Obstetrics and Gynecology
Normal menstrual cycle

University Of Fallujah
College Of Medicine

Lecture : 6

Stage : 5th Year

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Date: 27|10|2025

Learning objectives

1. Understanding the main pathophysiological changes behind normal menstrual cycle.
2. Identify the different phases of the cycle.
3. Know the marker for ovarian reserve.

The normal menstrual cycle

- The menstrual cycle is the presence of regular vaginal bleeding occurs as a result of the shedding of the endometrial lining following failure of fertilization of the oocyte or failure of implantation.
- The cycle depends on of interaction between hypothalamus, pituitary, ovary and uterus

Hypothalamus

The hypothalamus secretes the gonadotrophin-releasing hormone (GnRH), GnRH must be released in a pulsatile fashion to stimulate pituitary secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH).

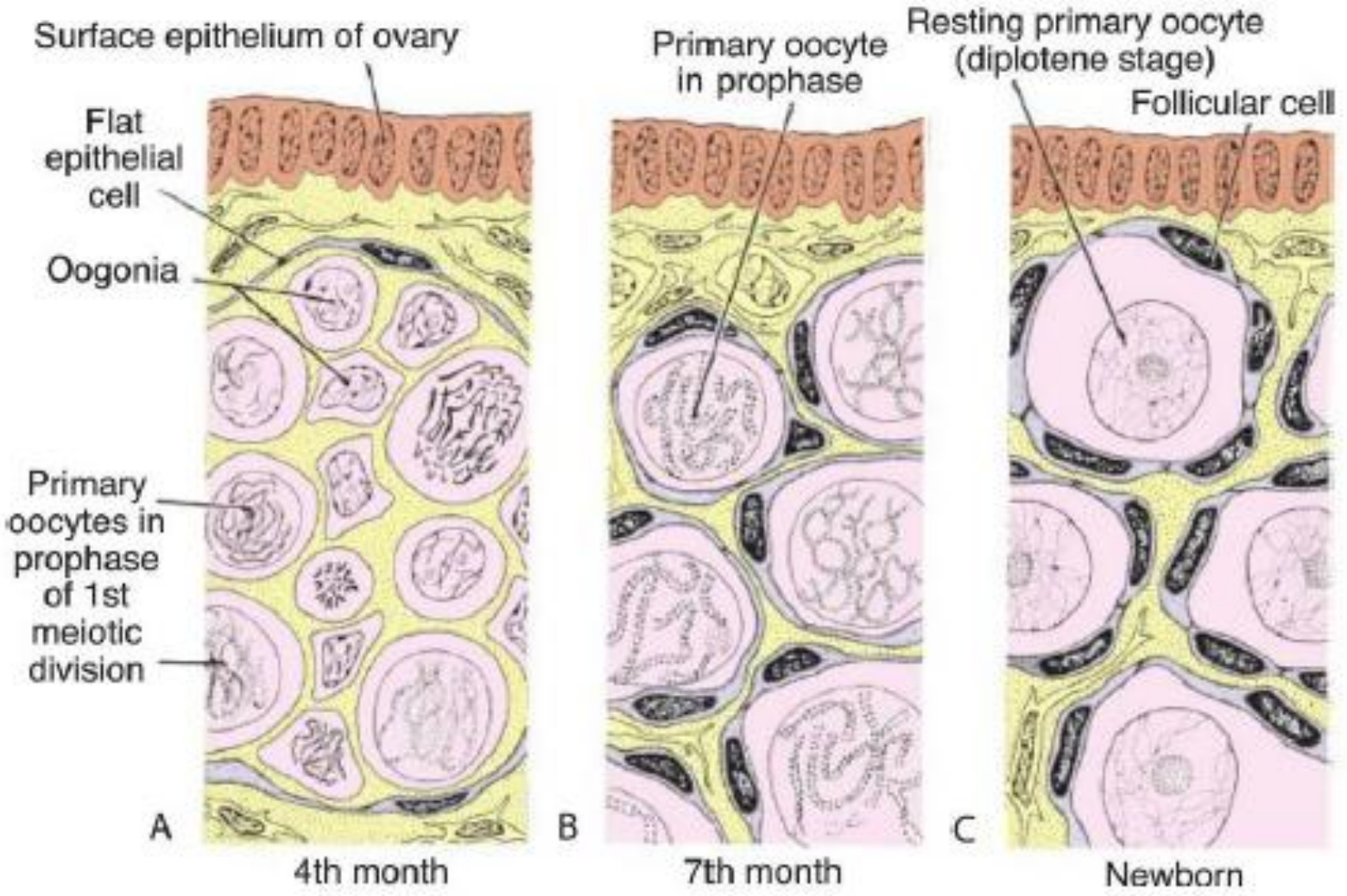
If GnRH is given in a constant high dose, it desensitizes the GnRH receptor and reduces LH and FSH release.

