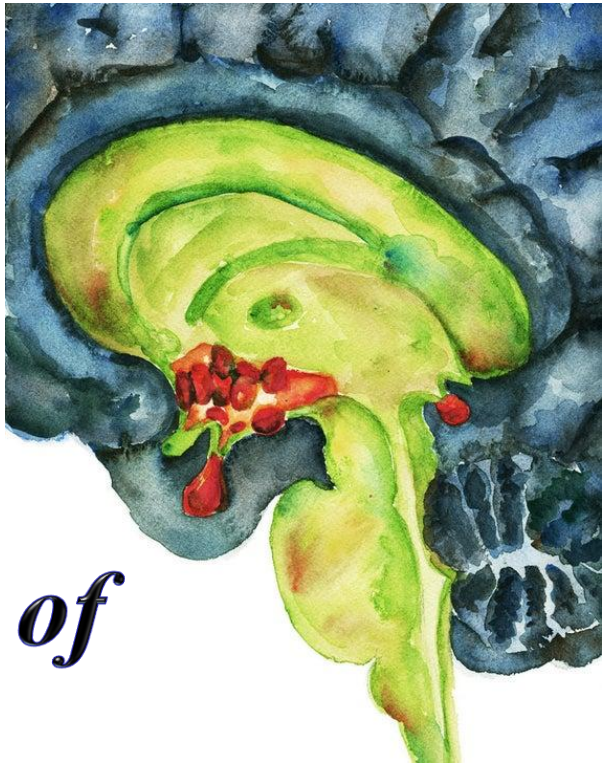
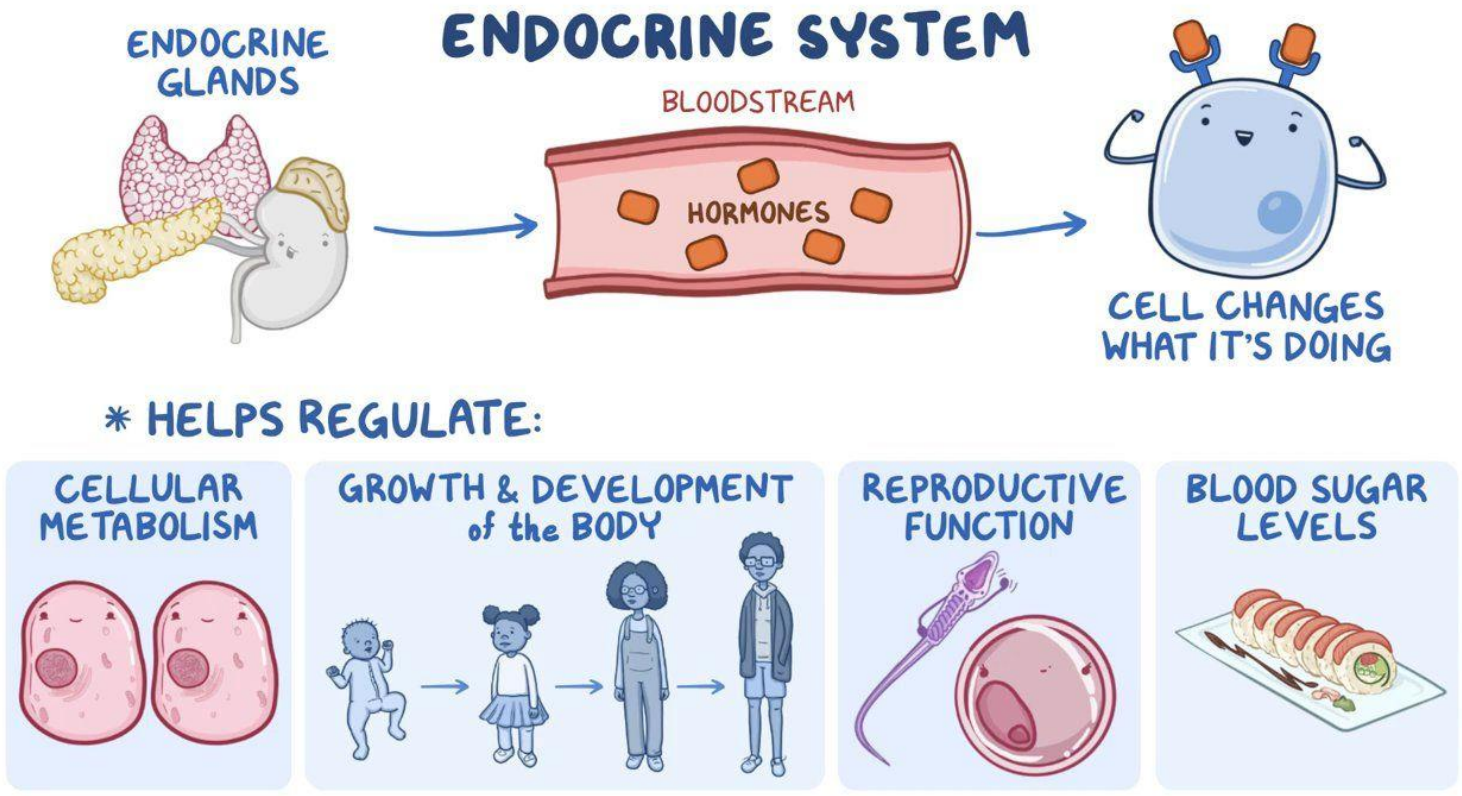
EMBRYOLOGY





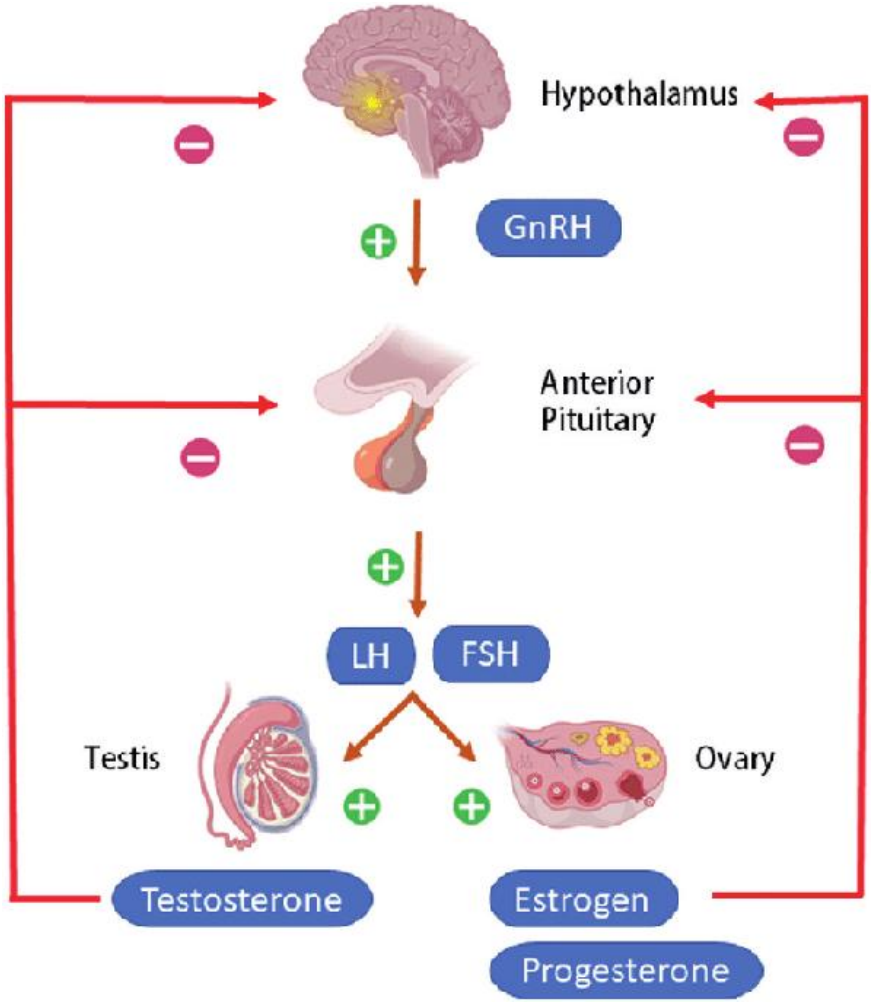
Hormonal regulation of hypothalamus – hypophysis – ovary – uterus axis. Gamete formation and menstrual cycle.

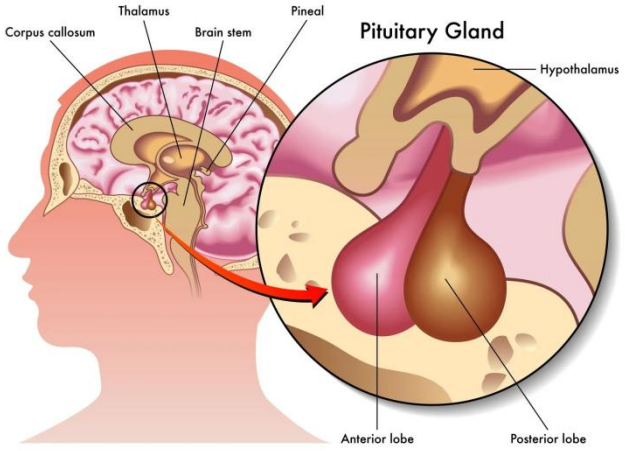
Hormones are chemical messengers that are secreted directly into the blood, which carries them to organs and tissues of the body to exert their functions.



the secretion of sex hormones depends on the activity of other secretory organs

The **hypothalamus** is the region in the ventral brain which **coordinates** the endocrine system. It receives many signals from various regions of the brain and in return, releases both **releasing** and **inhibiting** hormones, which then act on the **pituitary gland** to direct the functions of the thyroid gland, adrenal glands, and reproductive organs.

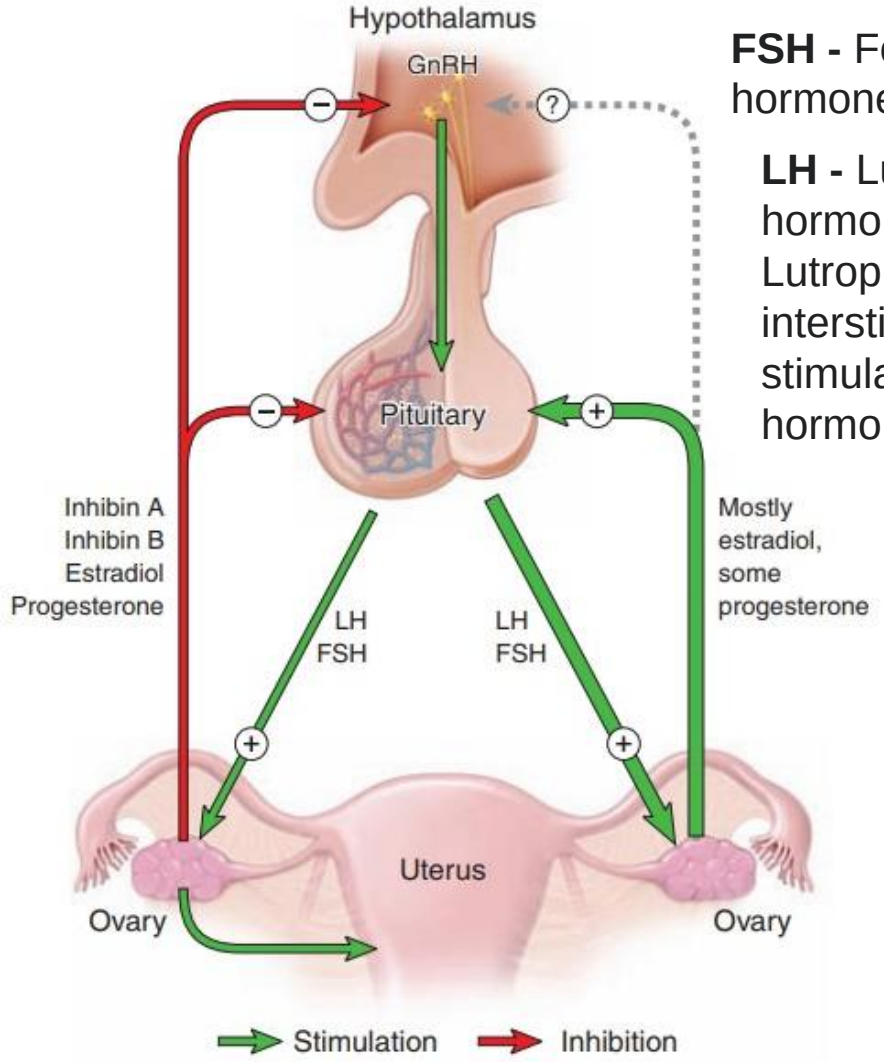




The **pituitary gland** (the hypophysis) is a **major gland** of the endocrine system.
It secretes hormones that control the actions of other endocrine organs and various tissues around the body.

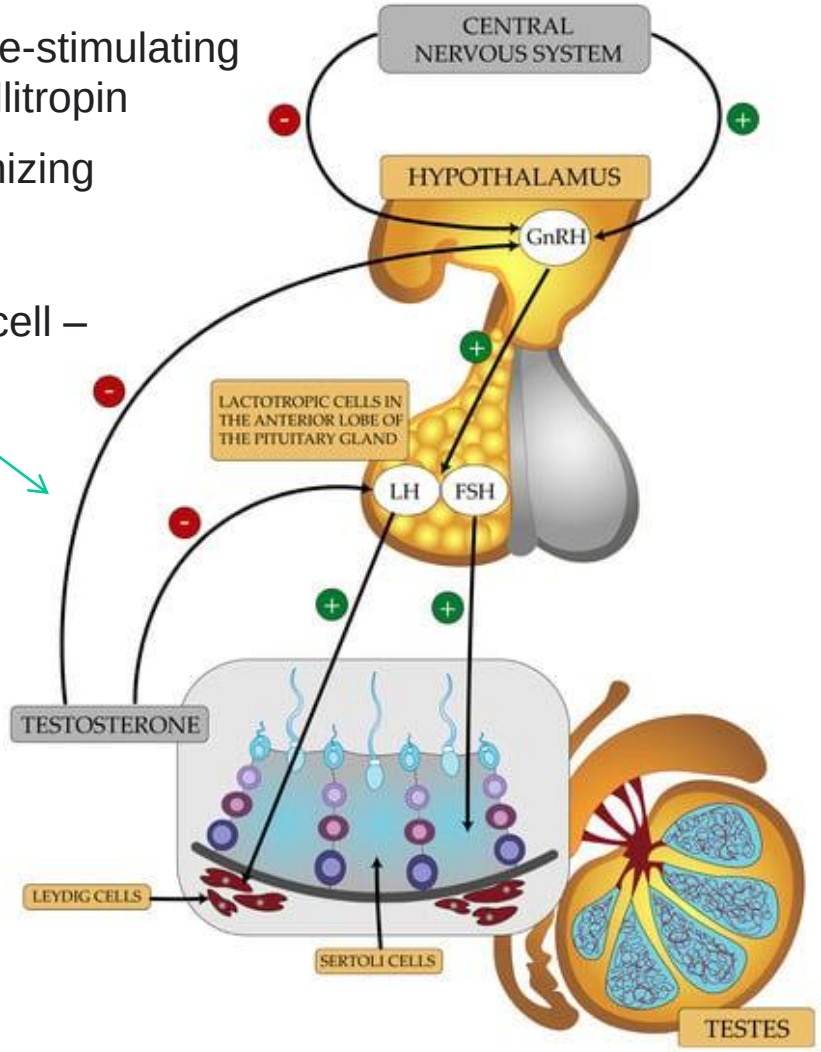
The **hypothalamic–pituitary–gonadal** (HPG) **axis** is primarily responsible for regulating reproductive activity and the release of ovarian hormones

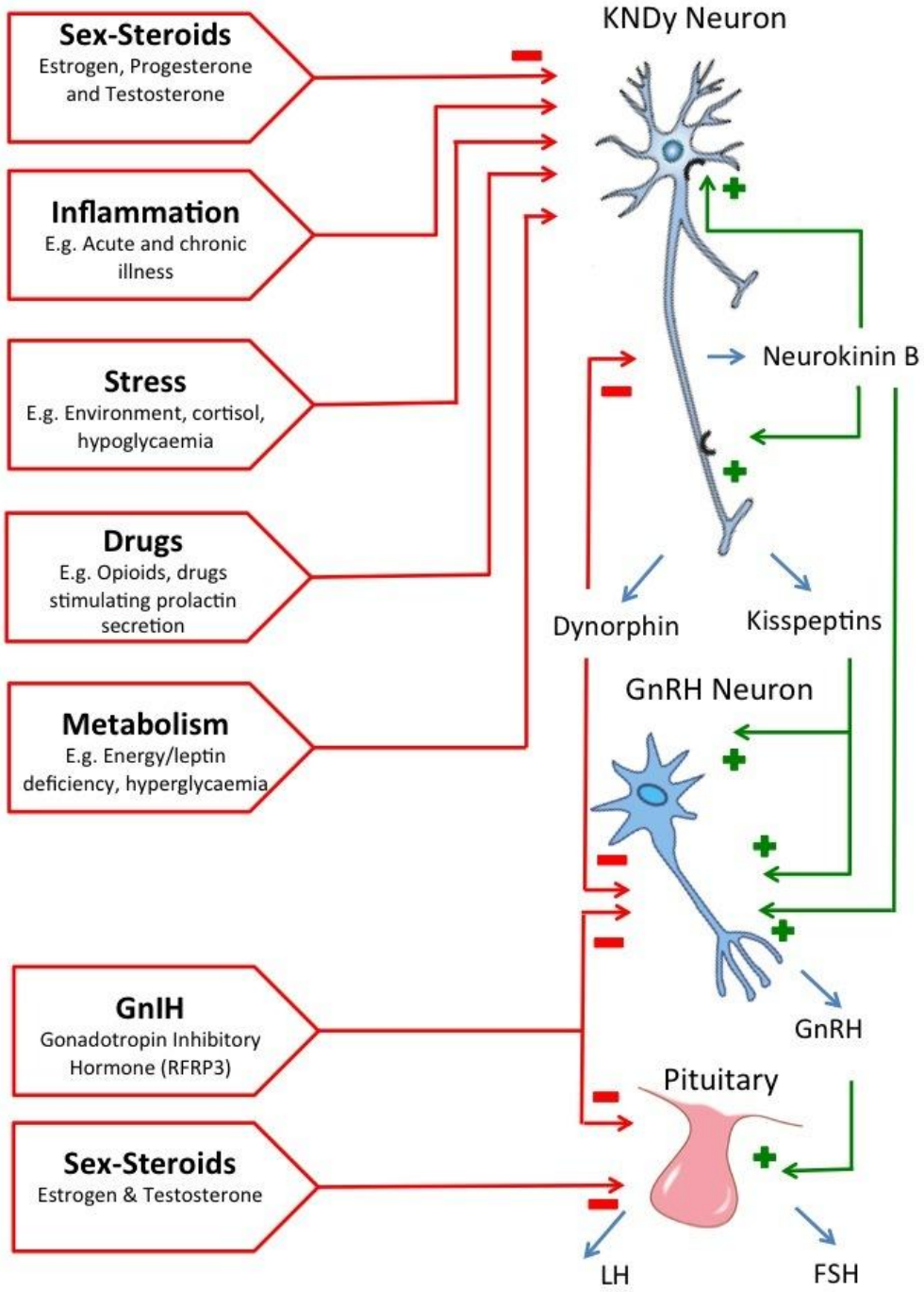
The **pulsatile** release of **GnRH** (and by nonpulsative release of leptin) results in **pulsatile** release of **gonadotropins**



FSH - Follicle-stimulating hormone, follitropin

LH - Luteinizing hormone, Lutropin, interstitial cell – stimulating hormone





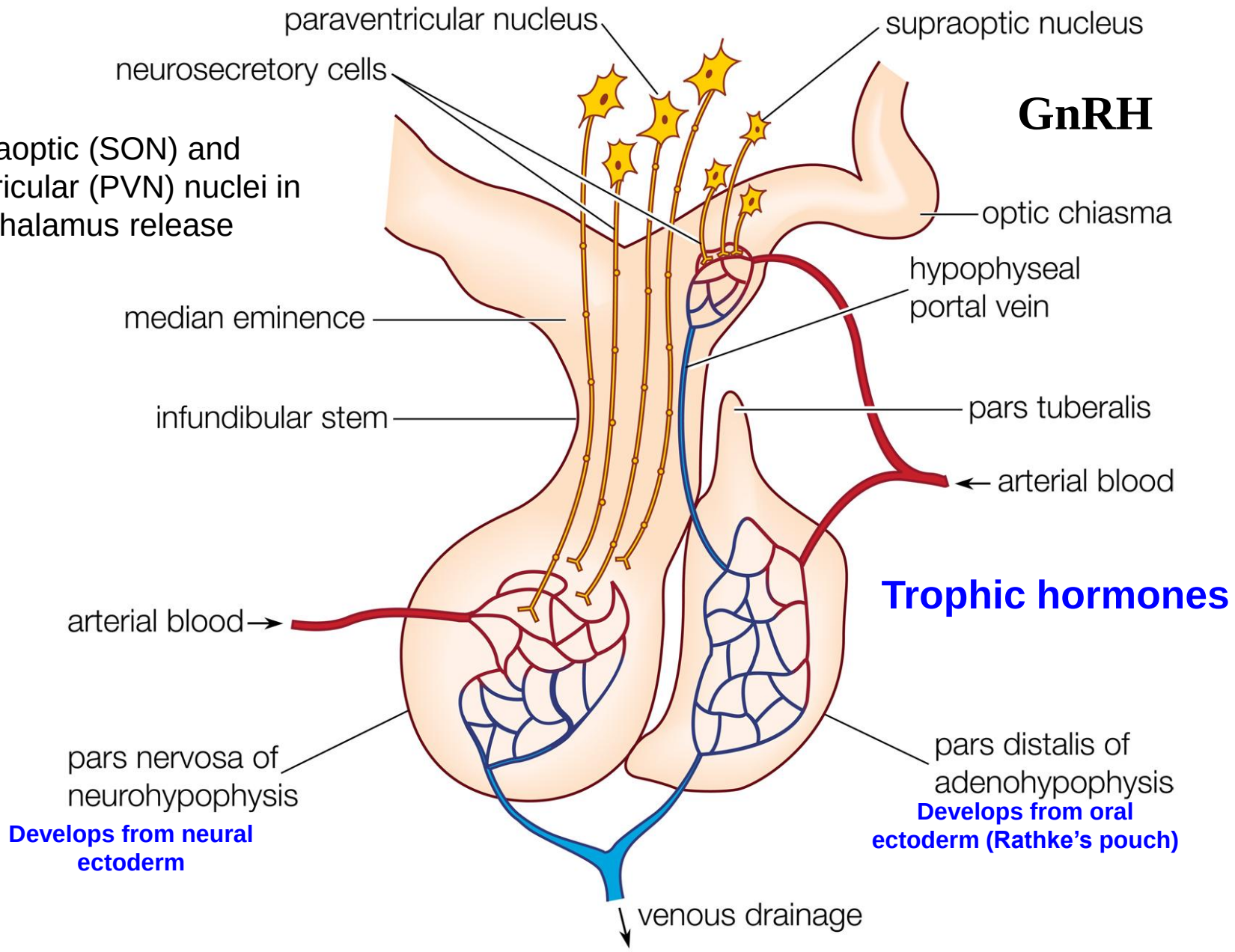
Kisspeptin is located at the apex of the hypothalamic-pituitary-gonadal axis and regulates reproductive functions by modulating gonadotropin-releasing hormone (GnRH)