Pituitary gland

GnRH stimulation of the basophil cells in the anterior pituitary gland causes synthesis and release of the gonadotrophic hormones, FSH and LH. This process is modulated by the ovarian sex steroid hormones oestrogen and progesterone.

Ovary

- Ovaries with developing oocytes are present in the female fetus from an early stage of development. By the end of the second trimester in utero, the number of oocytes has reached a maximum of about 7 million. After that they undergo atresia so at birth, the human ovaries contain approximately 1 million primordial follicles, arrested at prophase of the first meiotic division.


Surface epithelium of ovary
Flat epithelial cell
Oogonia
Primary oocytes in prophase of 1st meiotic division
Primary oocyte in prophase
Resting primary oocyte (diplotene stage)
Follicular cell
A
4th month
B
7th month
C
Newborn

- Of the original pool, only about 400 will ever acquire gonadotrophin receptors and the possibility of ovulation
- With the onset of menarche, the primordial follicles containing oocytes will activate and grow in a cyclical fashion, causing ovulation and subsequent menstruation.

In the course of a normal menstrual cycle, the ovary will go through three phases:

1.Follicular phase

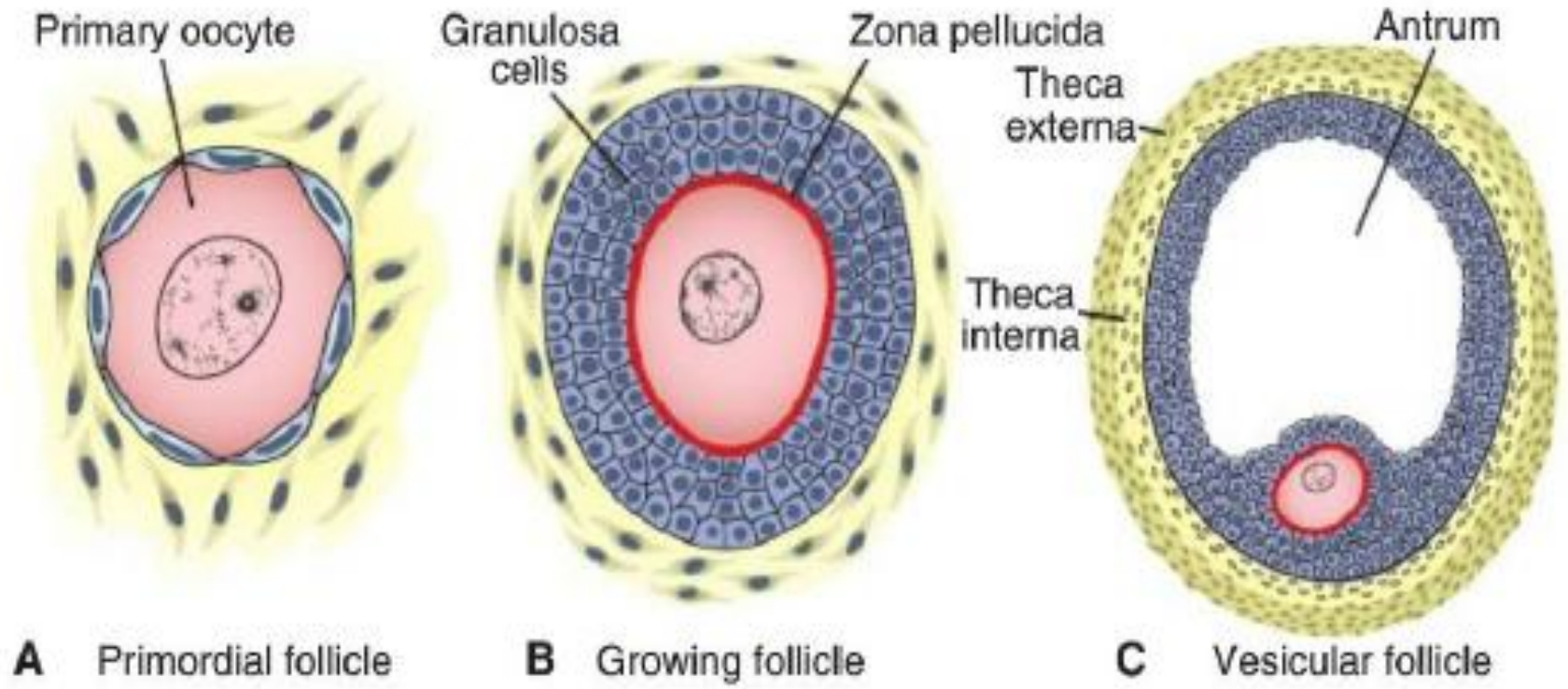
2. Ovulation

3. Luteal phase.

Follicular phase

- Follicular phase lasts an average of 14 days with great variation.
- The initial stages of follicular development are independent of hormone stimulation.
- in the first days of the menstrual cycle, when oestrogen, progesterone levels are low, FSH levels rise. This stimulates a cohort of small antral follicles on the ovaries to grow.

- Within the follicles, there are two cell types the theca and the granulosa cell. LH stimulates production of androgens from cholesterol within theca cells. These androgens are converted into oestrogens by the process of aromatization in granulosa cells, under the influence of FSH so both FSH and LH are required to generate a normal cycle with adequate amounts of oestrogen.


Primary oocyte
Granulosa cells
Zona pellucida
Antrum
Theca externa
Theca interna
A Primordial follicle
B Growing follicle
C Vesicular follicle

- As the follicles grow and oestrogen secretion increases, there is negative feedback on the pituitary to decrease FSH secretion. This assists in the selection of one follicle which has the most efficient aromatase activity to continue in its development towards ovulation (the dominant follicle), while smaller follicles will undergo atresia.

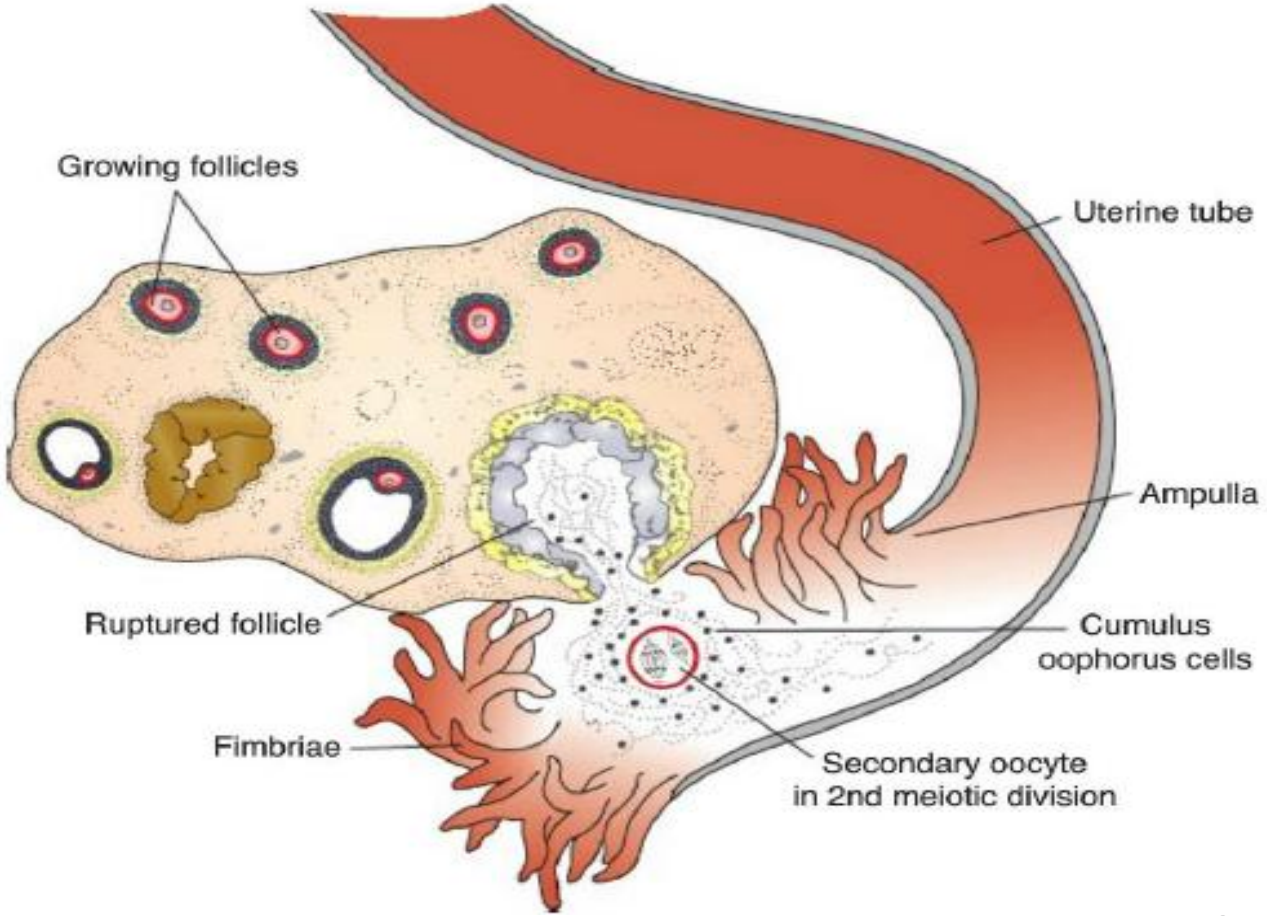
- Inhibin and activin are other hormones which are involved in pituitary gonadotrophin secretion**,** Inhibin is secreted by the granulosa cells within the ovaries. It participates in feedback to the pituitary to downregulate FSH release, and also appears to enhance ongoing androgen synthesis. Activin is structurally similar to inhibin, but has an opposite action, it is produced in granulosa cells and in the pituitary, and acts to increase FSH binding on the follicles.