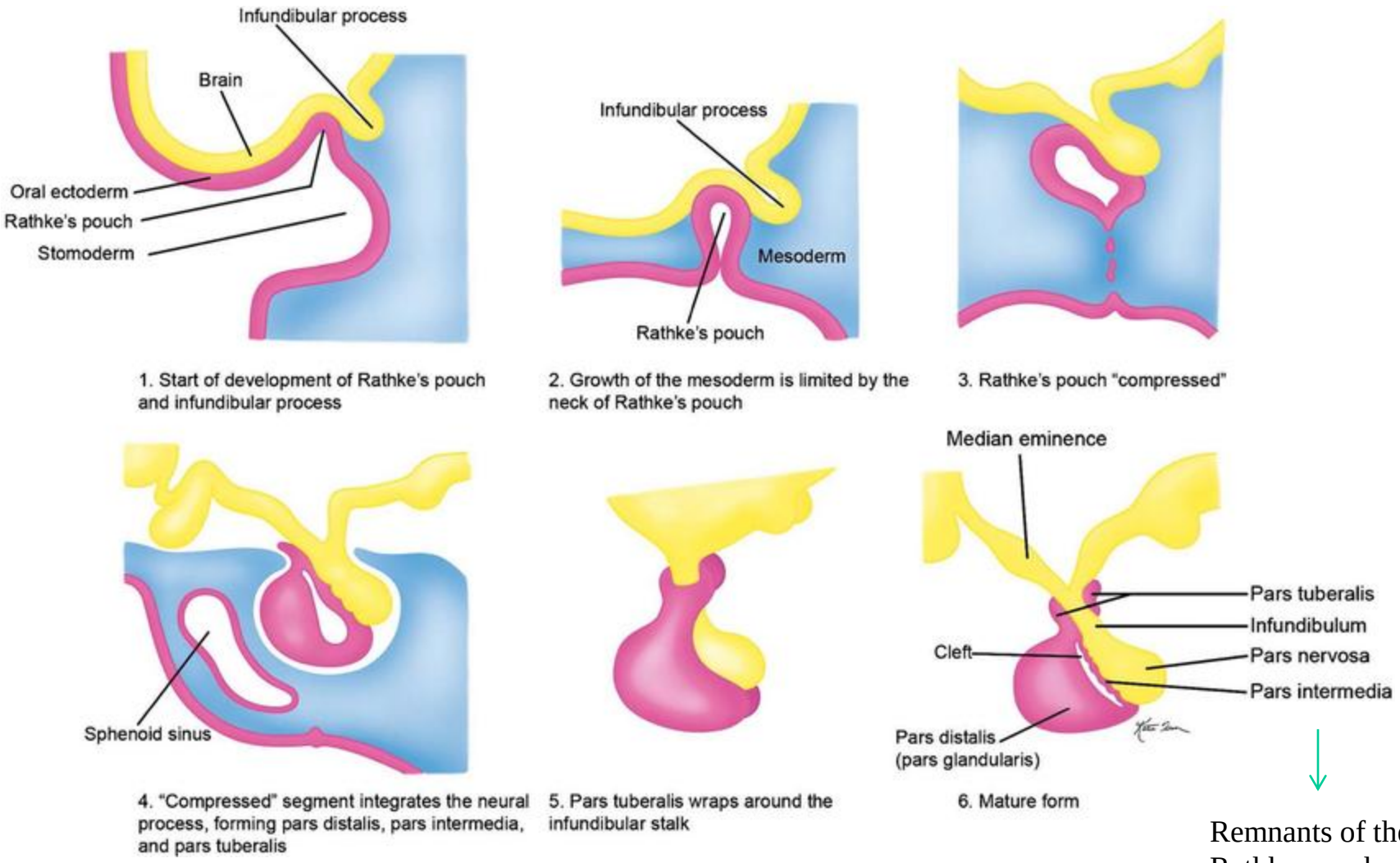
Kiss1 neurons co-express neurokinin B (NKB) and dynorphin and are thus termed KNDy neurons.

The arcuate, paraventricular, periventricular, and supraoptic nuclei of the hypothalamus release releasing hormones.

The supraoptic (SON) and paraventricular (PVN) nuclei in the hypothalamus release

oxytocin.





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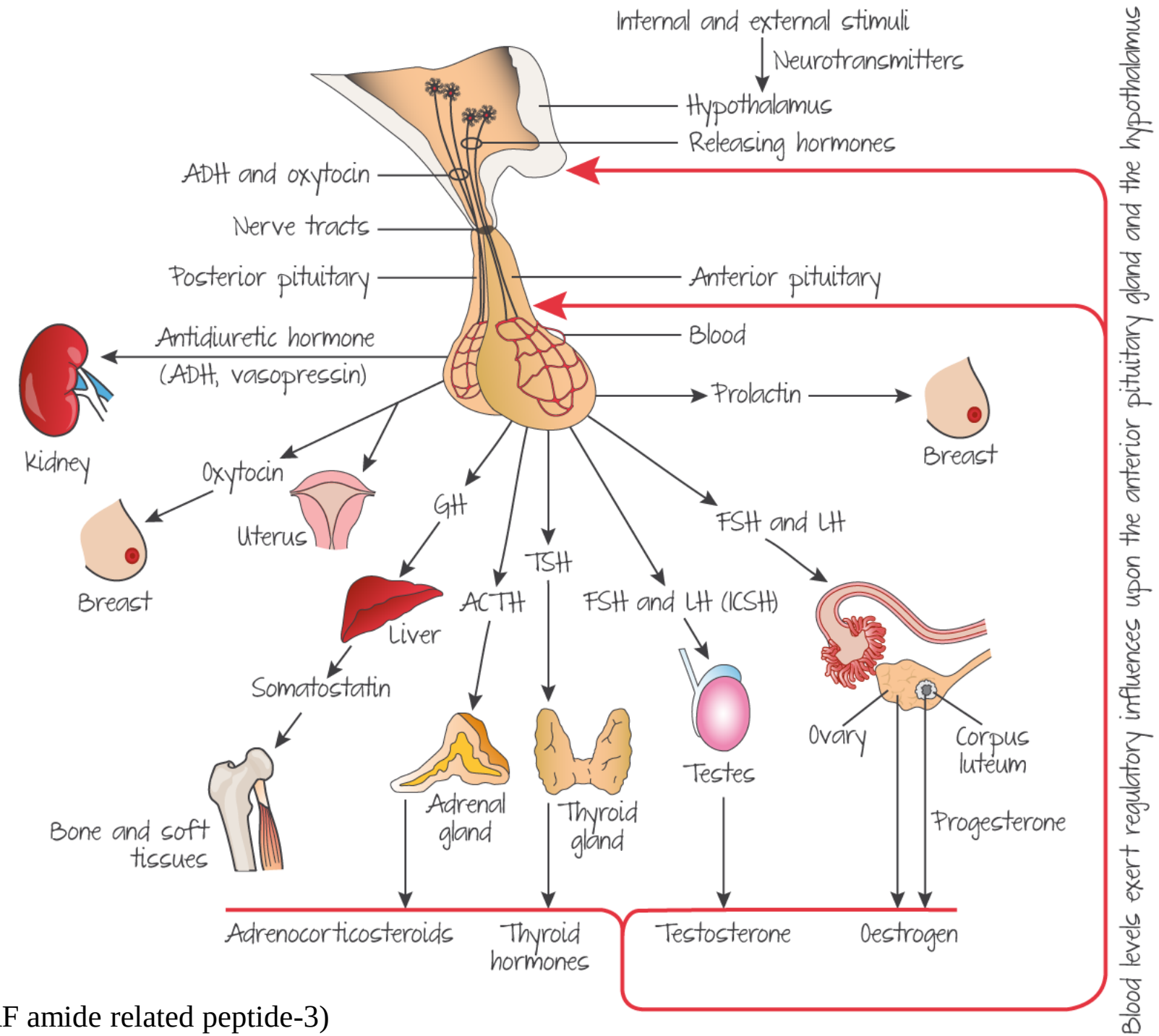
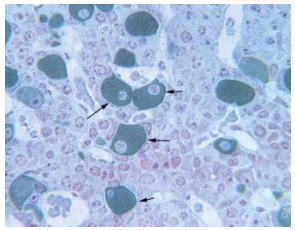


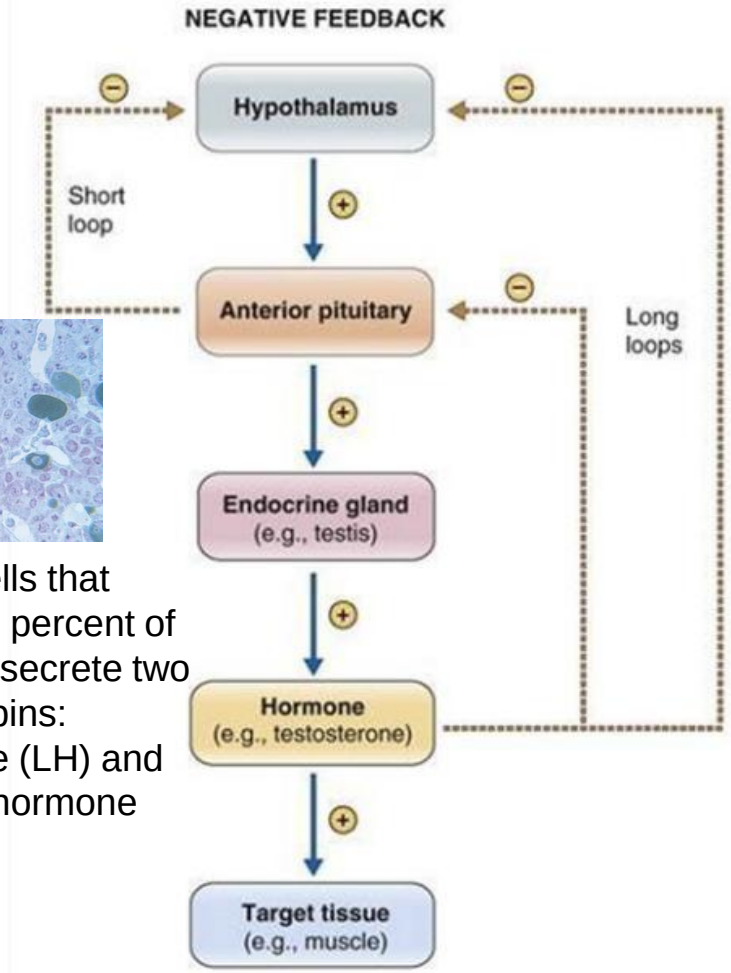
RFRP-3 (RF amide related peptide-3)

REGULATION OF HORMONE SECRETION

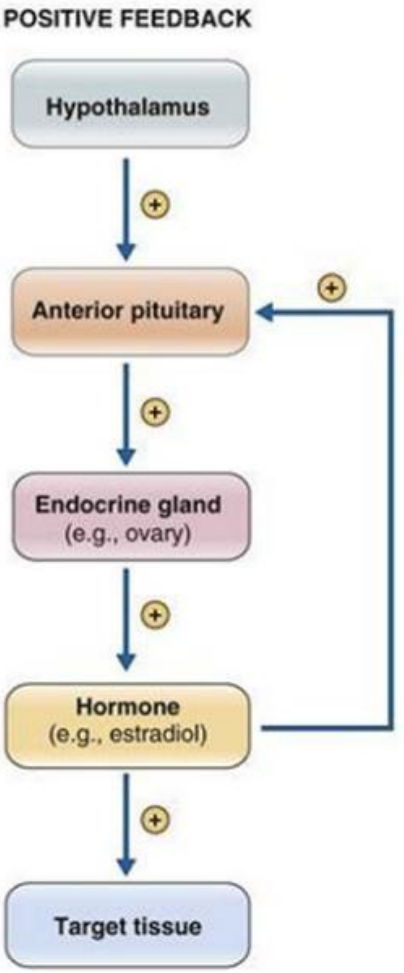
To maintain homeostasis, the secretion of hormones must be turned on and off as needed. Adjustments in secretory rates may be accomplished by **feedback mechanisms**.



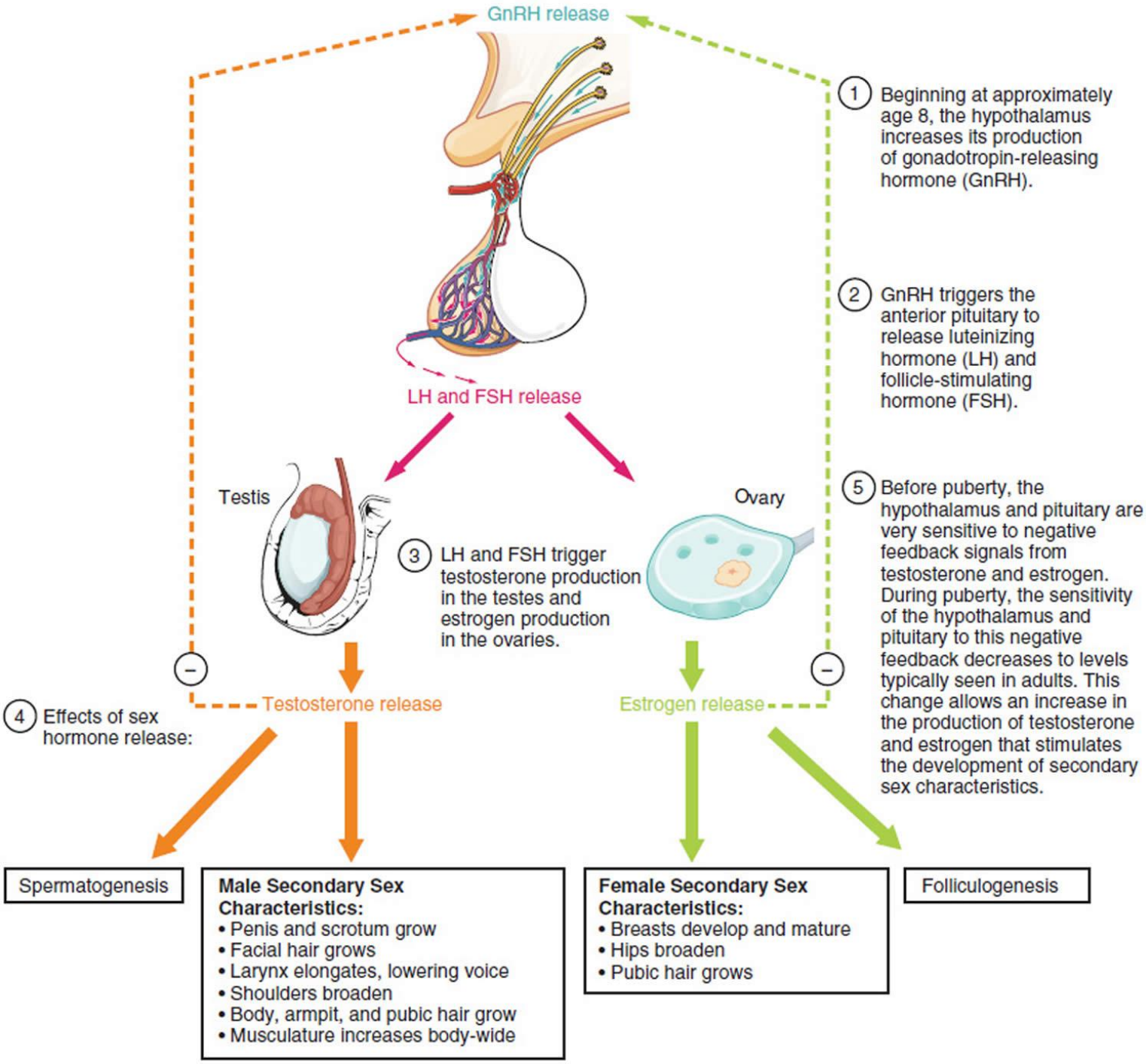
Gonadotrophs, cells that constitute about 10 percent of the pituitary gland, secrete two primary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).



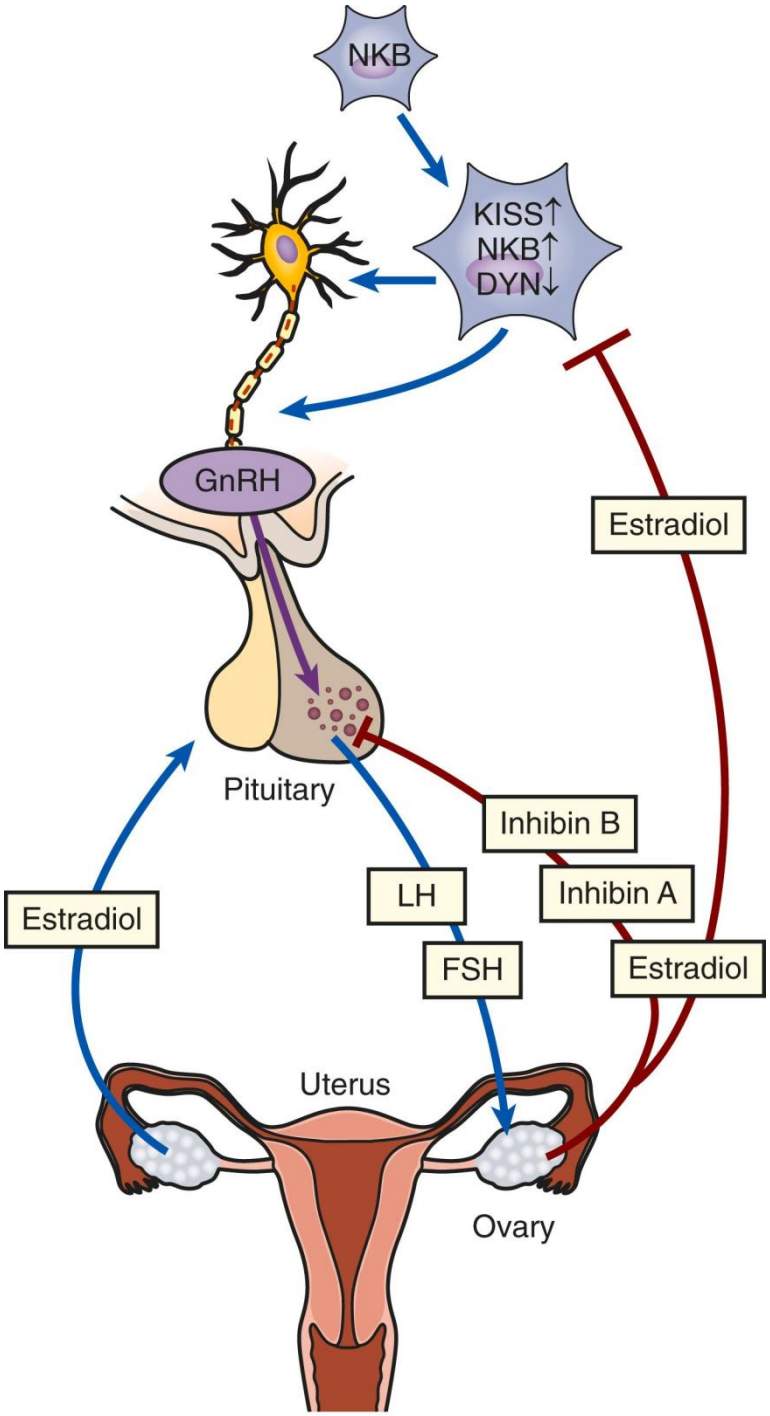
In a negative feedback loop, feedback serves to reduce an excessive response and keep a variable within the normal range.



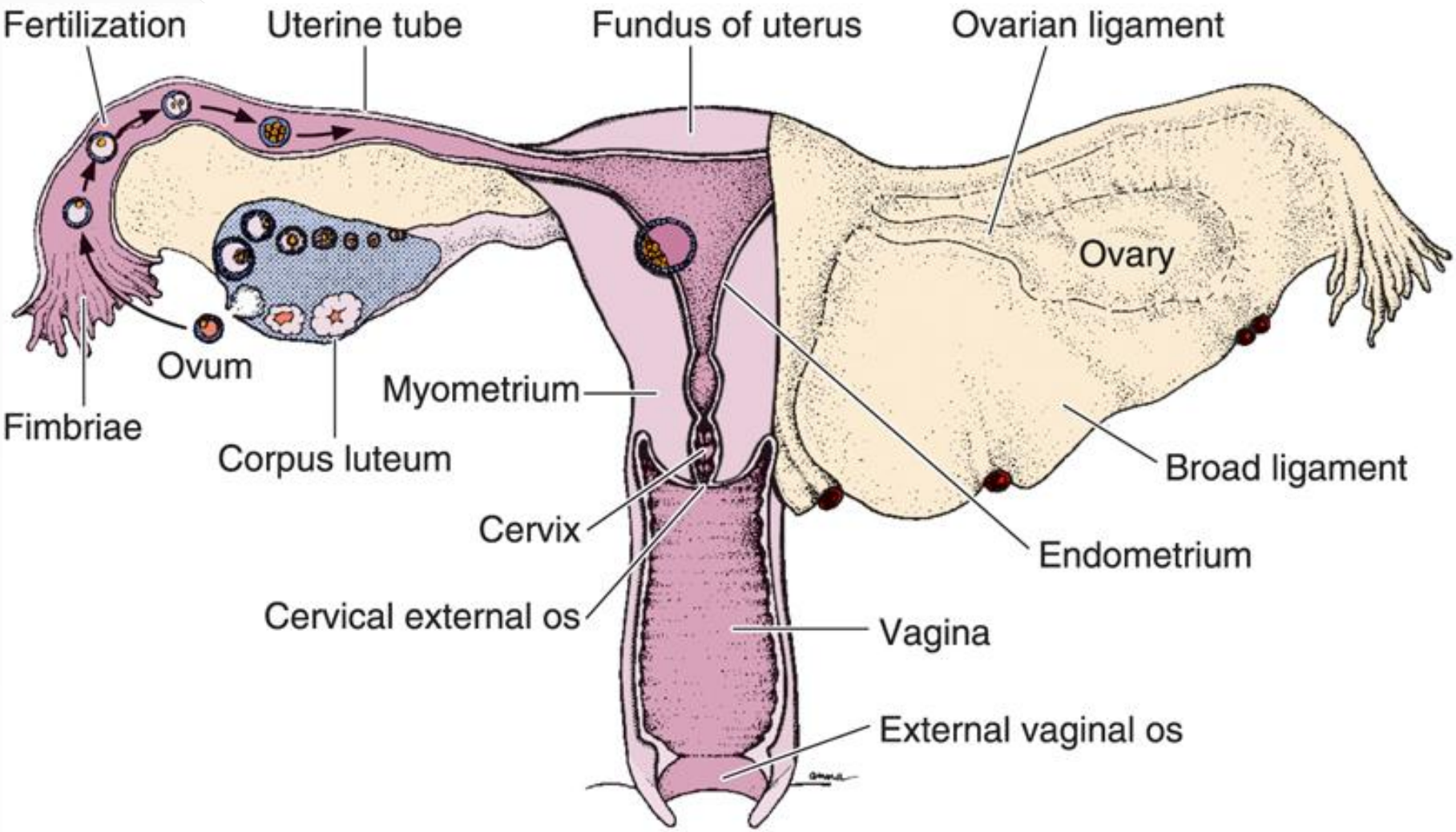
With positive feedback, some feature of hormone action causes *more* secretion of the hormone


GnRH release
1 Beginning at approximately age 8, the hypothalamus increases its production of gonadotropin-releasing hormone (GnRH).
2 GnRH triggers the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
LH and FSH release
Testis
Ovary
3 LH and FSH trigger testosterone production in the testes and estrogen production in the ovaries.
5 Before puberty, the hypothalamus and pituitary are very sensitive to negative feedback signals from testosterone and estrogen. During puberty, the sensitivity of the hypothalamus and pituitary to this negative feedback decreases to levels typically seen in adults. This change allows an increase in the production of testosterone and estrogen that stimulates the development of secondary sex characteristics.
Testosterone release
Estrogen release
4 Effects of sex hormone release:
Spermatogenesis
Male Secondary Sex Characteristics:
• Penis and scrotum grow
• Facial hair grows
• Larynx elongates, lowering voice
• Shoulders broaden
• Body, armpit, and pubic hair grow
• Musculature increases body-wide
Female Secondary Sex Characteristics:
• Breasts develop and mature
• Hips broaden
• Pubic hair grows
Folliculogenesis

Ovarian steroids and i**nhibins** act directly at the pituitary level. **Negative feedback restraint of FSH secretion** is critical to the development of the single mature oocyte that characterizes human reproductive cycles. In addition to negative feedback controls, the menstrual cycle is unique among endocrine systems in its dependence on **estrogen-positive feedback** to produce the **preovulatory LH surge** that is essential for ovulation.