Ovulation

- By the end of the follicular phase, the dominant follicle has grown to approximately 20 mm in diameter.
- Production of oestrogen increases until they reach the necessary threshold to exert a positive feedback effort on the hypothalamus and pituitary to cause the LH surge. This occurs over 24–36 hours, during which time the LH-induced luteinization of granulosa cells in the dominant follicle causes progesterone to be produced, adding further to the positive feedback for LH secretion and causing a small periovulatory rise in FSH.

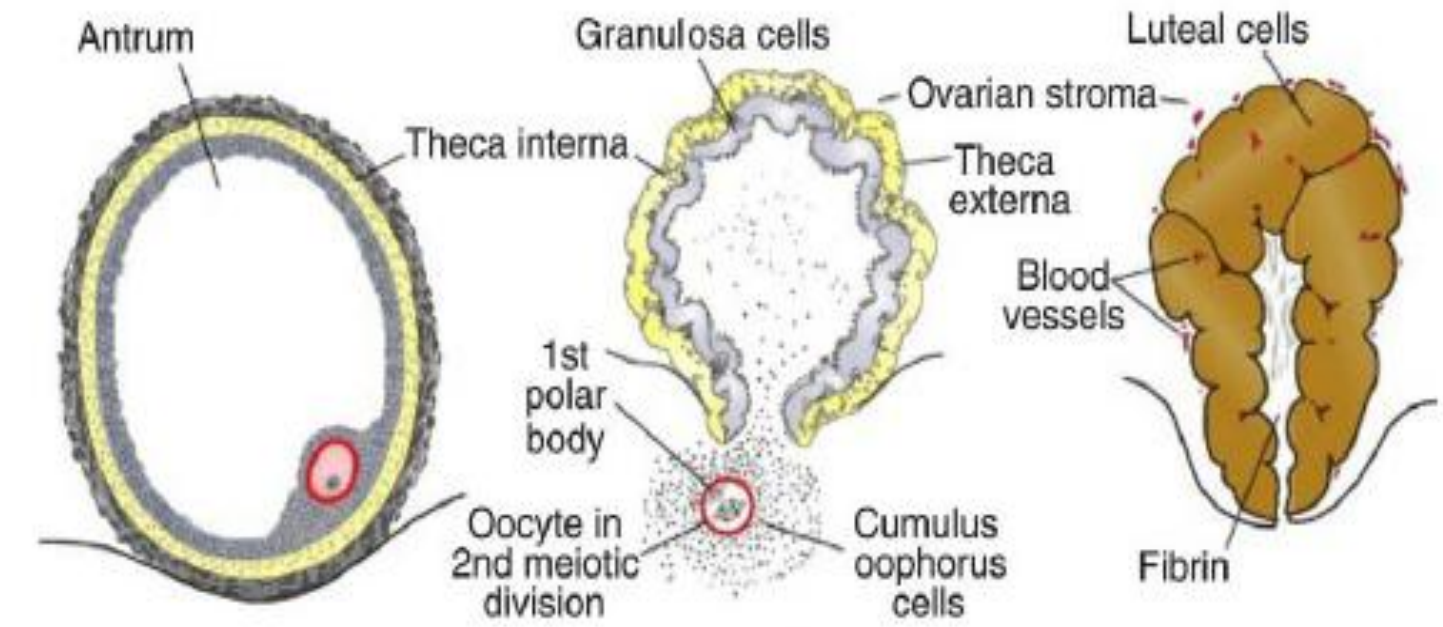
- Androgens, synthesized in the theca cells, also rise around the time of ovulation and this is thought to have an important role in stimulating libido, ensuring that sexual activity is likely to occur at the time of greatest fertility.
- The LH surge has another function in stimulating the resumption of meiosis in the oocyte just prior to its release.