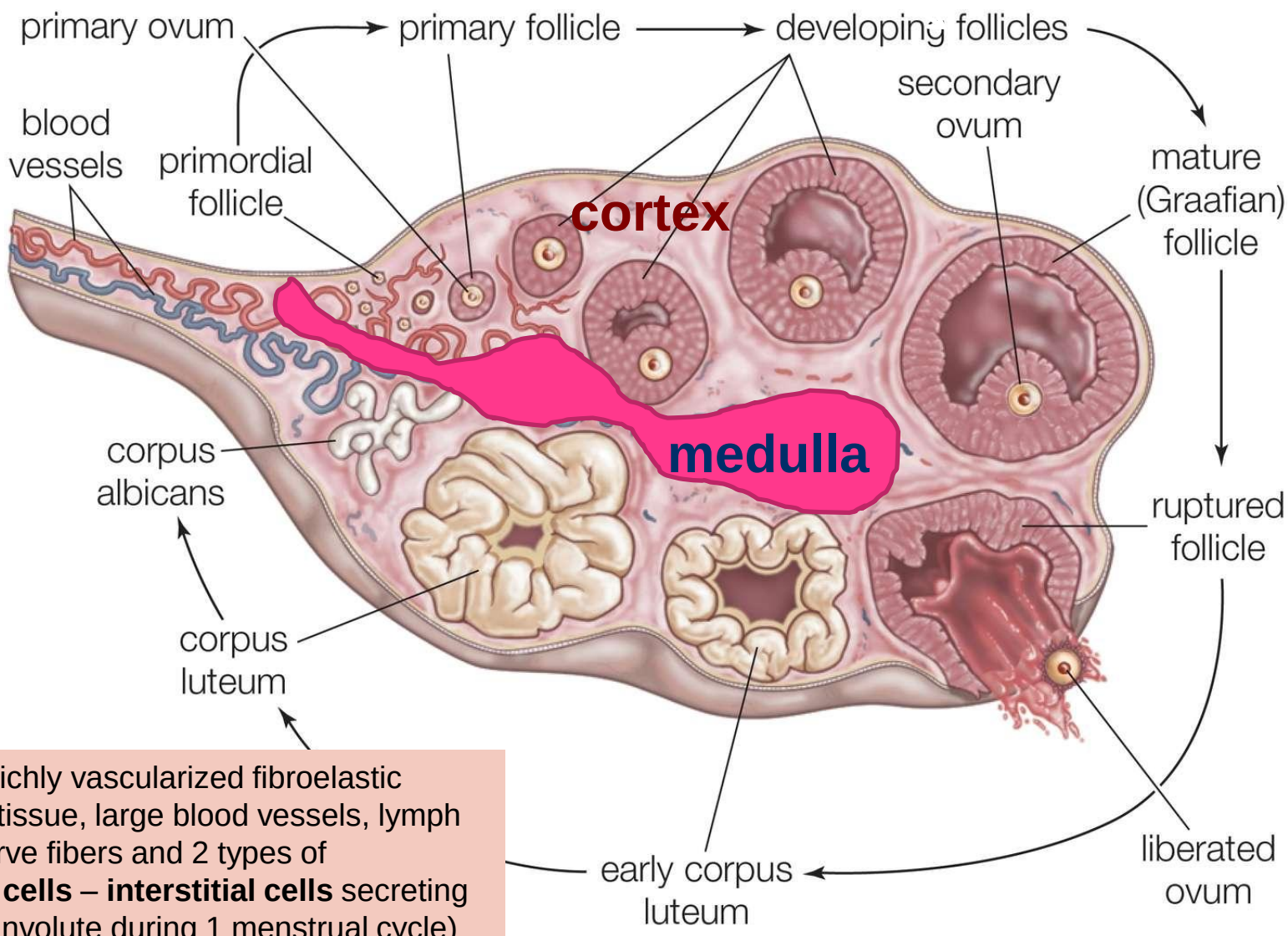


General outlook



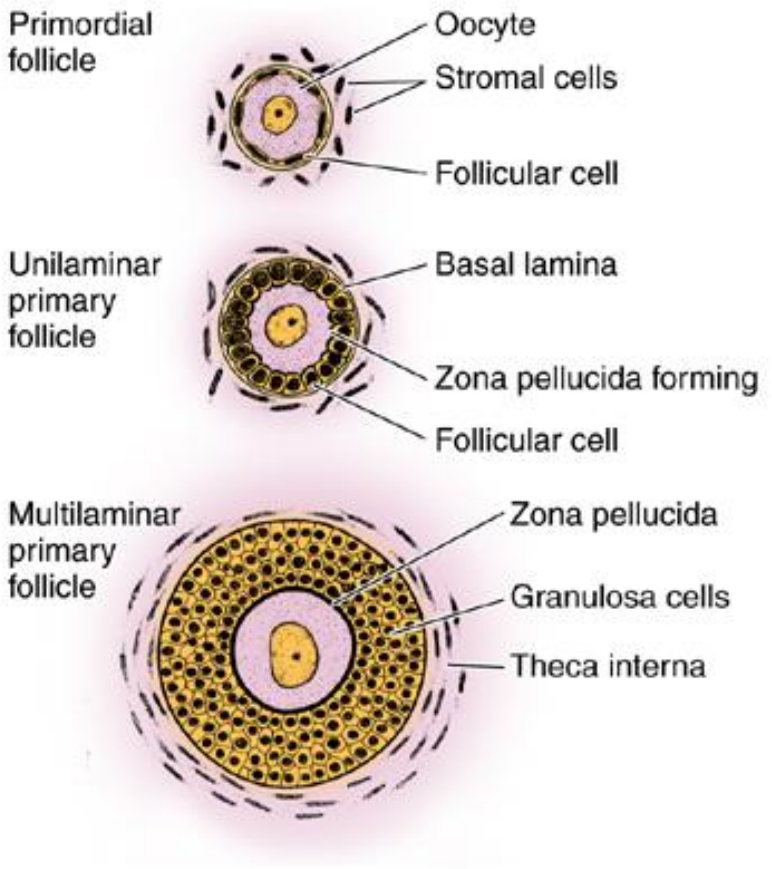
ovary

Cortex - connective tissue framework (stroma) and ovarian follicles.

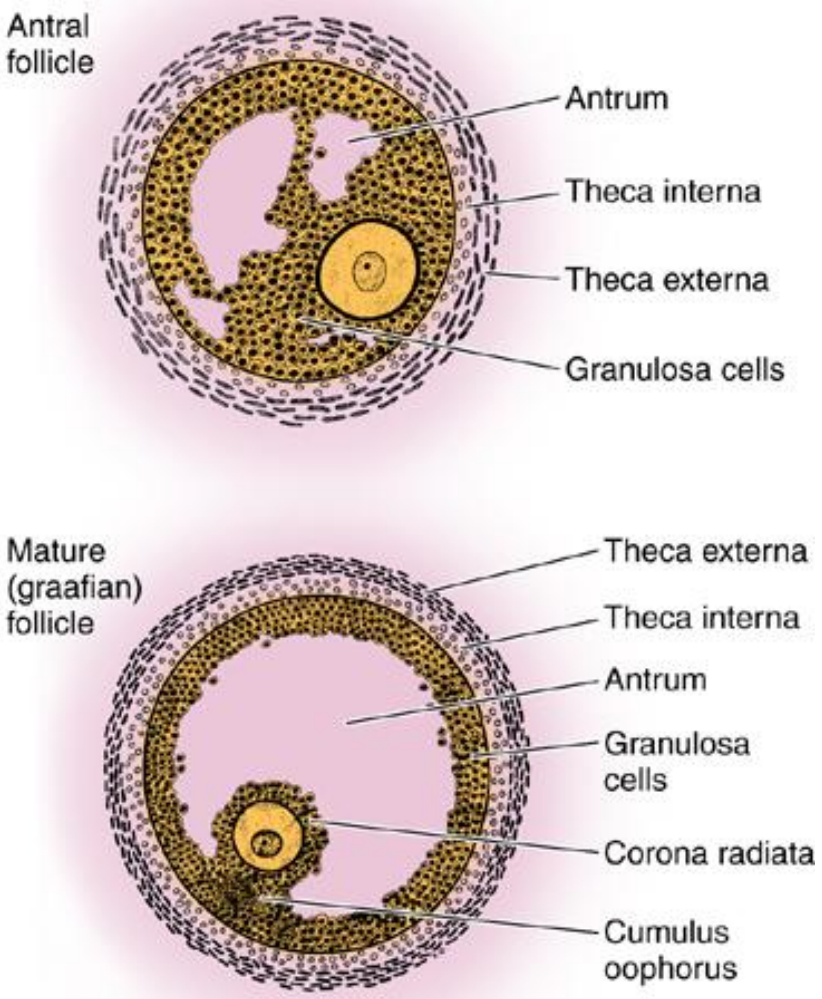


Medulla – richly vascularized fibroelastic connective tissue, large blood vessels, lymph vessels, nerve fibers and 2 types of **epithelioid cells – interstitial cells** secreting estrogens (involute during 1 menstrual cycle) and hilus cells secreting androgens.

Types of ovarian follicles, from primordial to mature



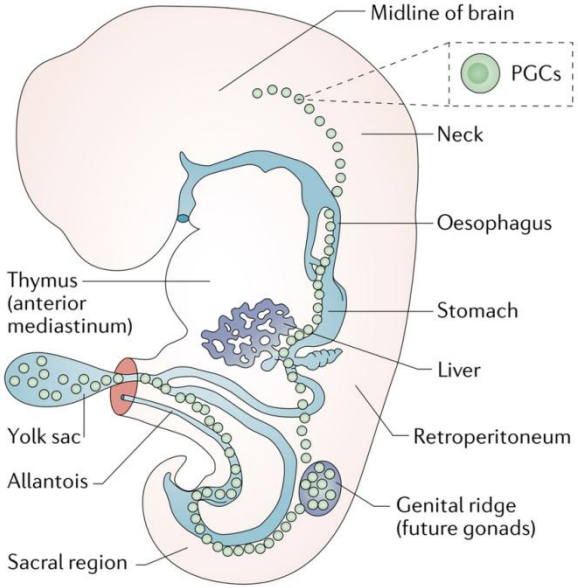
Secondary follicle

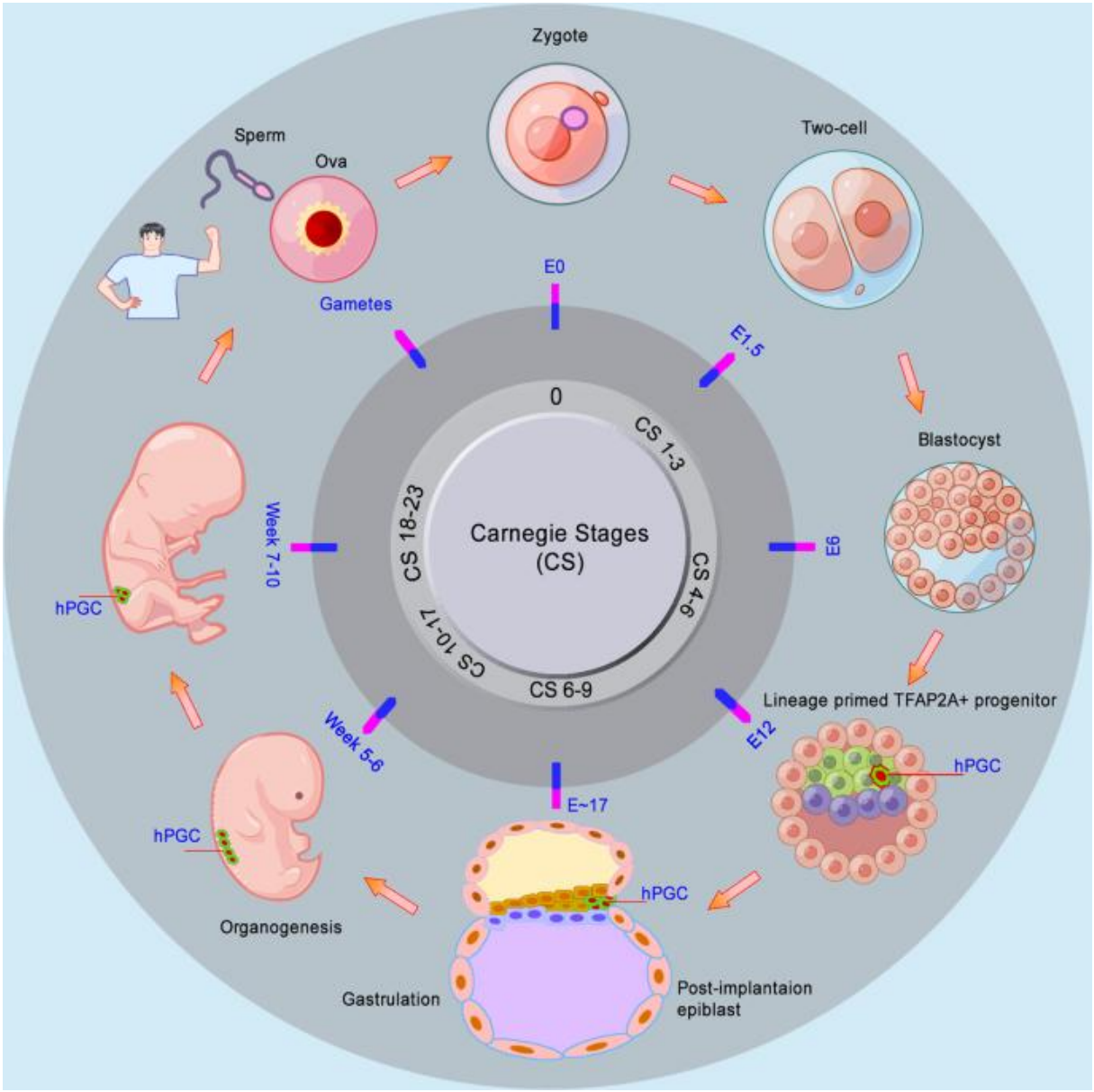


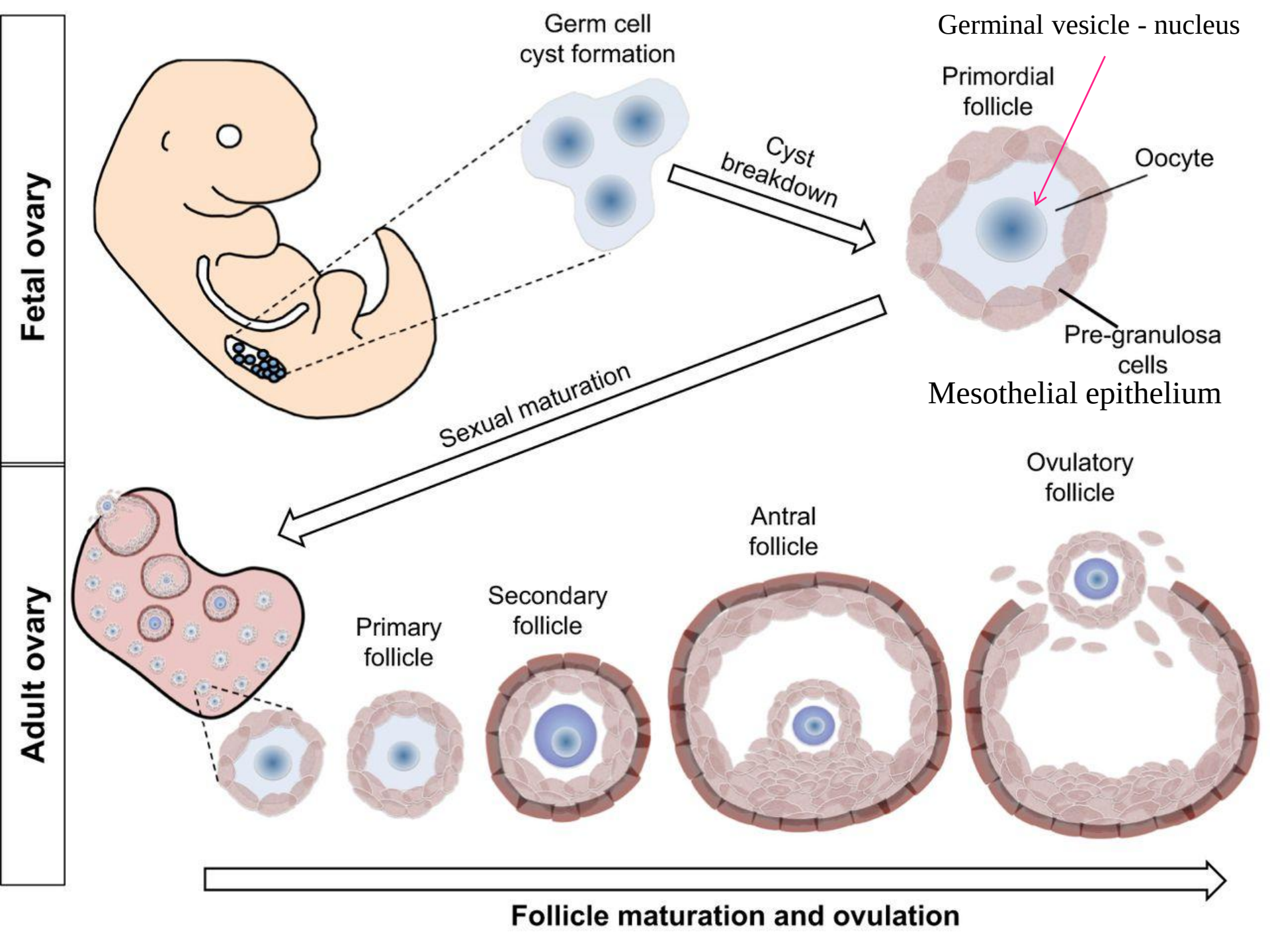
Proliferative activity of the granulosa cells is due to the **activin, BMP-15, growth differentiation factor-9** produced by primary oocyte

SCF/c-Kit signaling is essential for oocyte growth during early follicular development. It is suggested that SCF produced by granulosa cells

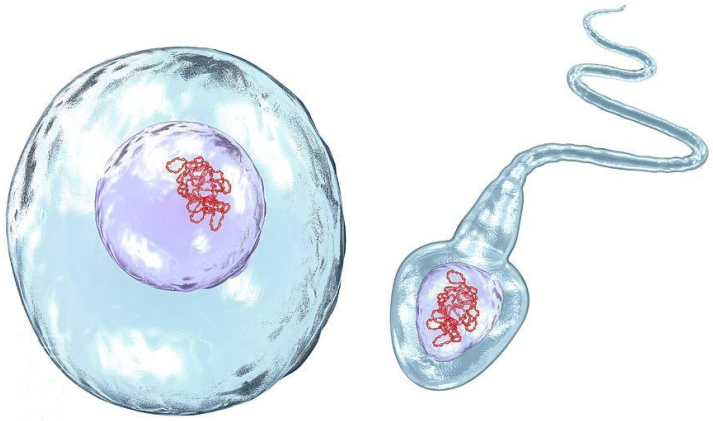
Human primordial germ cells - hPGC





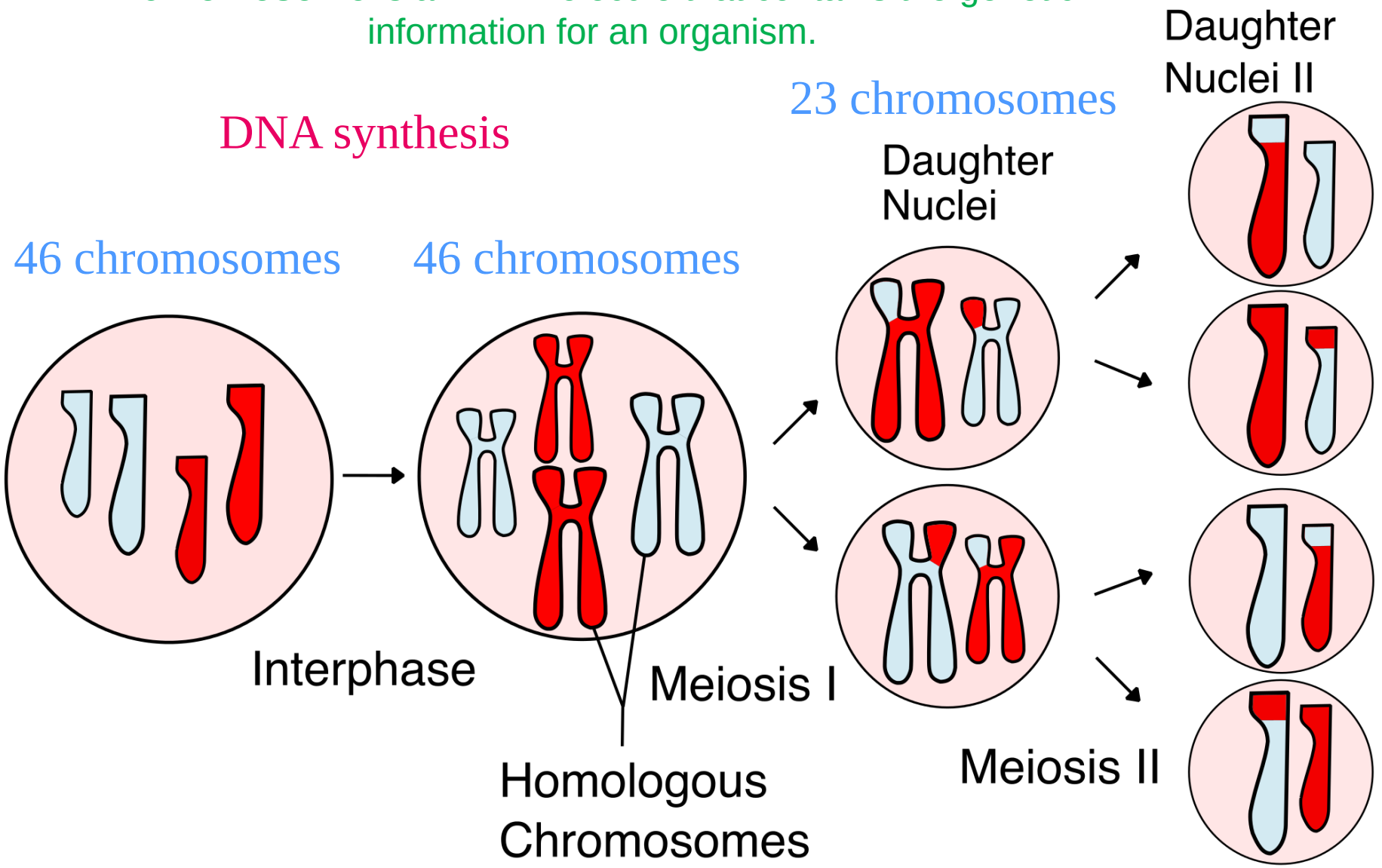

Fetal ovary
Adult ovary
Germ cell
cyst formation
Germinal vesicle - nucleus
Primordial
follicle
Cyst
breakdown
Oocyte
Pre-granulosa
cells
Mesothelial epithelium
Sexual maturation
Ovulatory
follicle
Antral
follicle
Secondary
follicle
Primary
follicle
Follicle maturation and ovulation

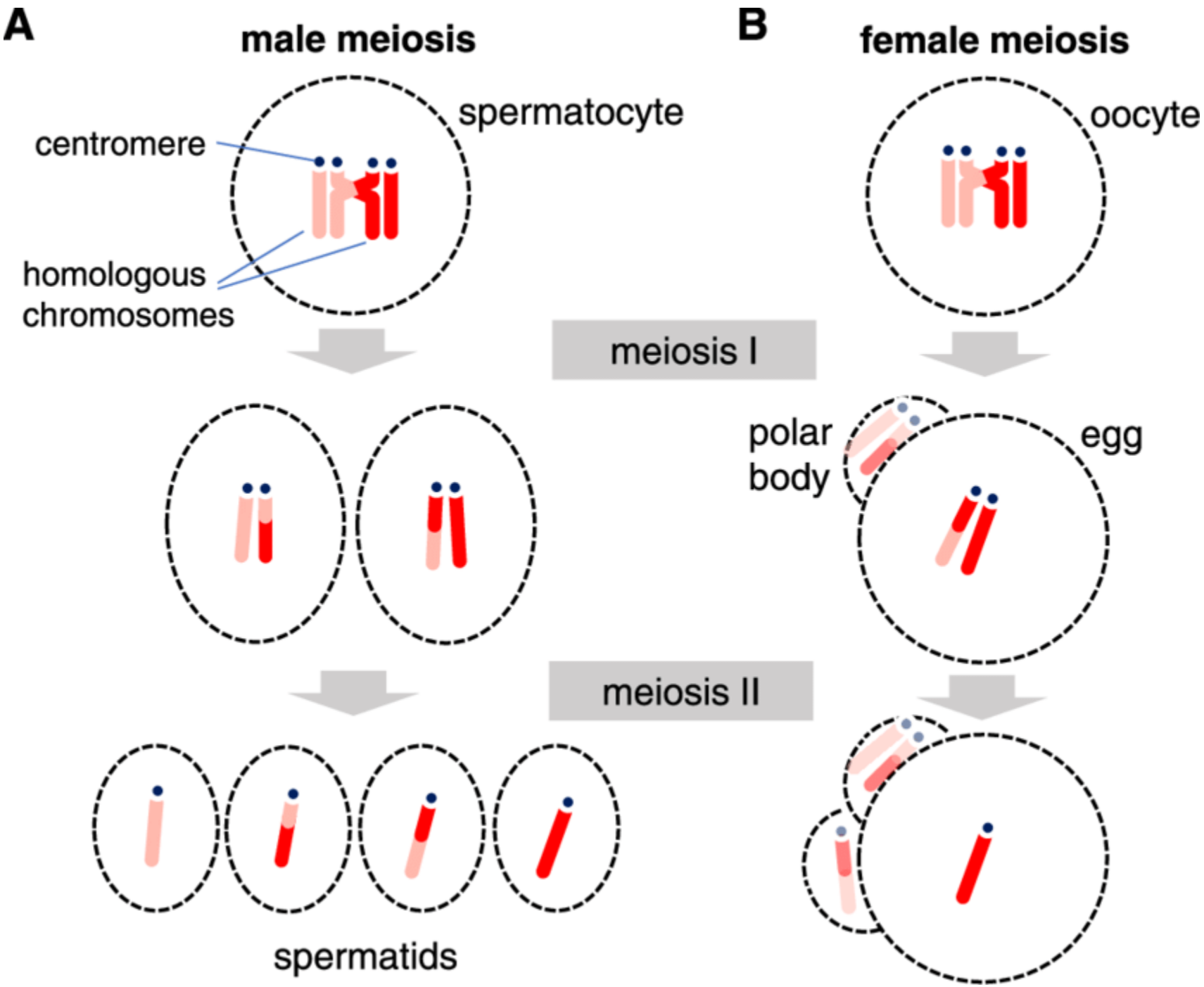
Meiosis is the unique division of germ cells resulting in the recombination of the maternal and paternal genomes and the production of **haploid gametes**. In mammals, it begins during the **fetal life** in **females** and during **puberty** in **males**.

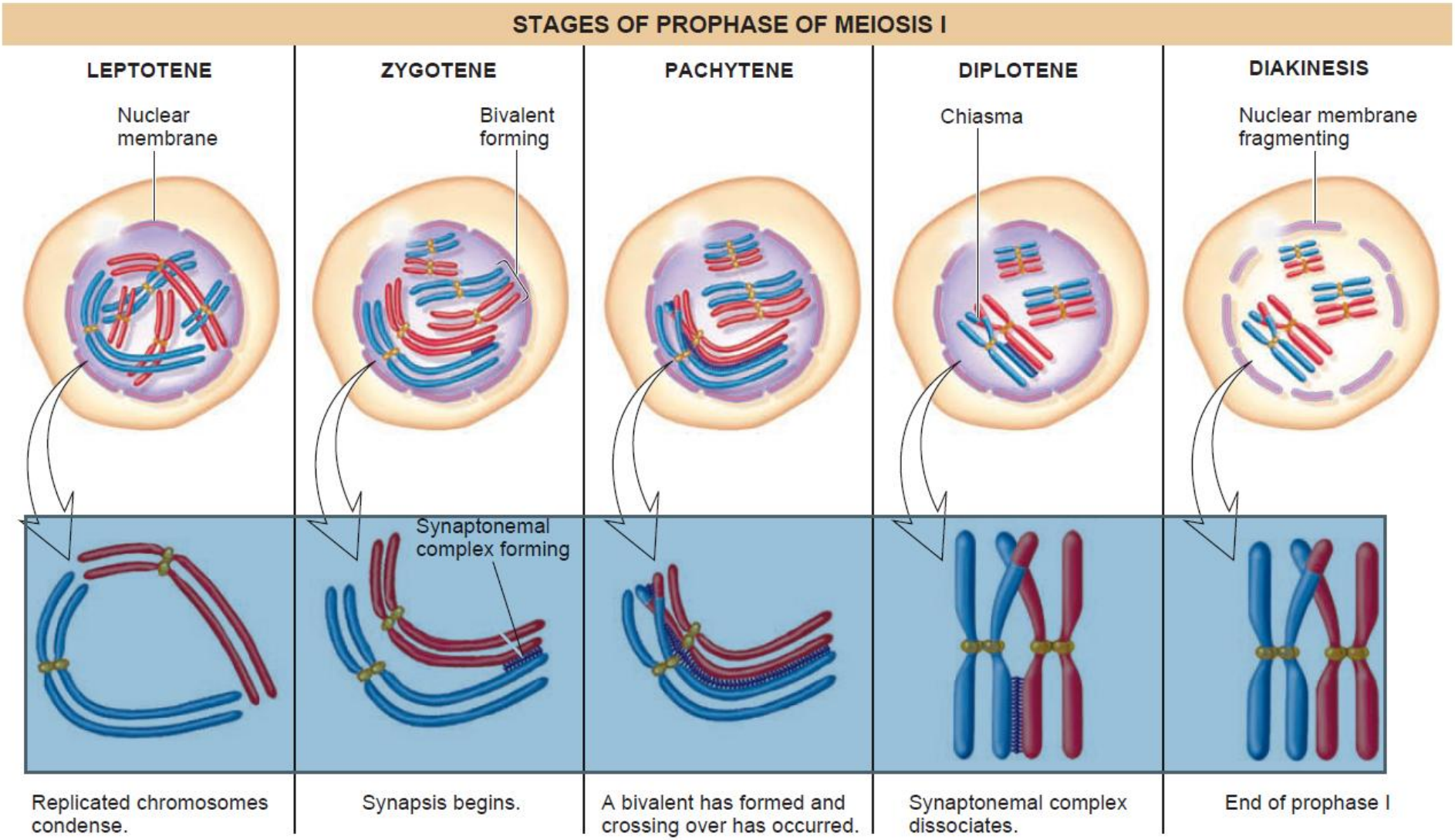


MEIOSIS

A **chromosome** is a DNA molecule that contains the genetic information for an organism.




A
male meiosis
spermatocyte
centromere
homologous chromosomes
meiosis I
meiosis II
spermatids
B
female meiosis
oocyte
polar body
egg

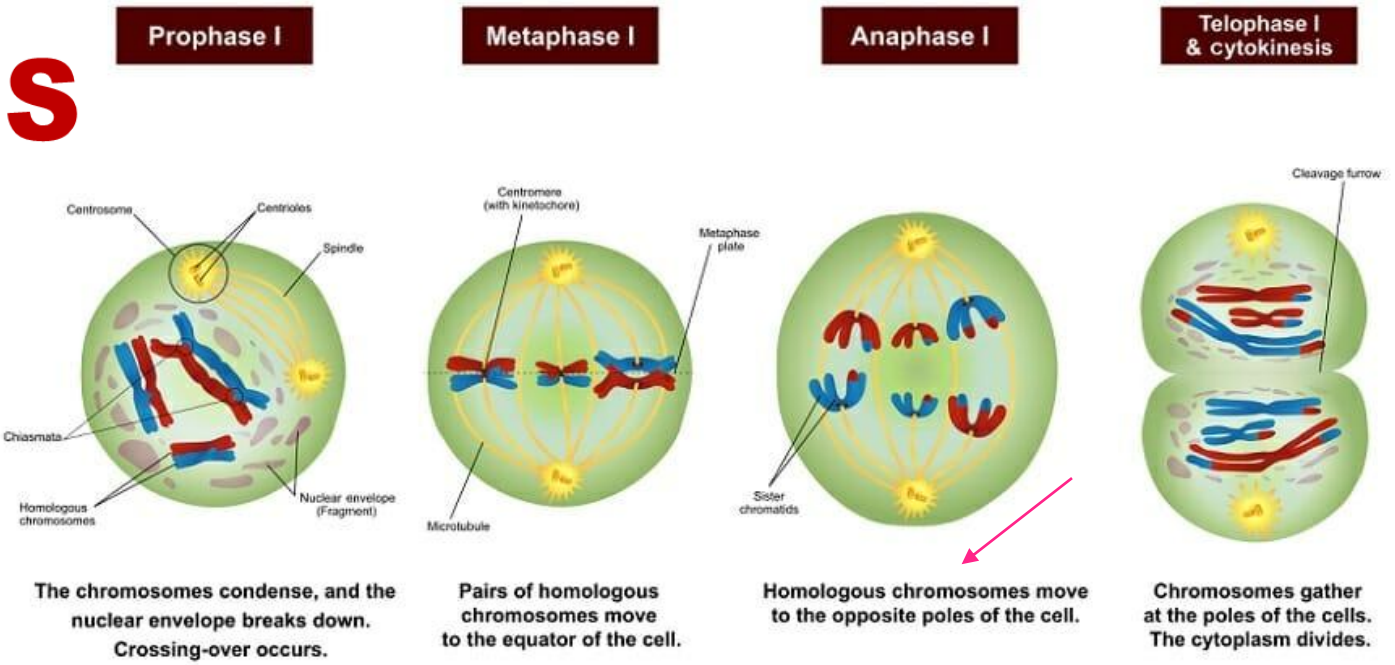


Crossing-over is the exchange of genetic material during sexual reproduction between two homologous chromosomes,non-sister chromatids that results in recombinant chromosomes.

MEIOSIS

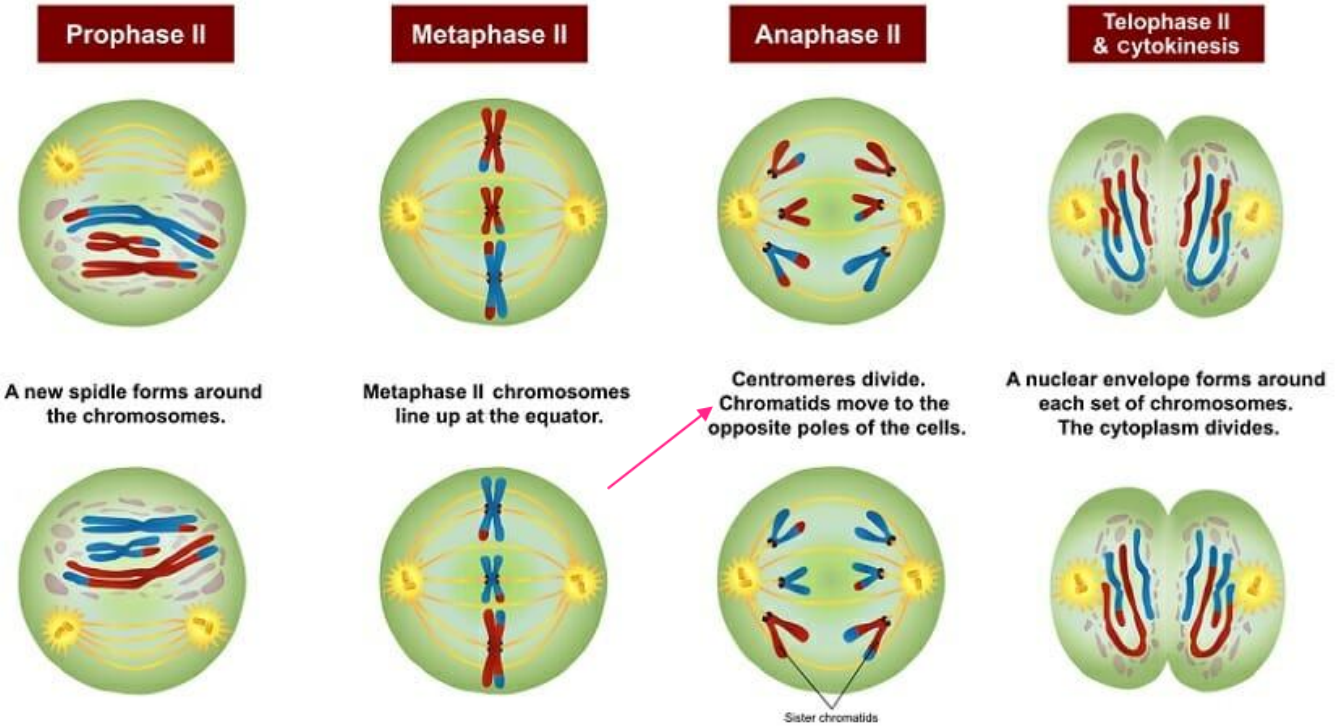
the number of chromosomes is reduced from diploid to haploid

46 chromosomes



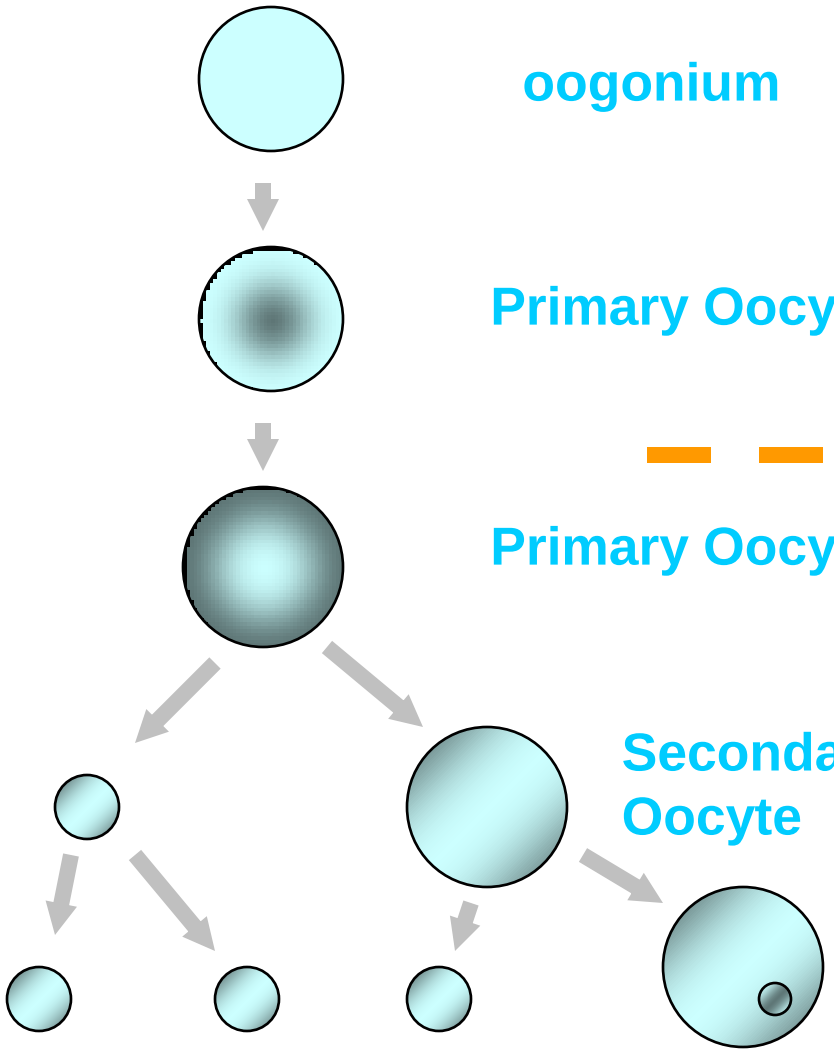
Chromatids are identical copies of a chromosome formed during DNA replication

23 chromosomes



Female meiosis

Primordial germ cells originate in epiblast, migrate through the primitive streak, endoderm of the yolk sac, along the dorsal mesentery of the hindgut, and arrive at the primitive gonads at the beginning of 5-th week.



oogonium

Primary Oocyte

Primary Oocyte

Secondary Oocyte

ovum

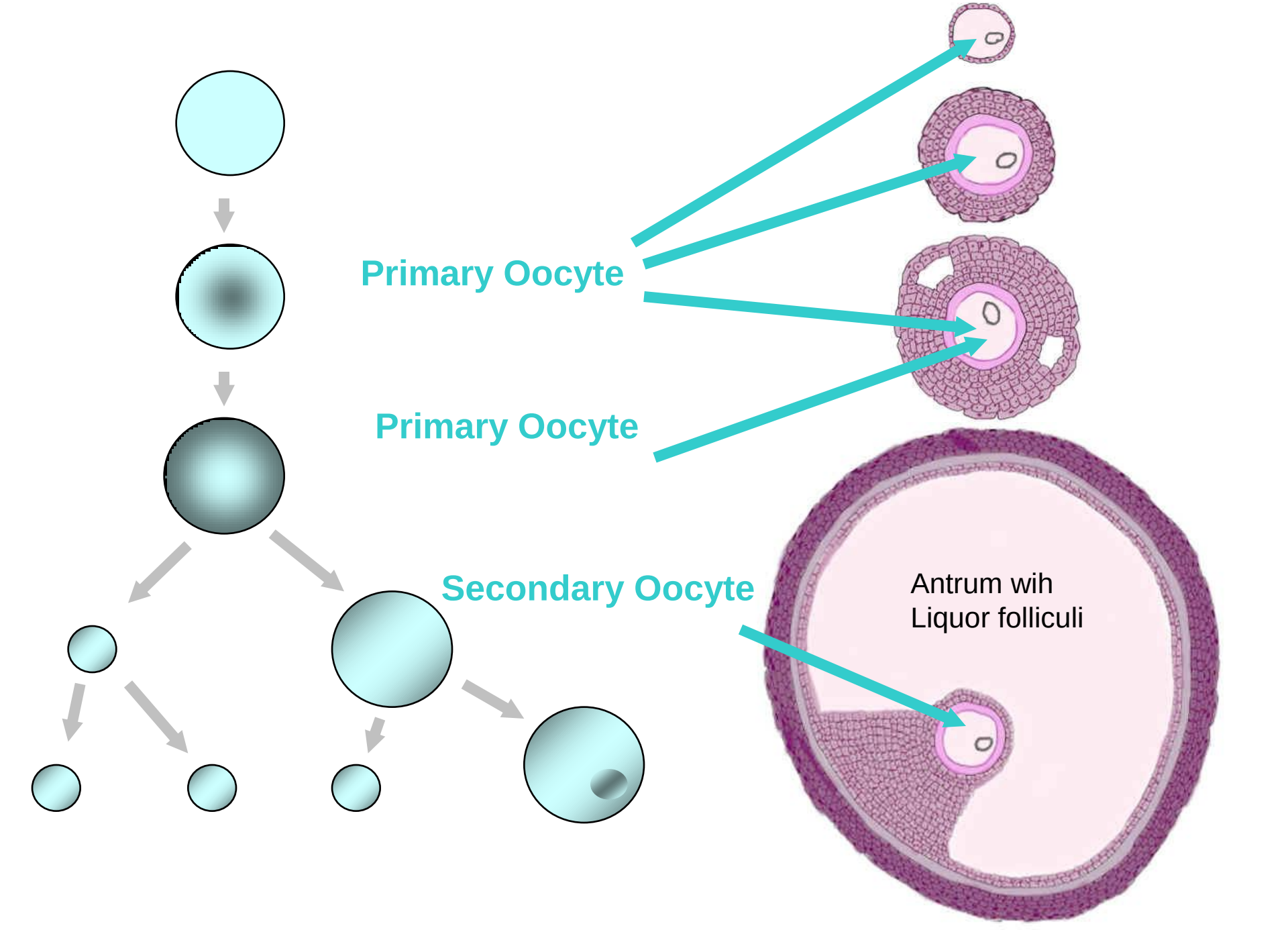
Fetal period

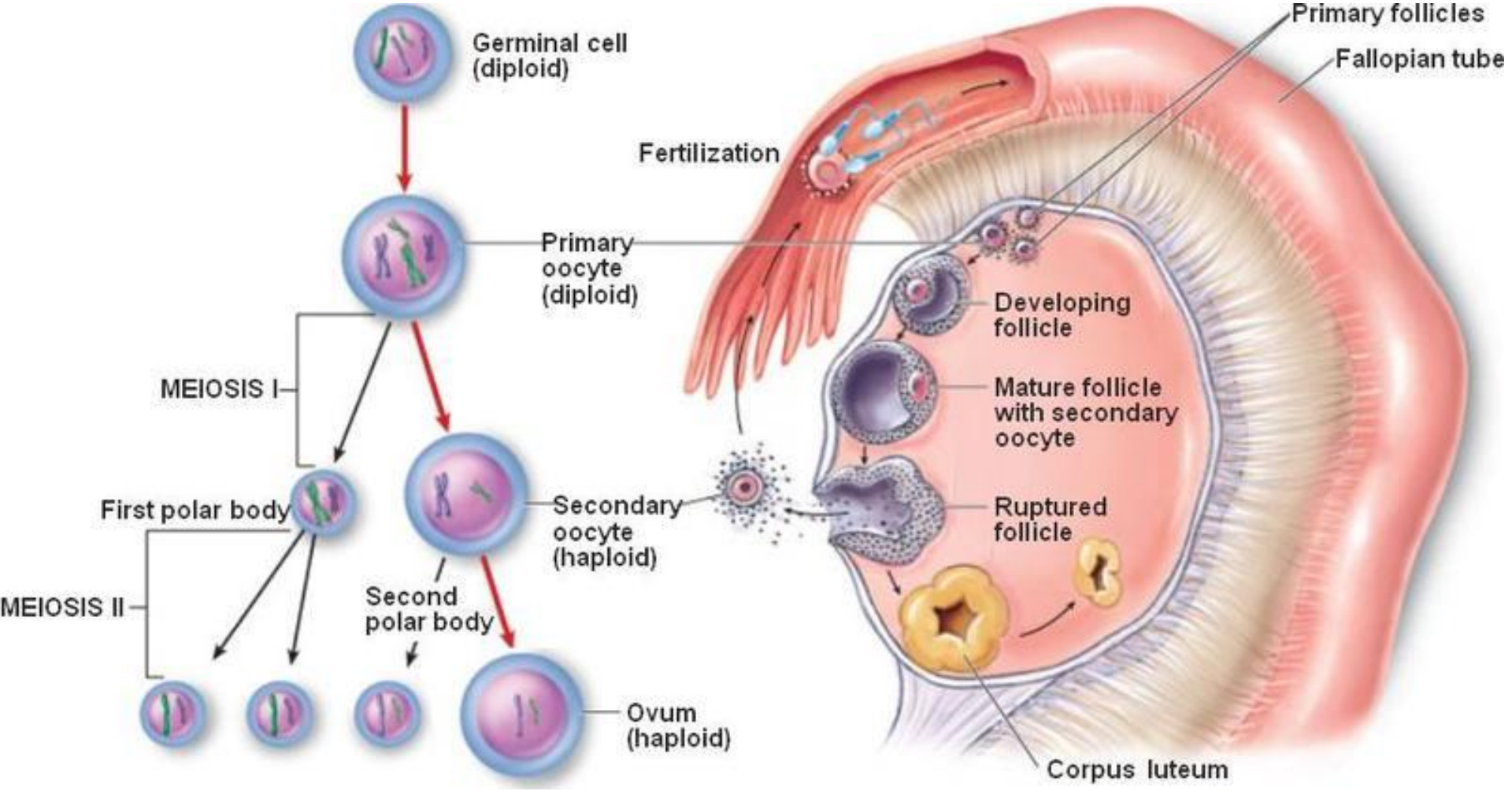
First arrest -
Diplotene, in prophase of I meiotic division
(OMI, oocyte maturation inhibitor, from theca interna)