- The physical ovulation of the oocyte occurs after breakdown of the follicular wall occurs under the influence of LH, FSH and progesterone controlled proteolytic enzymes, such as plasminogen activators and prostaglandins which may assist in extrusion of the oocyte.
- Studies have shown that inhibition of prostaglandin production may result in failure of ovulation. Thus, women wishing to become pregnant should be advised to avoid taking prostaglandin synthetase inhibitors, such as aspirin and ibuprofen, which may inhibit oocyte release.


Growing follicles
Uterine tube
Ampulla
Ruptured follicle
Cumulus
oophorus cells
Fimbriae
Secondary oocyte
in 2nd meiotic division

Luteal phase

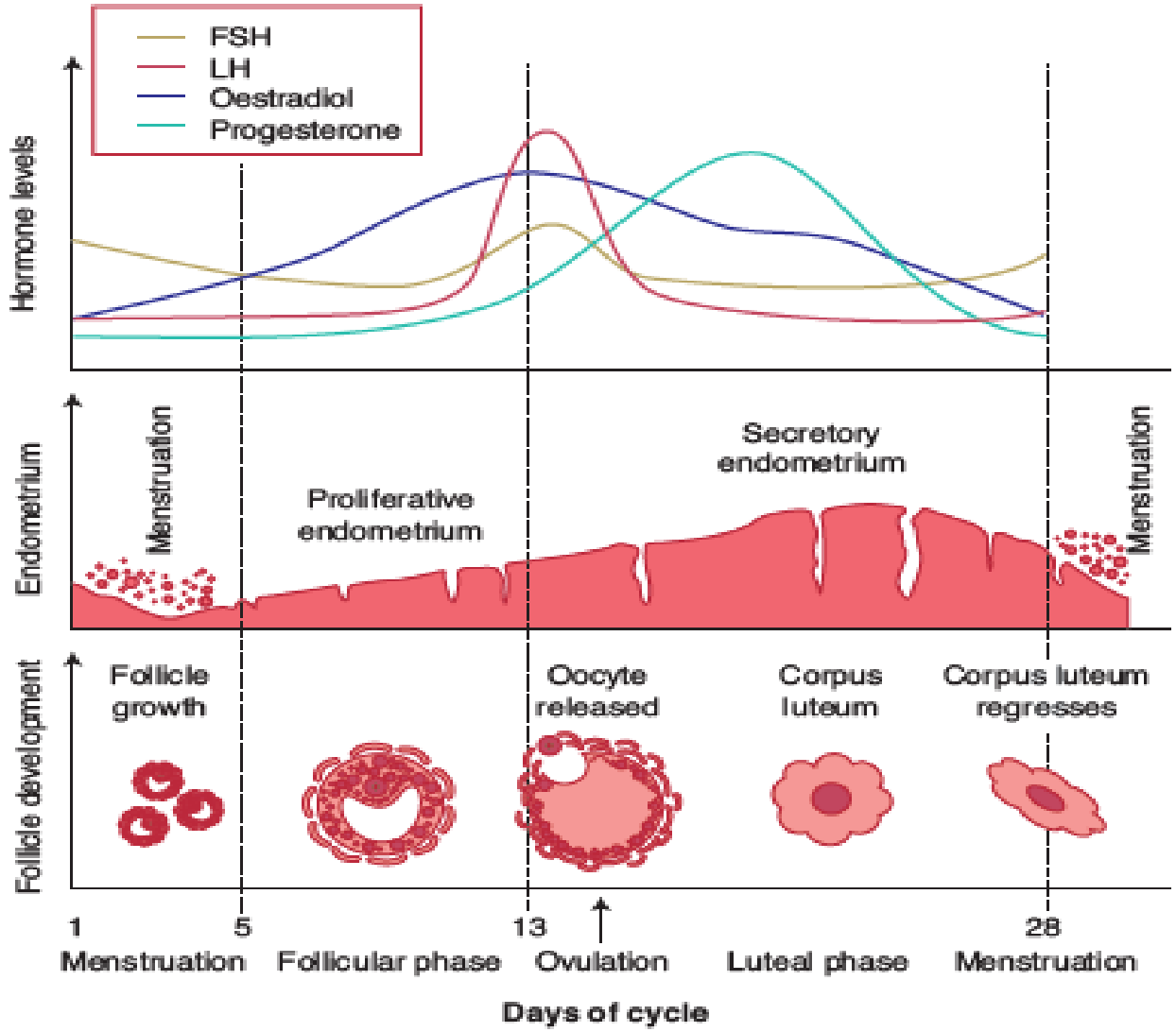
- After the release of the oocyte, the remaining granulosa and theca cells on the ovary form the corpus luteum. The granulosa cells have a vacuolated appearance with accumulated yellow pigment, hence the name corpus luteum (‘yellow body’).

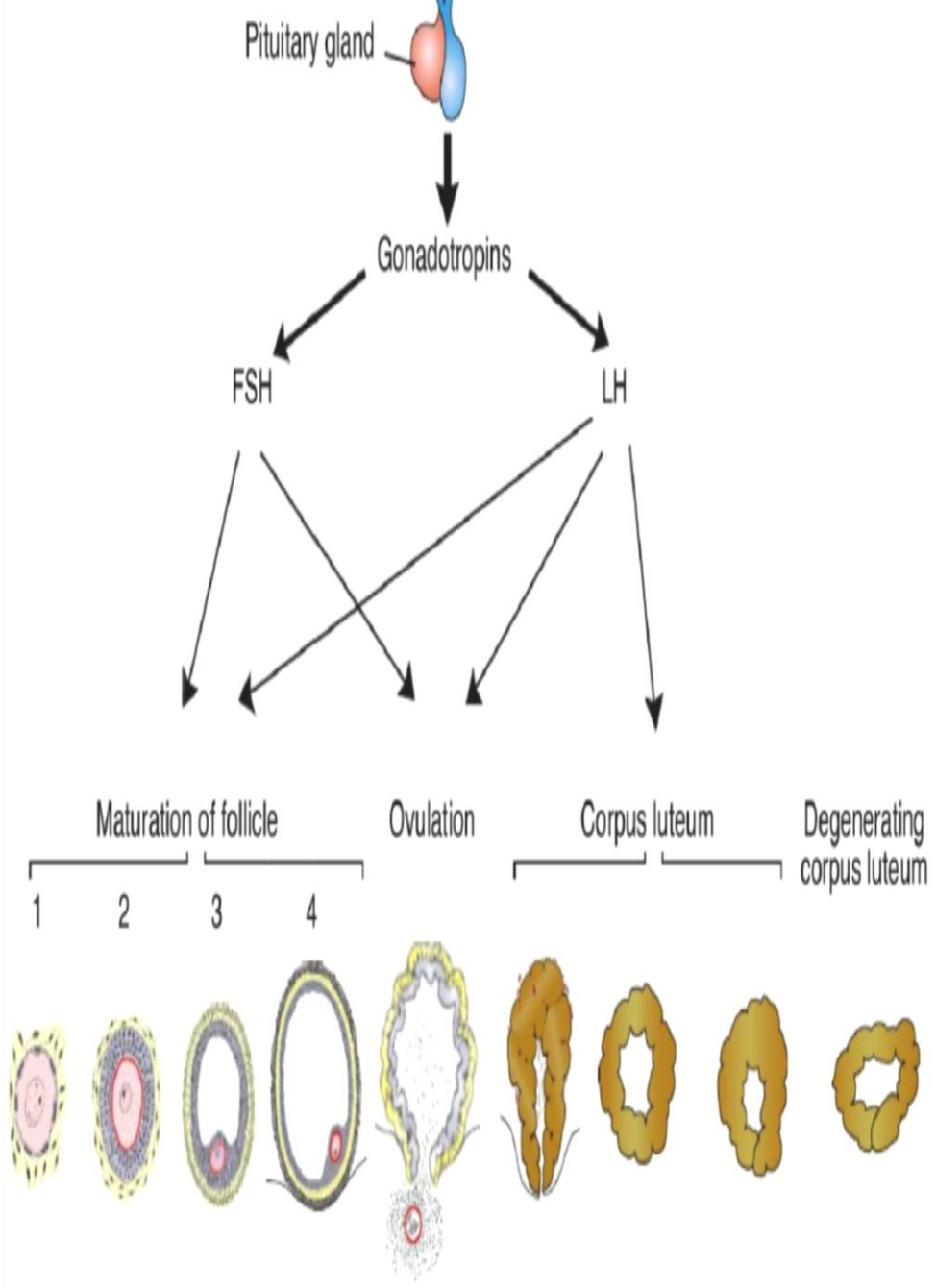

Antrum
Theca interna
Granulosa cells
Ovarian stroma
Theca externa
1st polar body
Oocyte in 2nd meiotic division
Cumulus oophorus cells
Luteal cells
Blood vessels
Fibrin
A Mature vesicular follicle
B Ovulation
C Corpus luteum

- Ongoing pituitary LH secretion and granulosa cell activity ensures a supply of progesterone which stabilizes the endometrium in preparation for pregnancy.
- Progesterone levels are at their highest in the cycle during the luteal phase. This also has the effect of suppressing FSH and LH secretion to a level that will not produce further follicular growth in the ovary during that cycle.