Ovulation – after puberty
Under the influence of **meiosis-inducing factor** primary oocyte completes the I meiotic division – secondary oocyte and first polar body.
MPF *(maturation promoting factor)*

Reproductive period

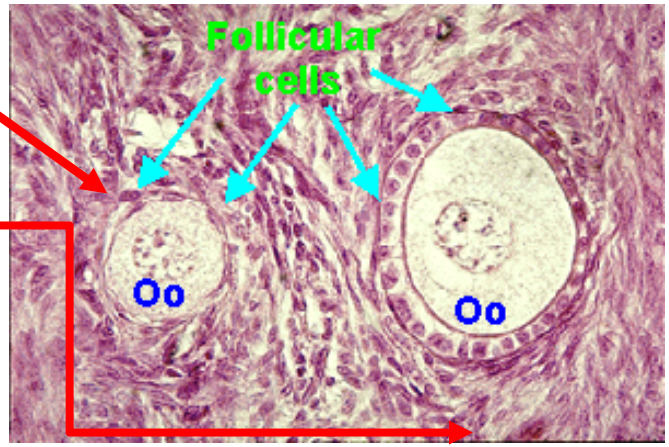
Second arrest -
in metaphase of the meiosis II
Meiosis II is completed only if the oocyte is fertalized


Primary Oocyte
Primary Oocyte
Secondary Oocyte
Antrum wih
Liquor folliculi


Germinal cell
(diploid)
Primary
oocyte
(diploid)
MEIOSIS I
First polar body
Secondary
oocyte
(haploid)
MEIOSIS II
Second
polar body
Ovum
(haploid)
Fertilization
Primary follicles
Fallopian tube
Developing
follicle
Mature follicle
with secondary
oocyte
Ruptured
follicle
Corpus luteum

Primordial follicle

Primary follicle



UNILAMINAR PRIMARY FOLLICLE

Primary oocyte
Diameter: ap. 35 μm

\+

Follicular cells
Basal lamina

Secondary follicle

the **human oocyte** grows from a **diameter** of 35 μm in the primordial follicle to a **diameter** usually exceeding 100–110 μm

Primary oocyte
Diameter: ap. 80 μm

\+

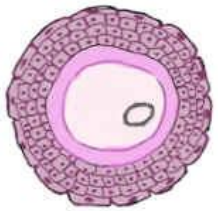
Zona pellucida

\+

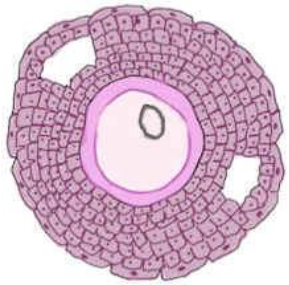
Granulosa cells

\+

Theca interna; Theca externa

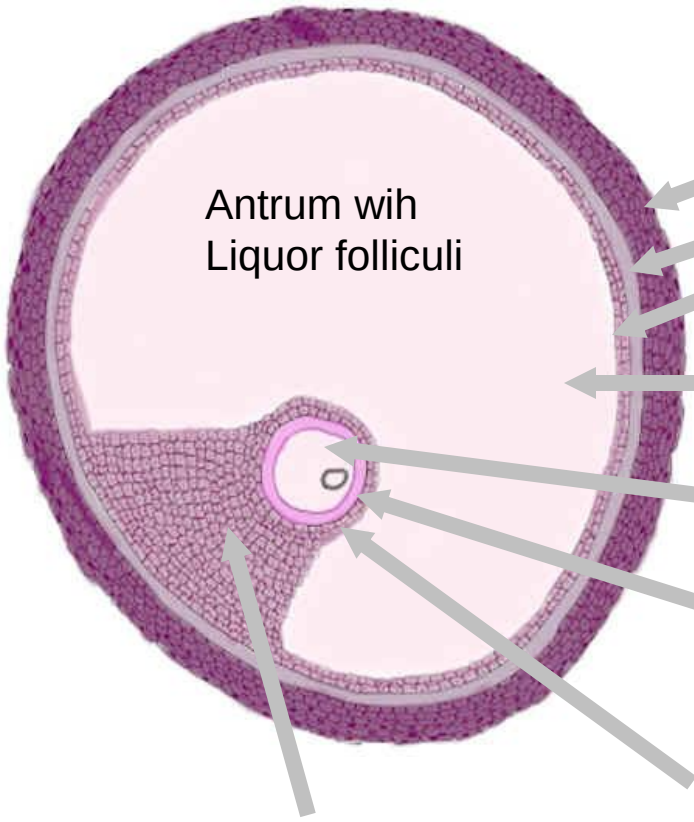


multilaminar



Antral = vesicular stage

Graafian follicle = mature follicle



Follicles wall:

Theca folliculi externa
Theca folliculi interna
Membrana (Mural) Granulosa cells

Connective tissue origin

Follicular antrium

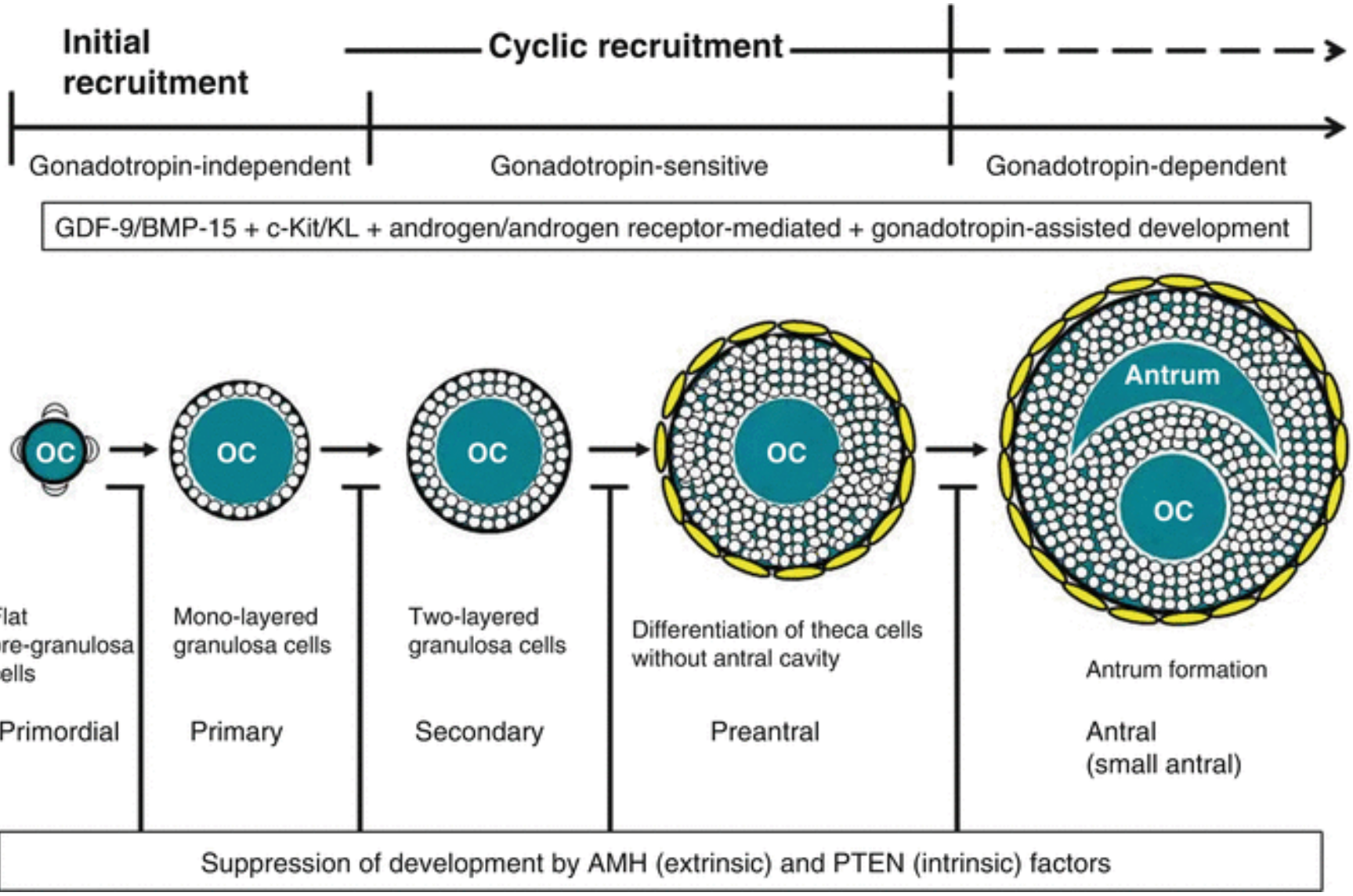
Secondary oocyte

Zonula pellucida

Corona radiata

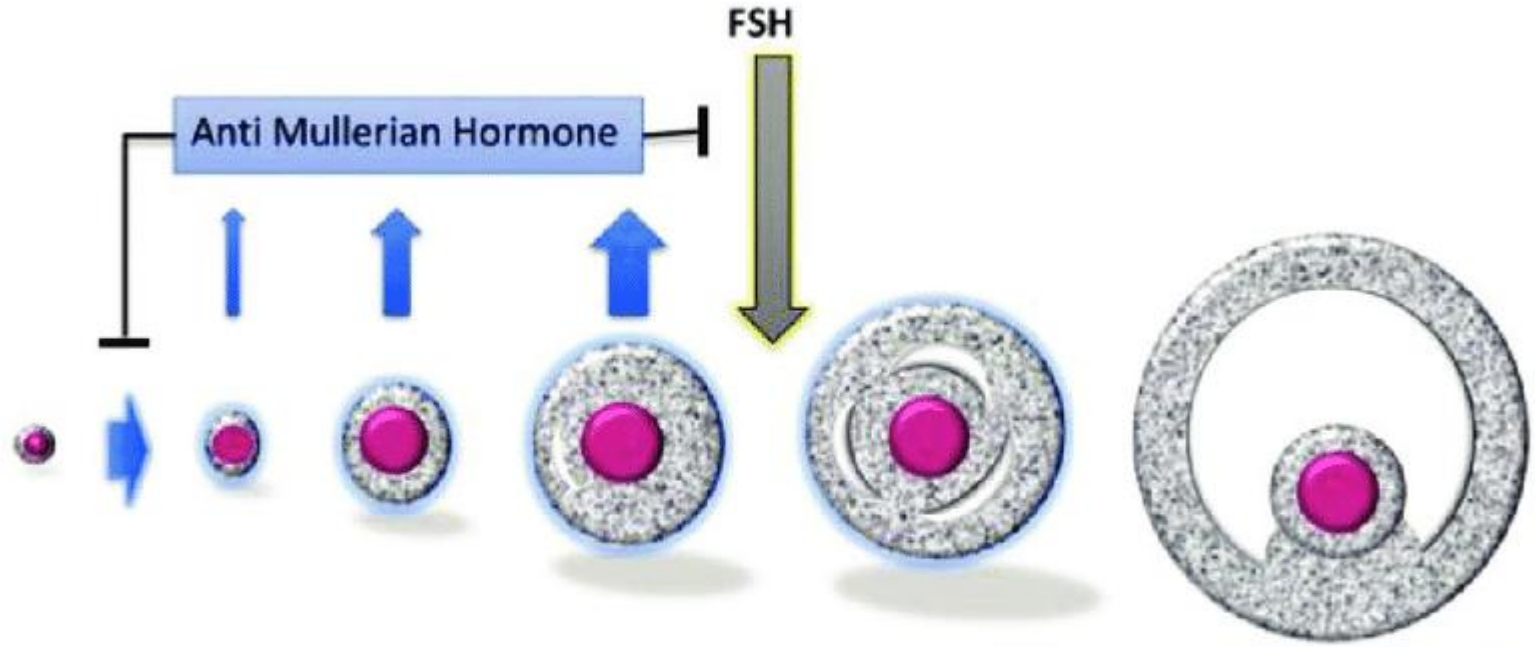
Cumulous oophorus

Folliculogenesis can be divided into two rather distinct stages: the gonadotropin-independent (preantral) and gonadotropindependent (antral or Graafian) periods



PTEN (ang. phosphatase and tensin homolog deleted on chromosome ten, MMAC1, mutated in multiple advanced cancers 1)

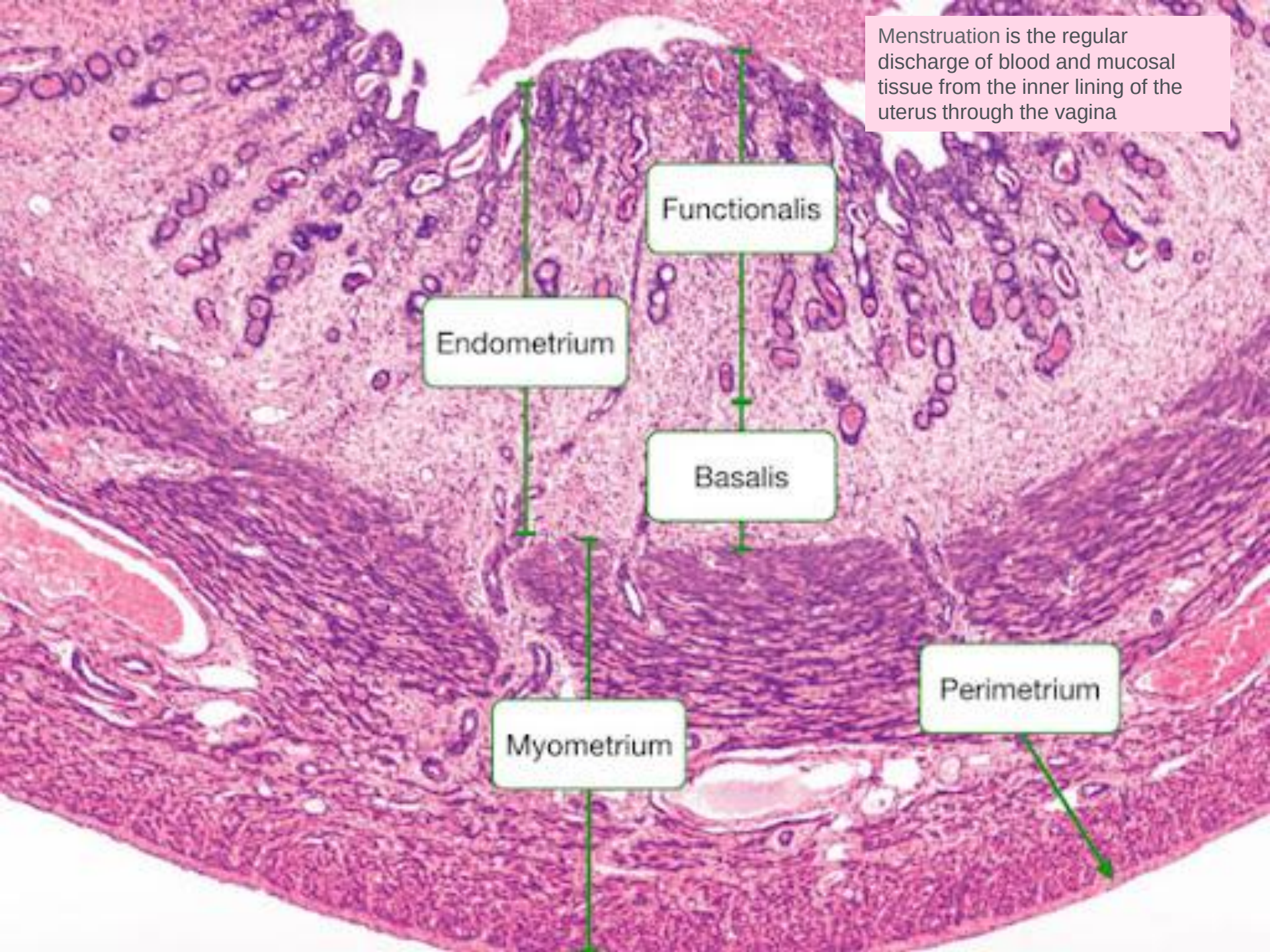
AMH is secreted by pre-antral and antral follicles



FOLLICLE	PREANTRAL		ANTRAL	ANTRAL	PREOVULATORY
PRIMORDIAL	SAMALL	BIG	2-7 mm	8-12 mm	

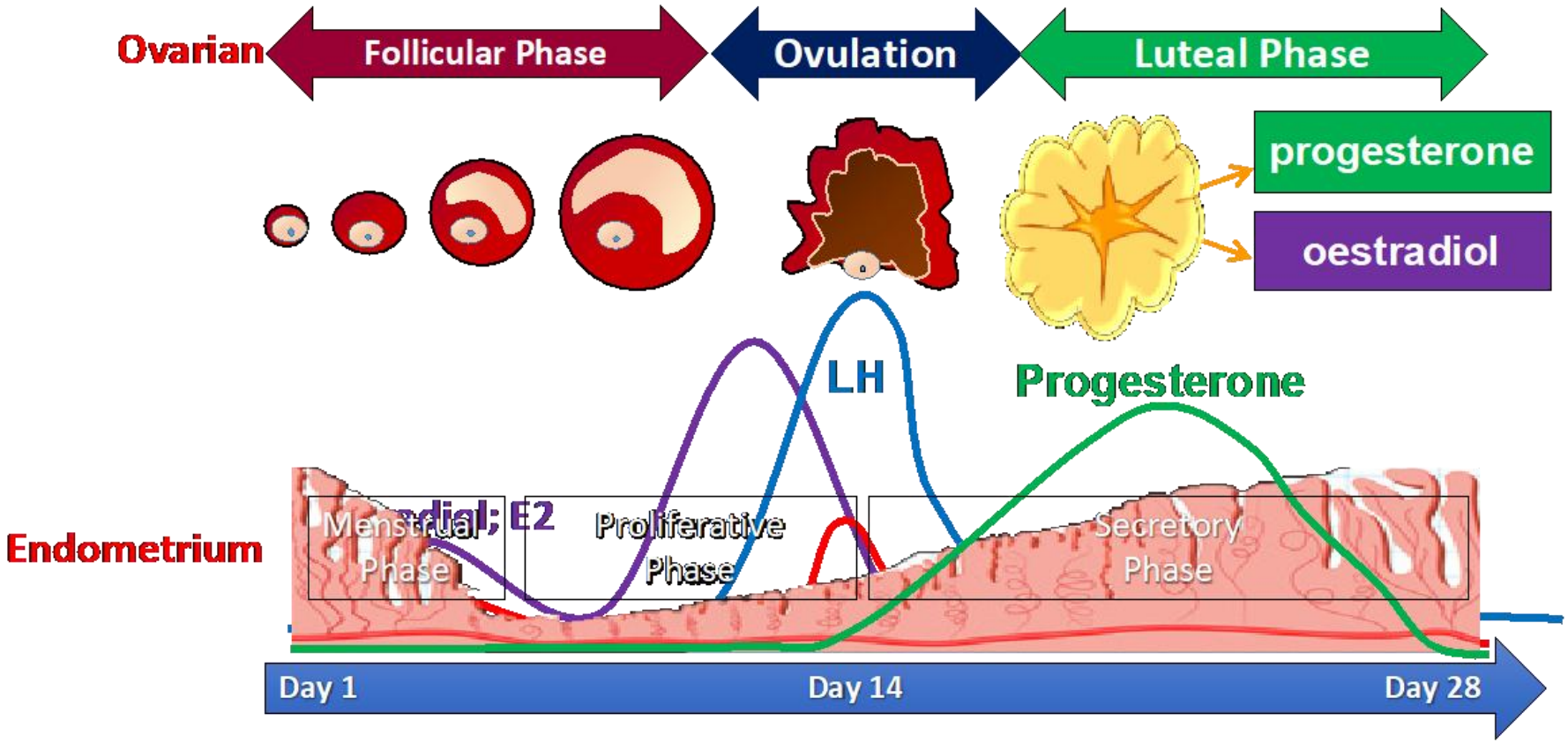
visible in ultrasound

Normal Menstrual Cycle Barriga-Pooley Patricio and Brantes-Glavic Sergio


Menstruation is the regular discharge of blood and mucosal tissue from the inner lining of the uterus through the vagina
Functionalis
Endometrium
Basalis
Perimetrium
Myometrium

Menstrual Cycle

The menstrual cycle is the monthly series of changes the body goes through to prepare for pregnancy. Each month, one of the ovaries releases an egg. This is called ovulation.

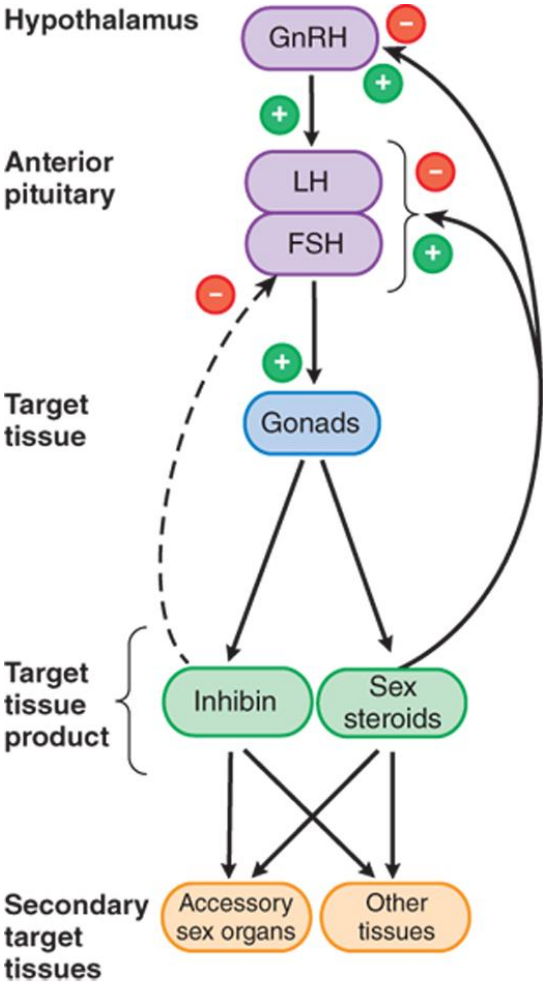


The four phases of the **menstrual cycle** are menstruation, the follicular phase, ovulation and the luteal phase

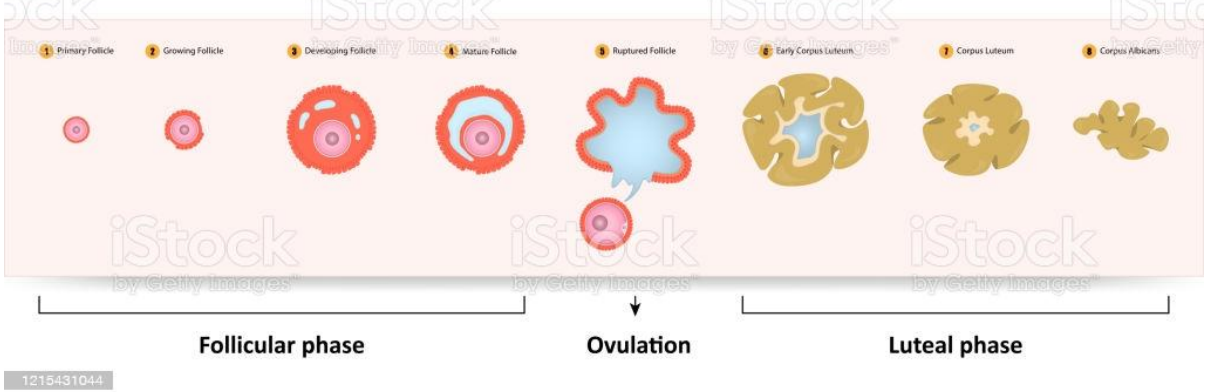
The first day of menstrual bleeding is considered Day 1 of the cycle.