- The luteal phase lasts 14 days in most women, without great variation.
- In the absence of beta human chorionic gonadotrophin (bHCG) being produced from an implanting embryo, the corpus luteum will regress in a process known as luteolysis. The mature corpus luteum will gradually disappear from the ovary.

- The withdrawal of progesterone has the effect on the uterus of causing shedding of the endometrium and thus menstruation. Reduction in levels of progesterone, oestrogen and inhibin feeding back to the pituitary cause increased secretion of gonadotrophic hormones, particularly FSH, new preantral follicles begin to be stimulated and the cycle begins anew.


FSH
LH
Oestradiol
Progesterone
Hormone levels
Endometrium
Menstruation
Proliferative endometrium
Secretory endometrium
Menstruation
Follicle development
Follicle growth
Oocyte released
Corpus luteum
Corpus luteum regresses
1
5
13
28
Menstruation
Follicular phase
Ovulation
Luteal phase
Menstruation
Days of cycle



wing showing the role of the hypothalamus and pituitary gland in regulating the ovarian cycle. Under the influence of GnRH from the

Endometrium

The hormone changes effected by the HPO axis during the menstrual cycle will occur whether the uterus is present or not.

Sequential exposure of the endometrium to oestrogen and progesterone will result in cellular proliferation and differentiation, in preparation for the implantation of an embryo in the event of pregnancy, followed by regular bleeding in response to progesterone withdrawal if the corpus luteum regresses

1. Menstrual phase (Menstruation)

- Menstruation (day 1) is the shedding of the ‘dead’ endometrium and ceases as the endometrium regenerates (which normally happens by day 5–6 of the cycle).
- A fall in circulating levels of oestrogen and progesterone approximately 14 days after ovulation leads to loss of tissue fluid, vasoconstriction of spiral arterioles and distal ischemia. This results in tissue breakdown, and loss of the upper layer along with bleeding from fragments of the remaining arterioles is seen as menstrual bleeding. Enhanced fibrinolysis reduces clotting.

- The effects of oestrogen and progesterone on the endometrium can be reproduced artificially, for example in patients taking the combined oral contraceptive pill or hormone replacement therapy who experience a withdrawal bleed during their pill free week each month.
- Vaginal bleeding will cease after 5–10 days as arterioles vasoconstrict and the endometrium begins to regenerate.

- Haemostasis in the uterine endometrium is different from haemostasis elsewhere in the body as it does not involve the processes of clot formation and fibrosis.

- Prostaglandin F2α, endothelin-1 and platelet activating factor (PAF) are vasoconstrictors which are produced within the endometrium and are thought likely to be involved in vessel constriction, both initiating and controlling menstruation. They may be balanced by the effect of vasodilator agents, such as prostaglandin E2, prostacyclin (PGI) and nitric oxide (NO), which are also produced by the endometrium.