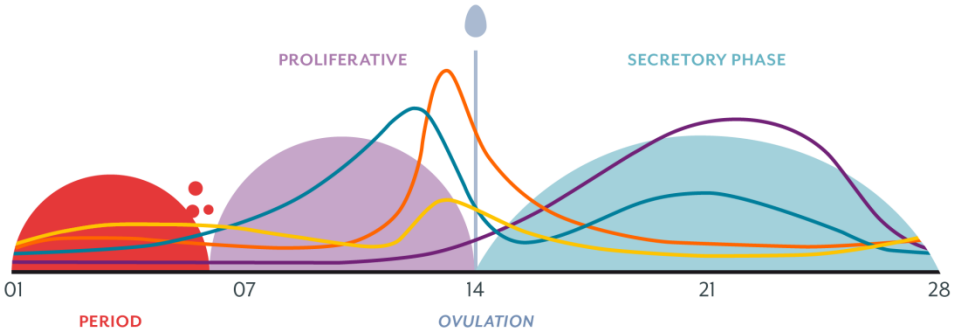
CYCLE	PRE-OVULATION		OVULATION	POST-OVULATION
Ovarian cycle	FOLLICULAR PHASE			LUTEAL PHASE
Uterine cycle	PERIOD	PROLIFERATIVE		SECRETORY

Menstrual cycle

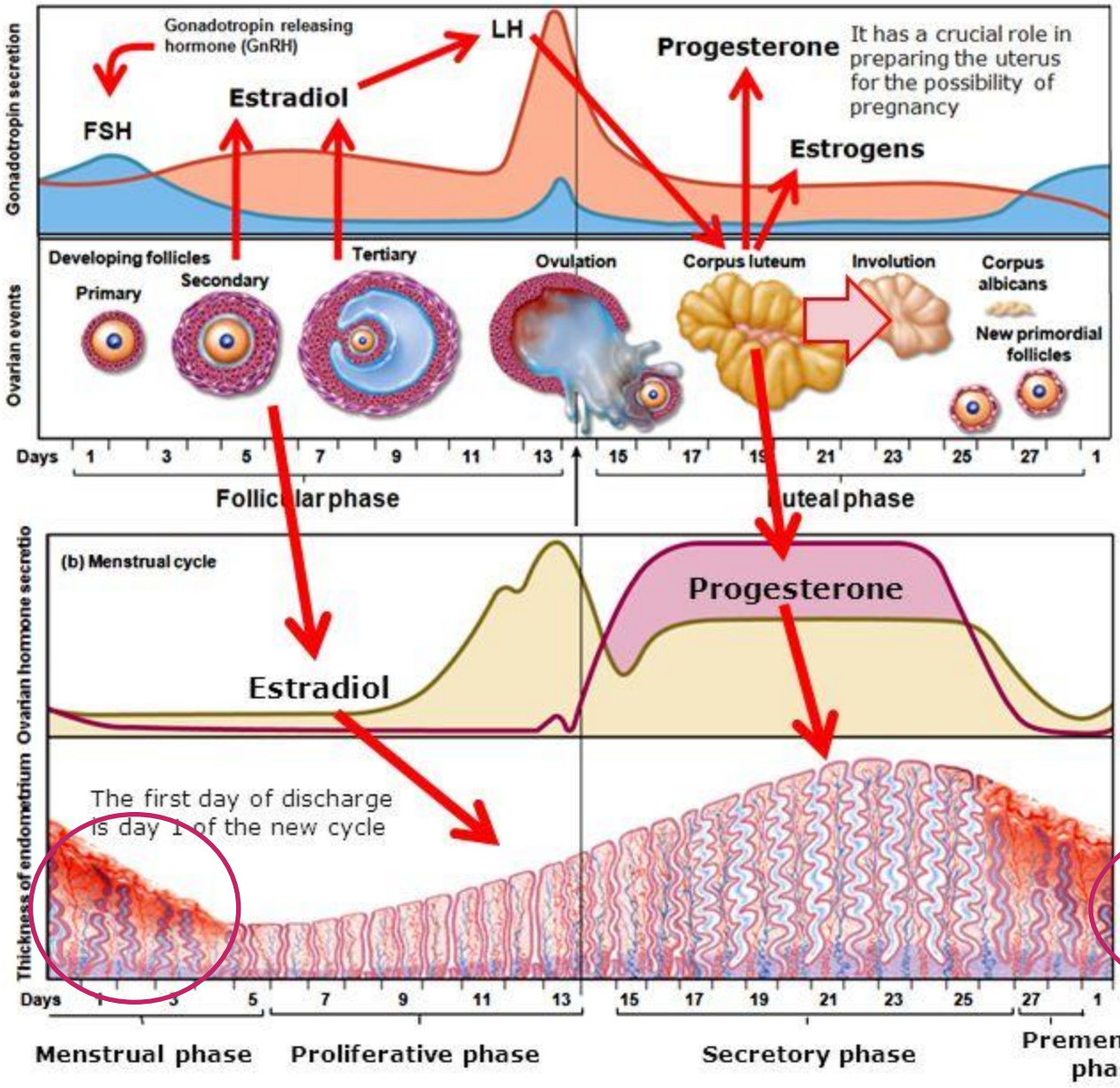


Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.





Uterine Cycle



Menstrual Cycle:

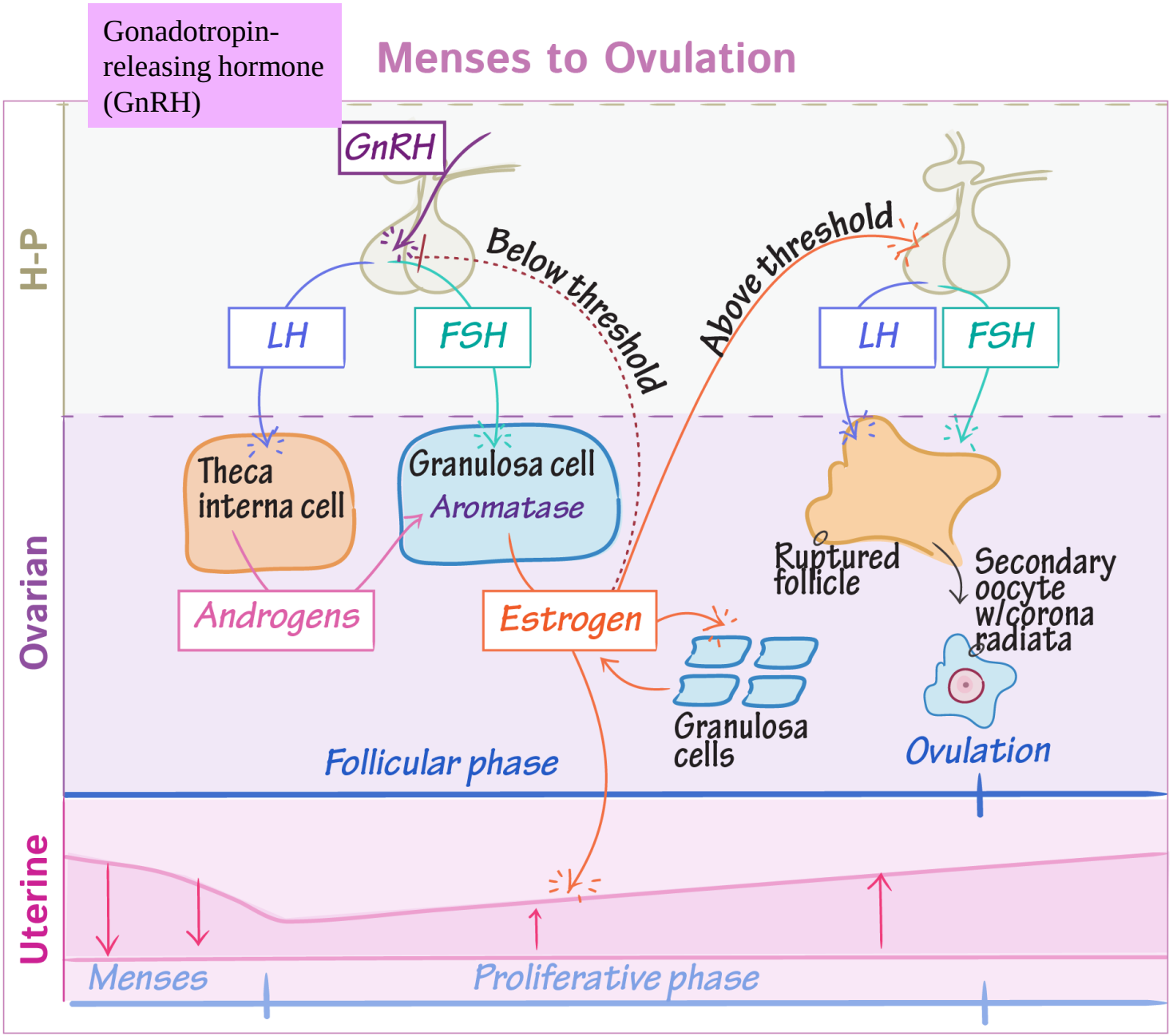
Proliferative phase
Estrogen stimulates mitosis in the stratum basalis and the prolific regrowth of blood vessels regenerating the stratum functionalis.

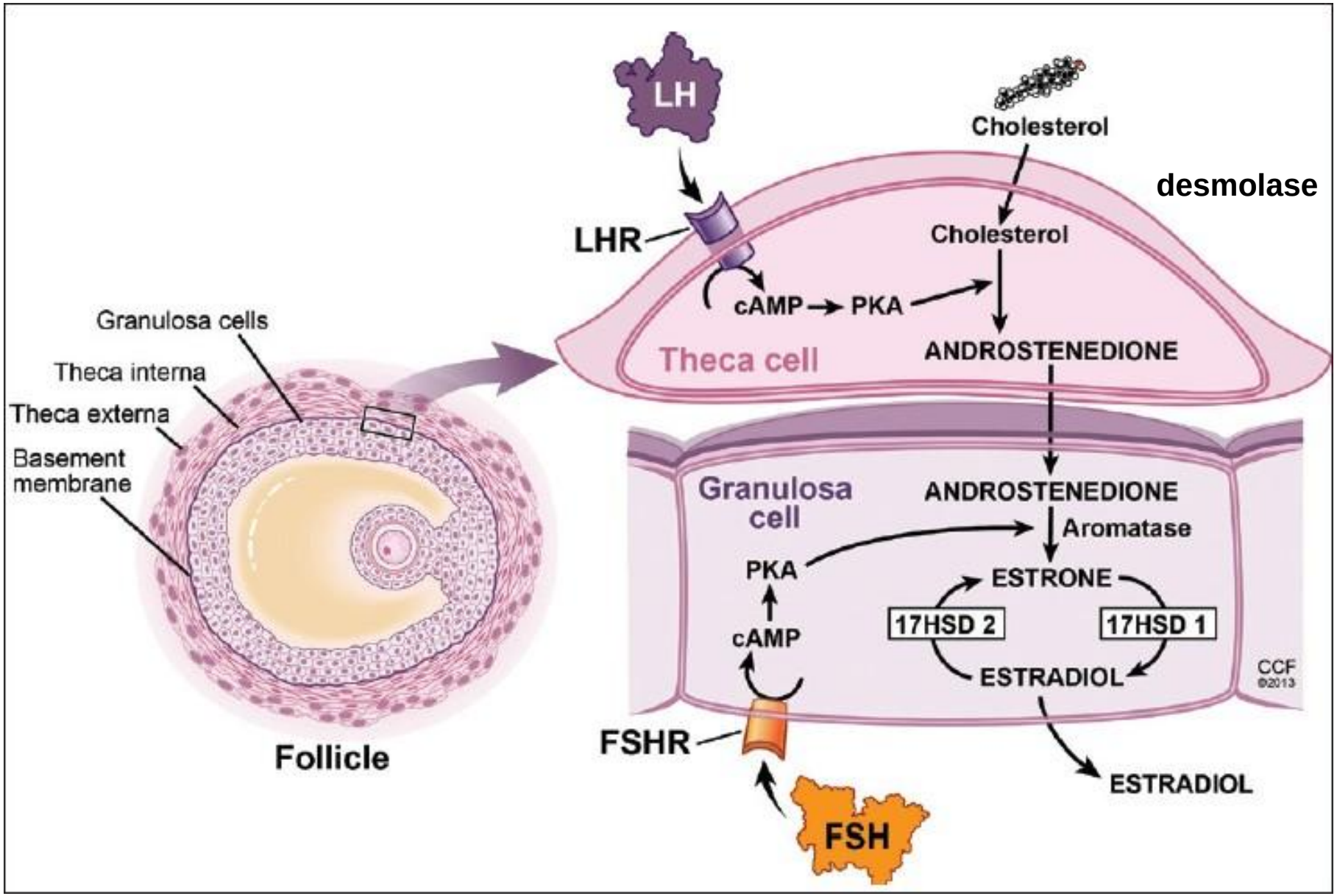
Secretory phase
The endometrium thickens still more in response to **progesterone** from corpus luteum.

Premenstrual phase
Corpus luteum atrophies and progesterone levels fall sharply. This causes endometrial ischemia with tissue necrosis and menstrual cramps.

Menstrual phase
Necrotic endometrium mixes with blood and serous fluid and produce the discharge of menstrual fluid from the vagina.

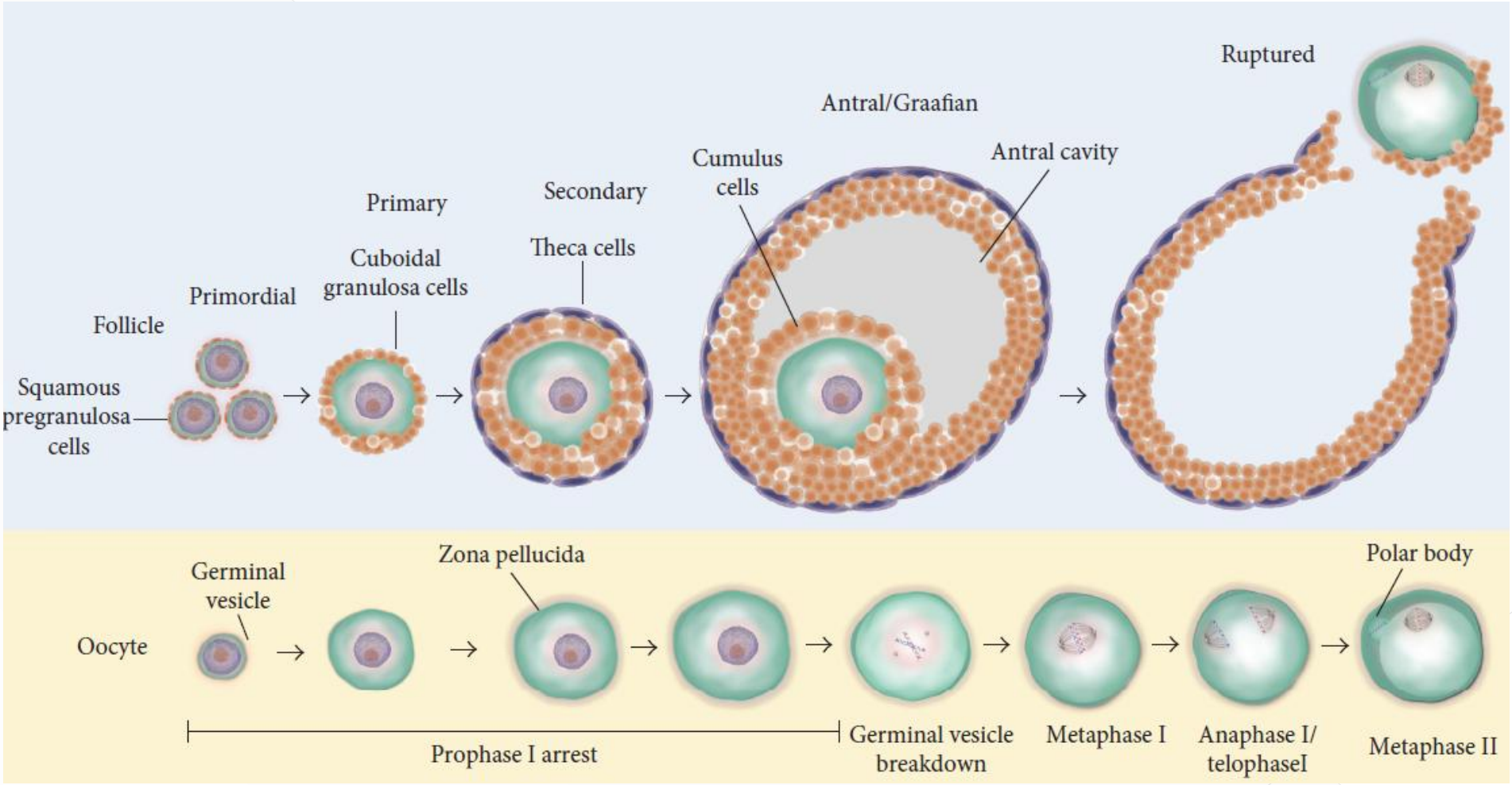
Gonadotropin-releasing hormone (GnRH)



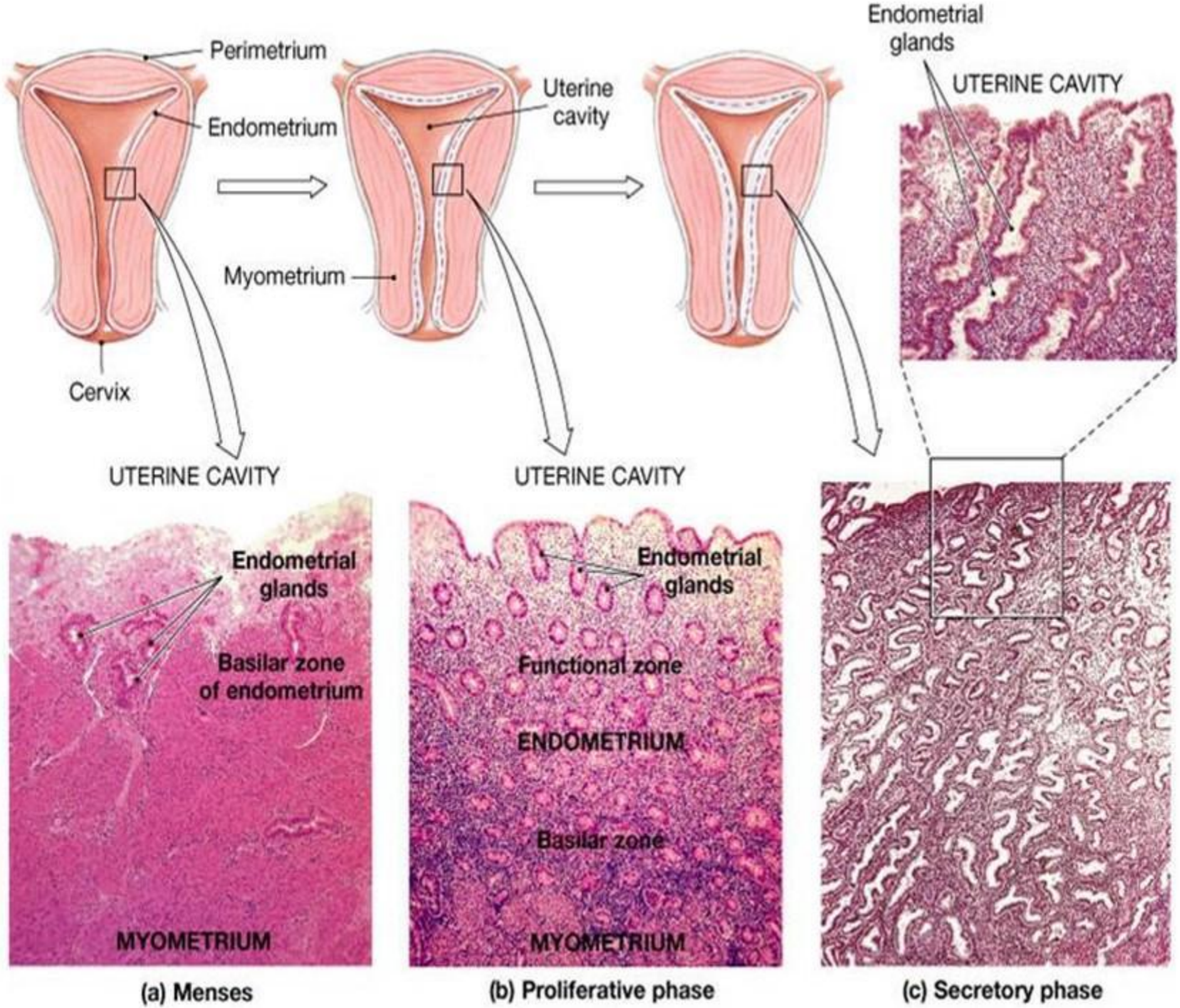


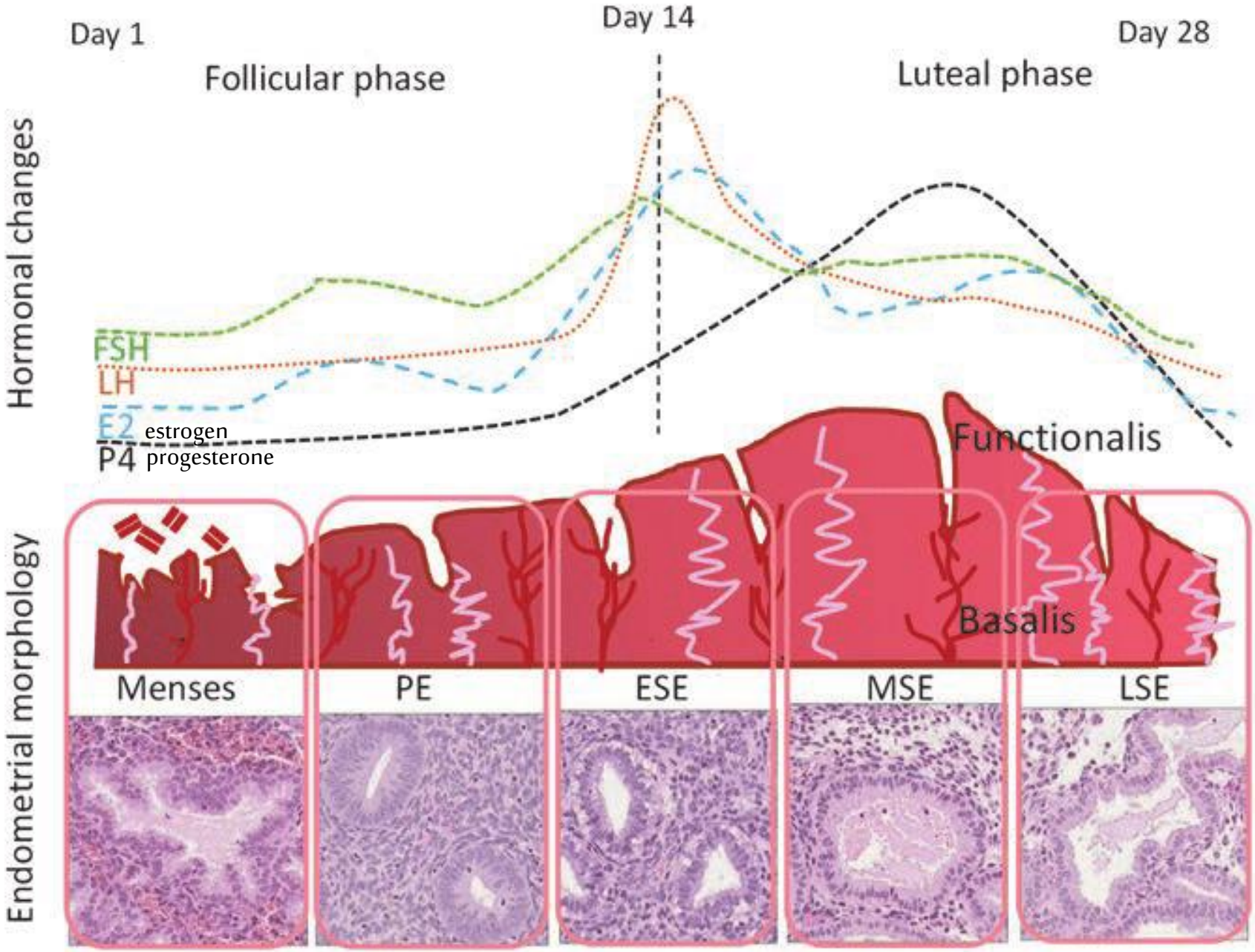
Normal Menstrual Cycle Barriga-Pooley Patricio and Brantes-Glavic Sergio

The **dominant follicle** produce large quantities of **inhibin** that shuts off FSH release by the pituitary gland. Follicles that are FSH dependent undergo atresia, whereas the dominant follicle progresses to ovulation.

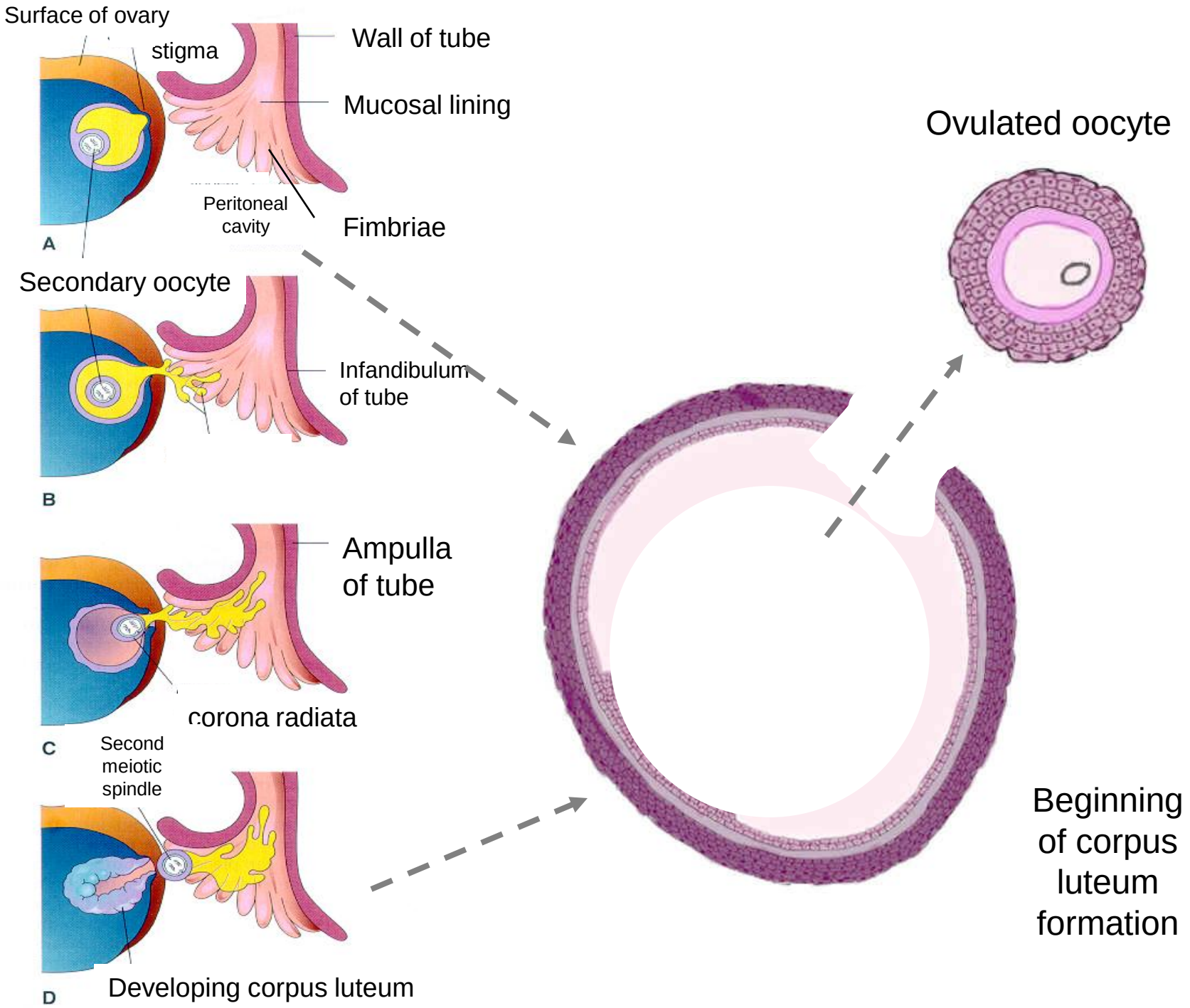


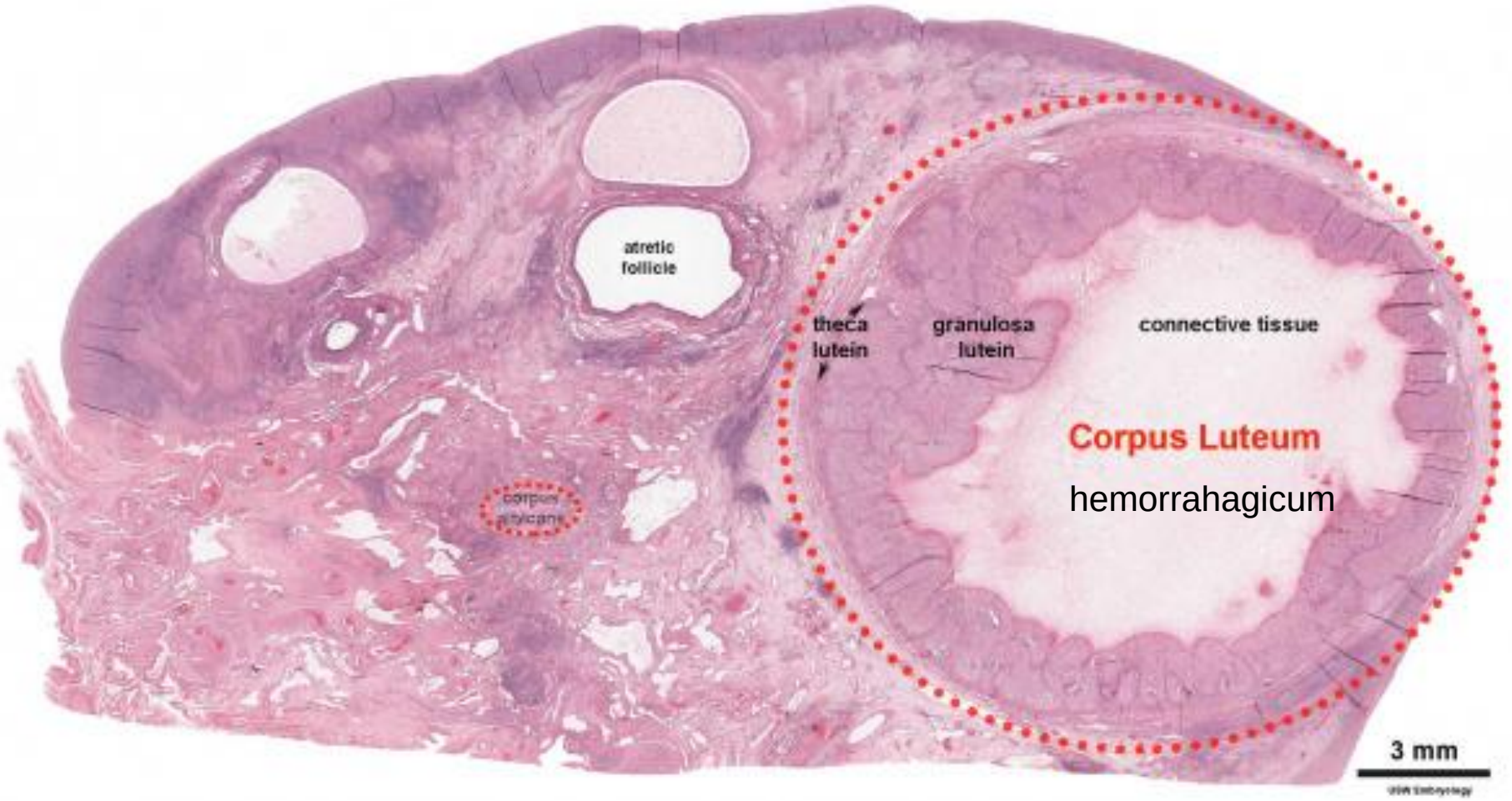
https://doi.org/10.1155/2017/4015874


Perimetrium
Endometrium
Myometrium
Cervix
UTERINE CAVITY
Uterine cavity
UTERINE CAVITY
Endometrial glands
UTERINE CAVITY
Endometrial glands
Basilar zone of endometrium
MYOMETRIUM
(a) Menses
Endometrial glands
Functional zone
ENDOMETRIUM
Basilar zone
MYOMETRIUM
(b) Proliferative phase
(c) Secretory phase



DOI: 10.13140/RG.2.2.13386.24009


Surface of ovary
stigma
Wall of tube
Mucosal lining
Peritoneal cavity
Fimbriae
A
Secondary oocyte
Infandibulum of tube
B
Ampulla of tube
corona radiata
C
Second meiotic spindle
D
Developing corpus luteum
Ovulated oocyte
Beginning of corpus luteum formation

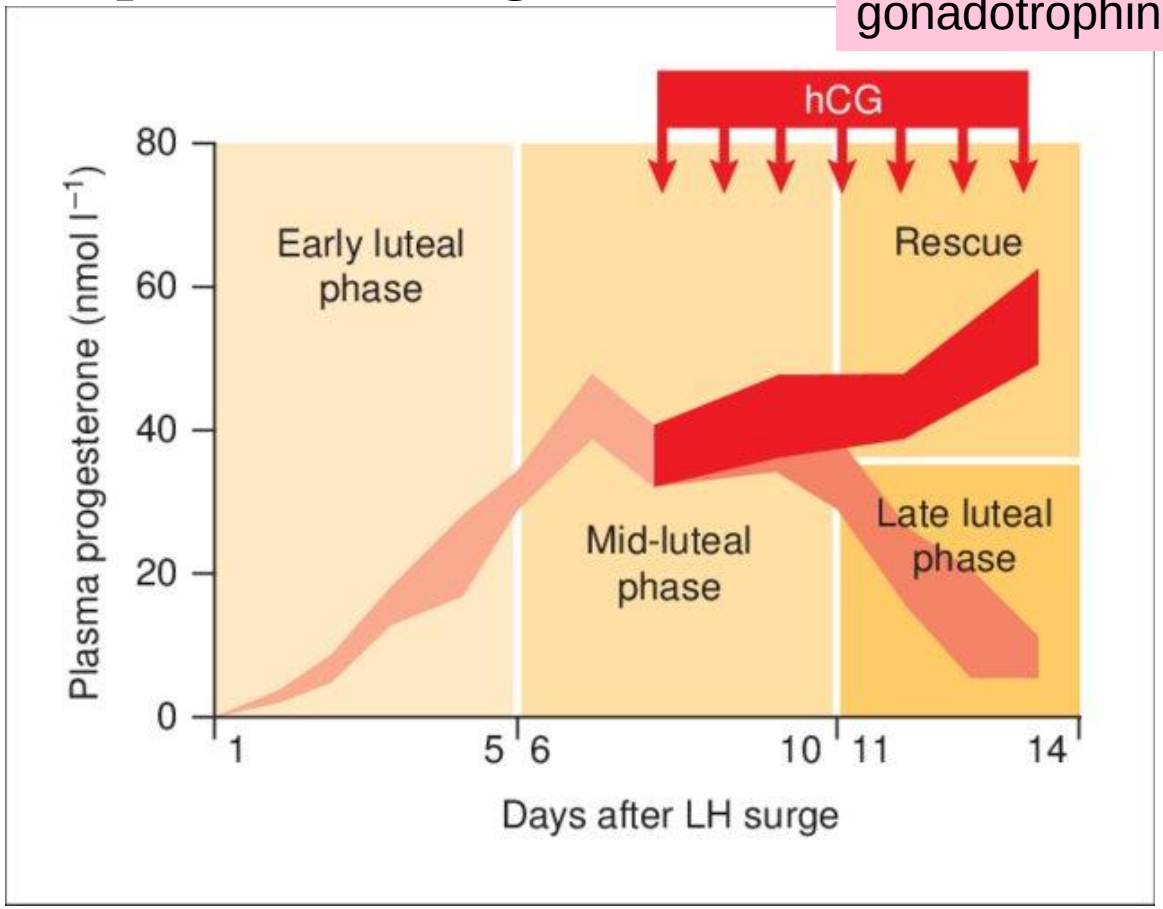


The primary **hormone** produced by the **corpus luteum** is progesterone, but it also produces inhibin A and estradiol.

Corpus luteum degeneration

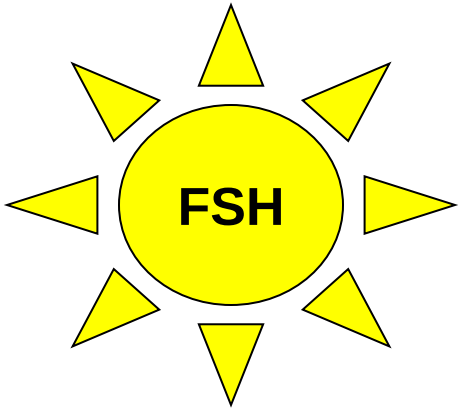
Human chorionic gonadotrophin

The maintenance of the corpus luteum is LH dependent.



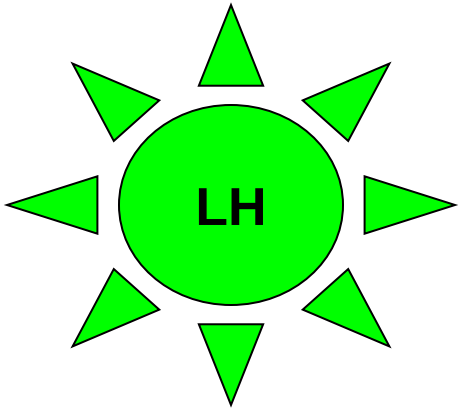
The secretion of hormones from the corpus luteum will stop within 14 days after ovulation if the oocyte is not fertilized. It then degenerates into a scar within the ovary, known as a corpus albicans.

when progesterone levels drop, bleeding begins and a new menstrual cycle begins



Stimulates follicle growth,

Estrogens secretion



Stimulates ovulation,

Corpus luteum formation,

Progesterone secretion

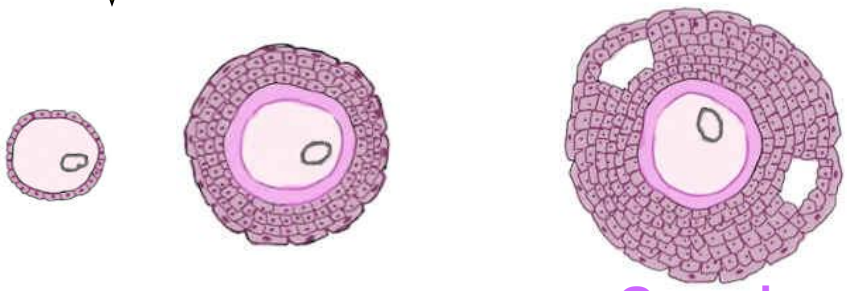
Pituitary

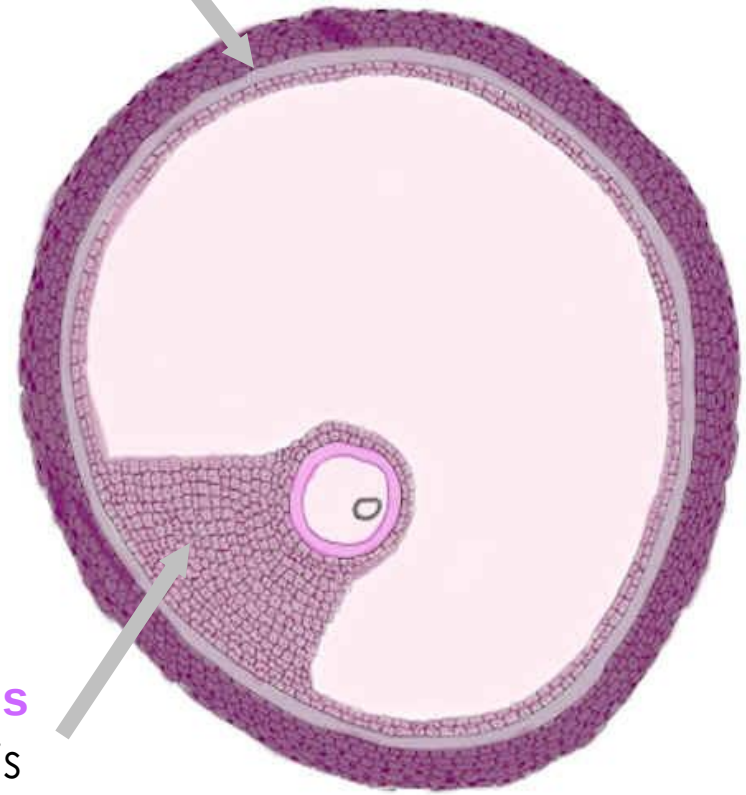
FSH

FSH

FSH

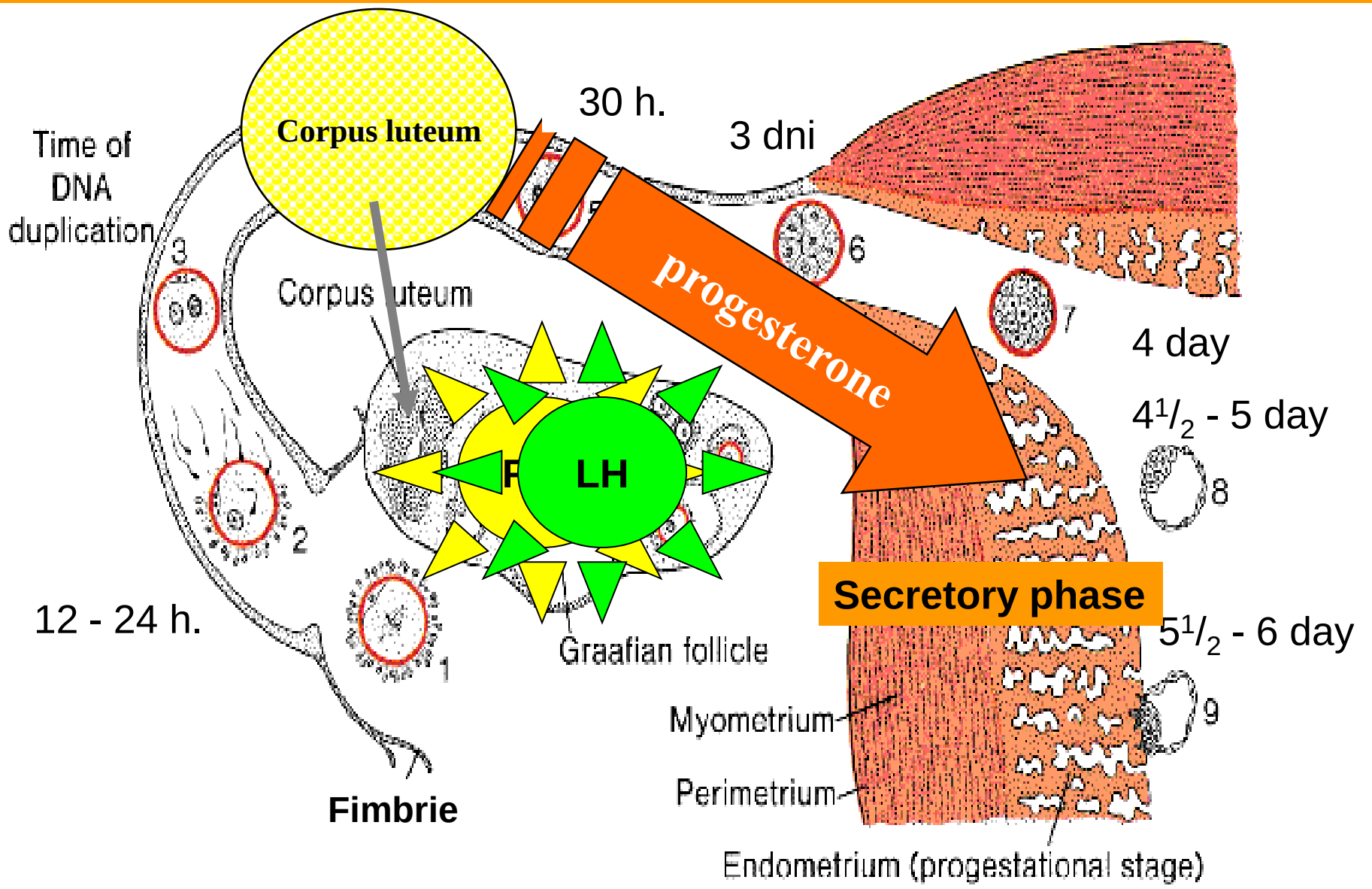
Theca interna
possess LH receptors and produce male sex hormone – **androstenedione**