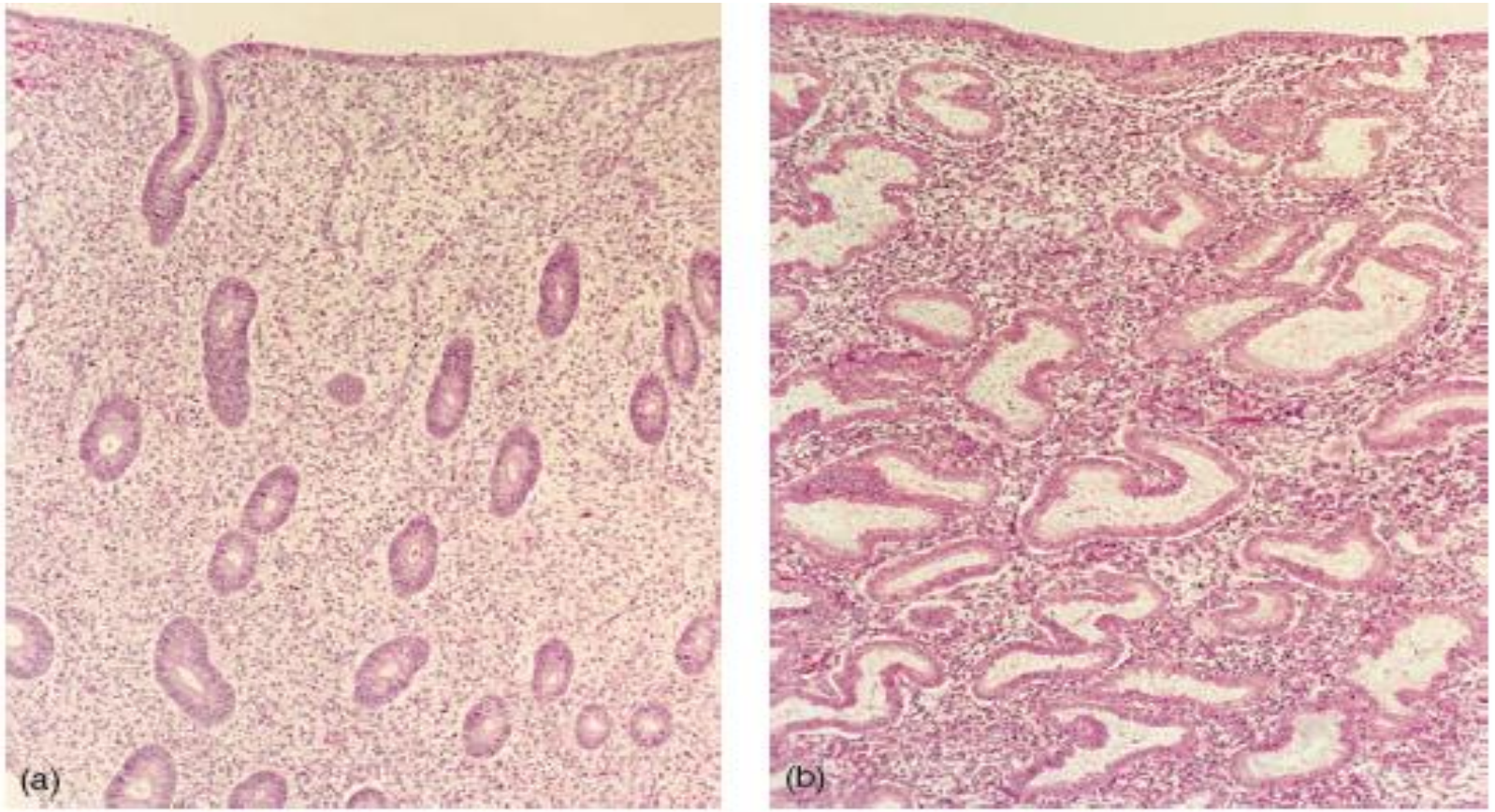
- Mefenamic acid is a PG synthetase inhibitor which is widely used as a treatment for heavy menstrual bleeding. It is believed to act by increasing the ratio of the vasoconstrictor PGF2α to the vasodilator PGE2. Mefenamic acid reduces menstrual loss by a mean value of 20–25 % in women with very heavy bleeding

2. The proliferative phase

- This phase is coinciding with follicular phase of the ovarian cycle.
- Menstruation will normally cease after 5–7 days, once endometrial repair is complete. After this time, the endometrium enters the proliferative phase, when glandular and stromal growth occur.
- The epithelium lining the endometrial glands changes from a single layer of columnar cells to a pseudostratified epithelium with frequent mitoses.
- Endometrial thickness increases rapidly, from 0.5 mm at menstruation to 3.5–5 mm at the end of the proliferative phase.

3. The secretory phase

- This phase is coinciding with the luteal phase of the ovarian cycle.
- After ovulation (generally around day 14), there is a period of endometrial glandular secretory activity. Following the progesterone surge endometrial thickness does not increase any further, however, the endometrial glands will become more tortuous, spiral arteries will grow, and fluid is secreted into glandular cells and into the uterine lumen.
- Later in the secretory phase, progesterone induces the formation of a temporary layer, known as the decidua, in the endometrial stroma. Histologically, this is seen as occurring around blood vessels. Stromal cells show increased mitotic activity, nuclear enlargement and generation of a basement membrane.


(a)
(b)

Immediately prior to menstruation, three distinct layers of endometrium can be seen.

1. **The basalis** is the lower 25 per cent of the endometrium, which will remain throughout menstruation and shows few changes during the menstrual cycle.
2. mid-portion is the stratum spongiosum with oedematous stroma and exhausted glands.
3. The superficial portion (upper 25 per cent) is the stratum compactum with prominent decidualized stromal cells.

On the withdrawal of both oestrogen and progesterone, the decidua will collapse, with vasoconstriction and relaxation of spiral arteries and shedding of the outer layers of the endometrium.

Measurement of ovarian reserve

Female reproductive potential is directly proportionate to the remaining number of oocytes in the ovaries. This number decreases from birth onwards, and the rate of loss accelerates after the age of 37 in an average healthy woman.

Markers used to calculate ovarian reserve include:

1. ultrasound measurements of ovarian volume, mean ovarian diameter and antral follicle count
2. Biochemical markers include day 3 FSH, oestradiol, inhibin B, anti-Mullerian hormone (AMH).

AMH is produced in the granulosa cells of ovarian follicles and does not change in response to gonadotrophins during the menstrual cycle. As a result, it can be measured and compared from any point in the cycle.