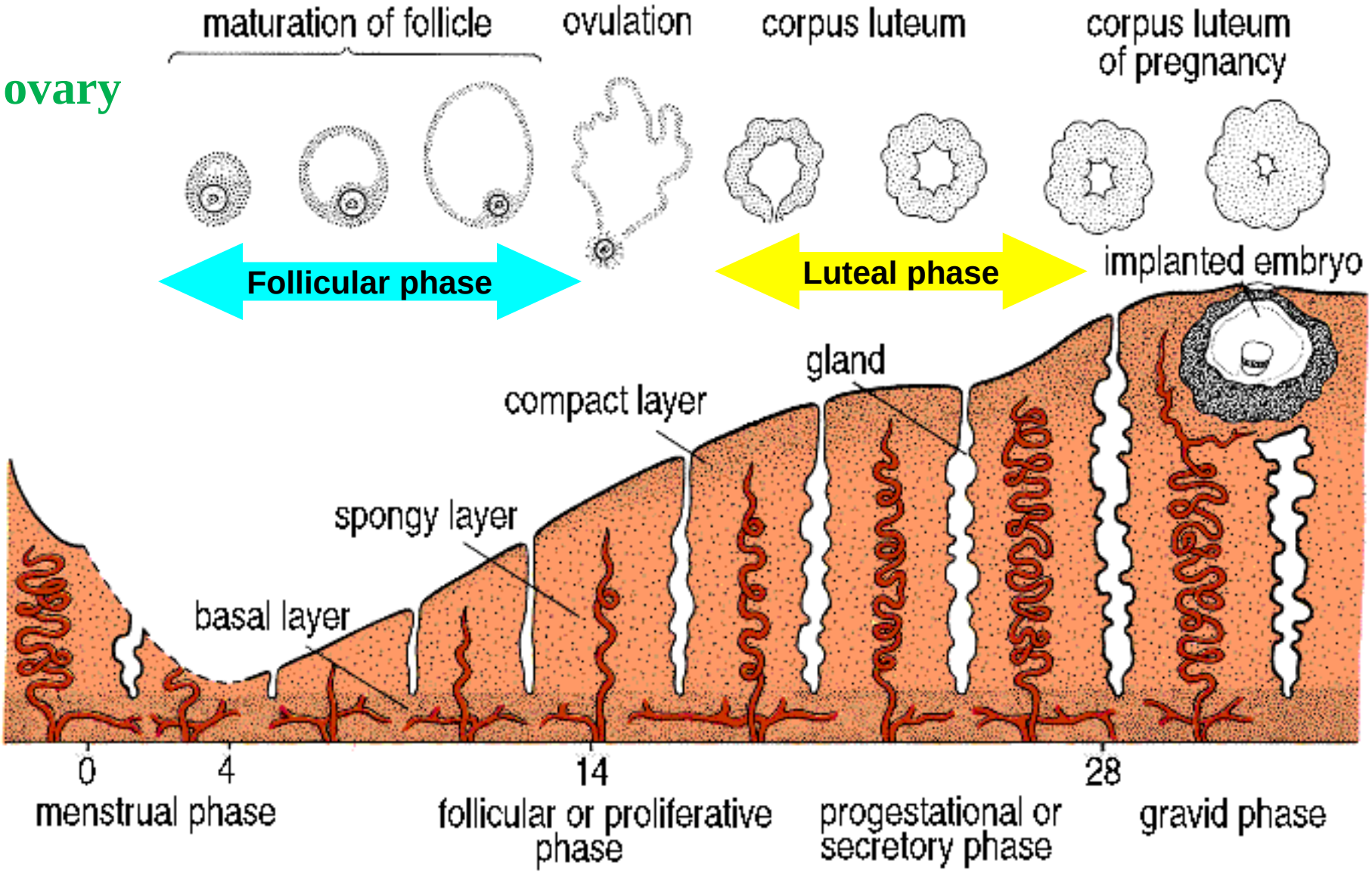


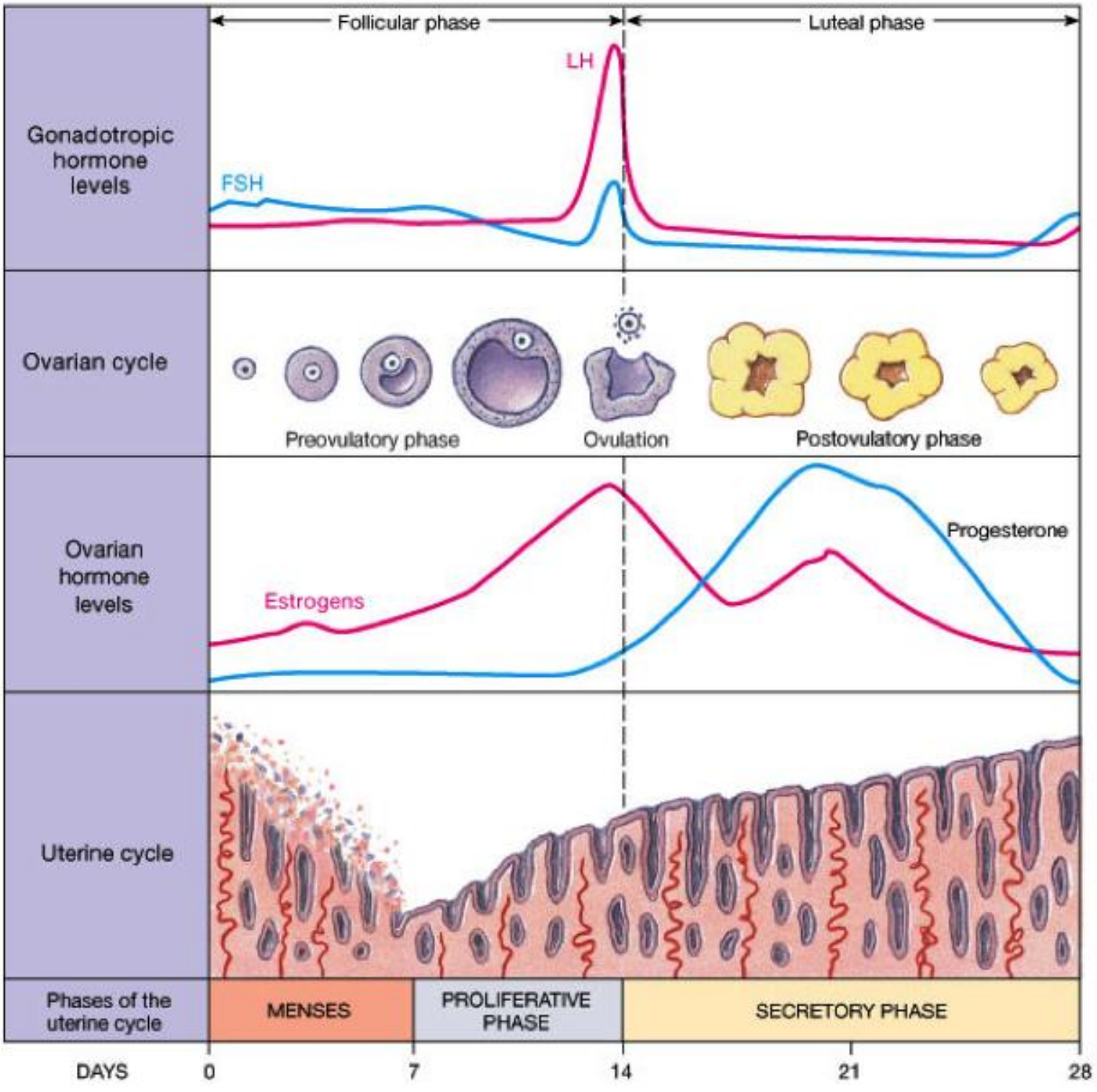


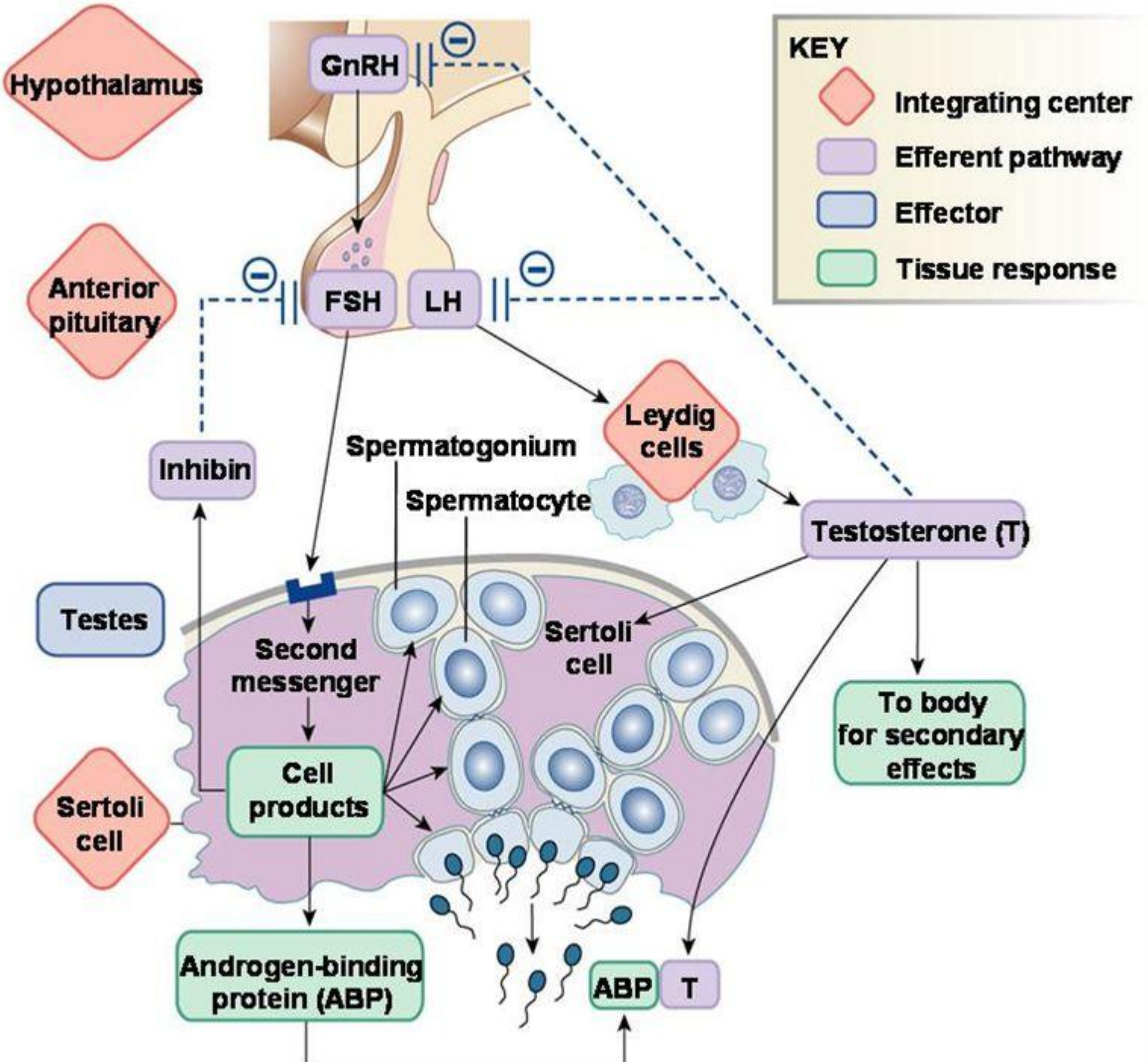
Granulosa cells
Androstenedione is converted by aromatase into **17-B estradiol**

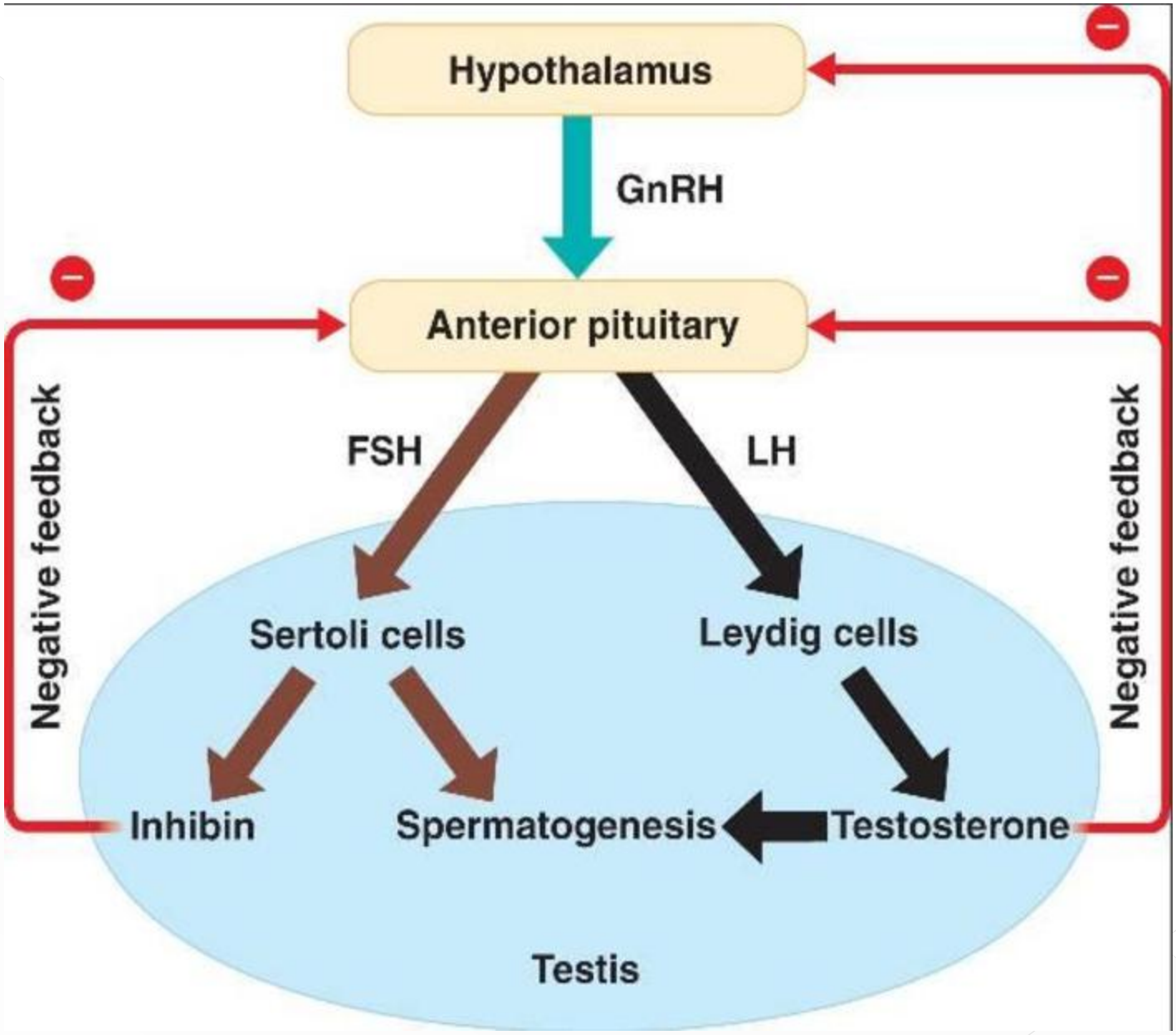
Uterus (proliferating phase)

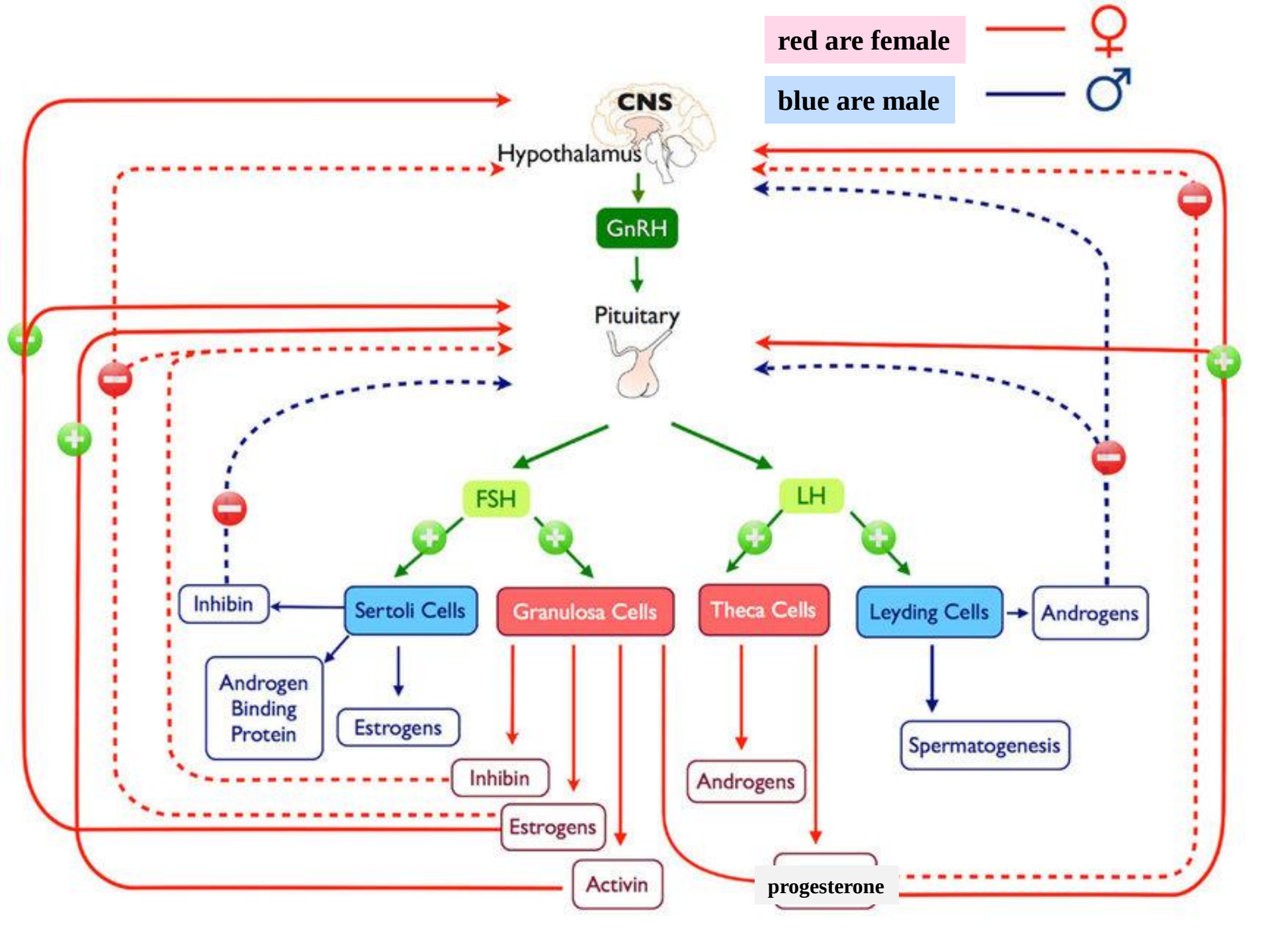

Corpus luteum
30 h.
3 dni
Time of DNA duplication
progesterone
Corpus luteum
LH
4 day
4 1/2 - 5 day
Secretory phase
5 1/2 - 6 day
12 - 24 h.
Graafian follicle
Myometrium
Perimetrium
Endometrium (progestational stage)
Fimbrie


ovary
maturation of follicle
ovulation
corpus luteum
corpus luteum of pregnancy
Follicular phase
Luteal phase
implanted embryo
gland
compact layer
spongy layer
basal layer
0
4
14
28
menstrual phase
follicular or proliferative phase
progestational or secretory phase
gravid phase
Estrogenic phase
uterus


Follicular phase
Luteal phase
Gonadotropic hormone levels
LH
FSH
Ovarian cycle
Preovulatory phase
Ovulation
Postovulatory phase
Ovarian hormone levels
Progesterone
Estrogens
Uterine cycle
Phases of the uterine cycle
MENSES
PROLIFERATIVE PHASE
SECRETORY PHASE
DAYS
0
7
14
21
28


KEY
Integrating center
Efferent pathway
Effector
Tissue response
Hypothalamus
GnRH
Anterior pituitary
FSH
LH
Leydig cells
Inhibin
Spermatogonium
Spermatocyte
Testosterone (T)
Testes
Second messenger
Sertoli cell
To body for secondary effects
Sertoli cell
Cell products
Androgen-binding protein (ABP)
ABP
T


Hypothalamus
GnRH
Anterior pituitary
FSH
LH
Sertoli cells
Leydig cells
Inhibin
Spermatogenesis
Testosterone
Testis
Negative feedback
Negative feedback


red are female
blue are male
CNS
Hypothalamus
GnRH
Pituitary
FSH
LH
Inhibin
Sertoli Cells
Granulosa Cells
Theca Cells
Leyding Cells
Androgens
Androgen Binding Protein
Estrogens
Inhibin
Androgens
Spermatogenesis
Estrogens
Activin
progesterone

Menstrual Cycle Physiology: Ovarian Cycle - Luteal Phase Explained

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Reviewers:
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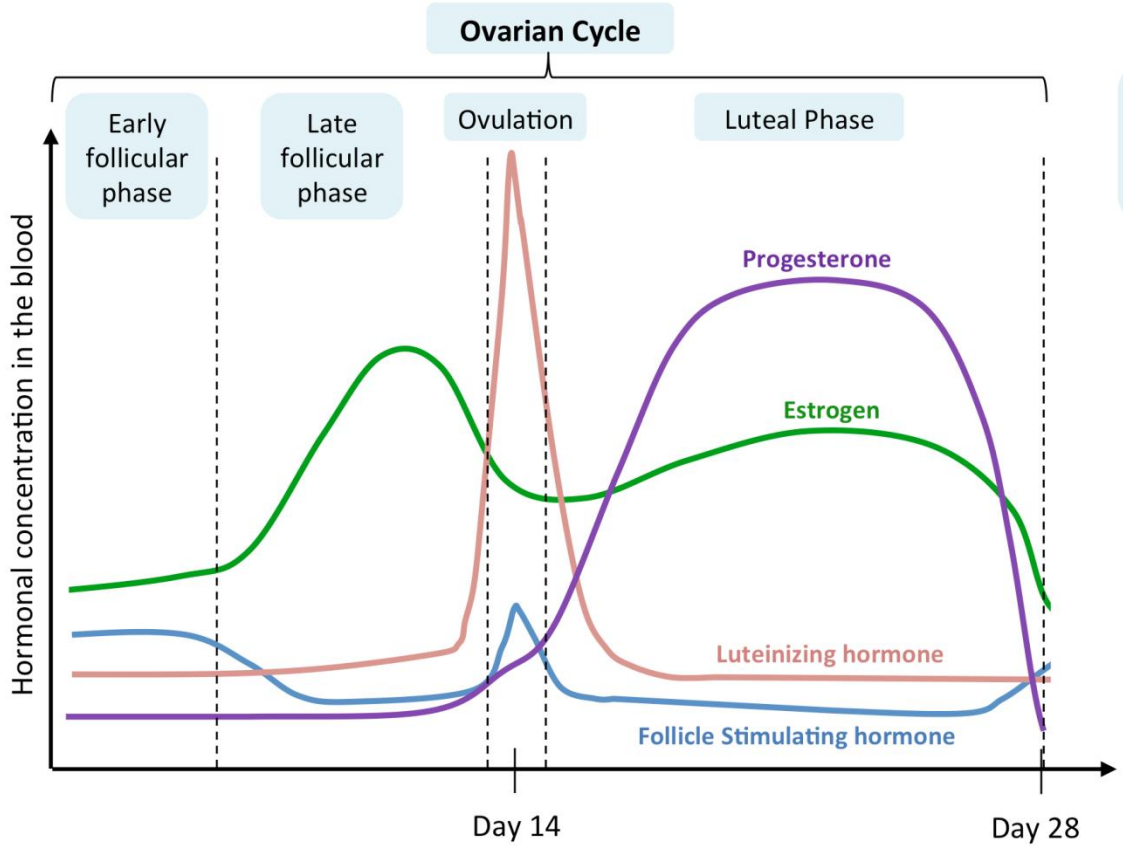
** MD at time of publication*



Besides ovulation, the Day 14 surge in LH also stimulates a process called "luteinization": the maturation of the ruptured follicle's granulosa cells into the corpus luteum

↓

Corpus luteum begins to secrete a large amount of progesterone and a smaller amount of estrogen

↓

The combination of high progesterone and estrogen negatively feed back on hypothalamus and anterior pituitary

↓

↓ Production of GnRH, FSH, and LH

↓ FSH means no new follicles grow in the ovary in this phase

↓ LH means less stimulation for continued corpus luteum growth

If implantation does occur, HCG (human chorionic gonadotropin) maintains the corpus luteum so progesterone (and therefore endometrium) will be maintained

If no implantation of embryo, corpus luteum degenerates after 14 days, allowing GnRH/ FSH/LH to restart the Ovarian Cycle

Note:
-The LH surge can be thought of as only providing enough "battery power" for the corpus luteum to run and make progesterone for 14 days, which is why the luteal phase is a fixed length.
-The timing and function of estrogen and progesterone during the ovarian cycle are also important to the uterine cycle (see Uterine Cycle slide)

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The end