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اسم المحاضرة السادسة والعشرون باللغة العربية: فسلجة الدورة الشهرية

اسم المحاضرة السادسة والعشرون باللغة الإنكليزية :Physiology of menstruation

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Physiology of menstruation

Regular monthly menstruation is an obvious marker that the various levels of interaction between hypothalamus, pituitary, ovary and uterus are functional. Interruption of this axis at any point leads to disordered menses.

Understanding the regulation of ovarian and menstrual function is therefore crucial to the rational management of many gynaecological disorders. These include delayed puberty, amenorrhoea, anovulatory infertility, abnormal uterine bleeding and also ovarian stimulation in assisted reproduction treatment.

THE OVARIAN CYCLE

Gonadotrophin-independent phase:

By 12 weeks of gestation some germ cells (oogonia) start to enter into meiosis and become primary oocytes surrounded by flattened granulosa cells to form primordial follicles. The primary oocytes are arrested in the prophase stage of the first meiotic division (diploid cell). The remaining oogonia have ongoing cycles of mitosis and reach a peak number of 5–6 million at 20 weeks' gestation.

The few primary oocytes that survive are those that are surrounded by flat, spindle-shaped follicular or pregranulosa cells. This oocyte pregranulosa cell complex is enclosed by a basement lamina. At this stage of development, the primary oocyte with its surrounding single layer of pregranulosa cells is called a primordial follicle. Primordial follicles are 30–60 μm in diameter.

The first step in follicular growth is that a primordial follicle becomes a primary follicle. The primary follicle forms as the spindle cells of the primordial follicle become cuboidal cells. In addition, the oocyte enlarges. Thus, the primary follicle contains a larger primary oocyte that is surrounded by a single layer of cuboidal granulosa cells.

The secondary follicle contains a primary oocyte surrounded by several layers of cuboidal granulosa cells. The granulosa cells of a primary follicle proliferate and give rise to several layers of cells. In addition, stromal cells differentiate, surround the follicle and become the theca cells. These theca cells are on the outside of the follicle’s basement membrane.The oocyte increases in size to a diameter of about 120 μm. As the developing follicle increases in size, the number of granulosa cells increases to about 600, and the theca cells show increasing differentiation. The progression to secondary follicles also entails the formation of capillaries and an increase in the vascular supply to developing follicular units.

The increasingly abundant granulosa cells secrete fluid into the center of the follicle creating a fluid-filled space called the antrum. At this stage, the follicle is now called a tertiary follicle. In tertiary follicles, gap junctions are formed between theca and granulosa cells. In addition, tight junctions and desmosomes exist between adjacent cells. Gap junctions may also exist between the oocyte and the granulosa cells closest to the oocyte and may function as channels to transport nutrients and paracrine signals from the granulosa cells to the oocyte and vice versa. The granulosa cells closest to the oocyte also secrete a layer of mucopolysaccharides (the zona pellucida).

These stages occur independent of gonadotrophin stimulation and under the effect of local autocrine and paracrine factors such as growth differentiation factor (GDF) and anti-Müllerian hormone (AMH). The latter is produced from the granulosa cells and reaches the systemic circulation in levels proportional to the secondary follicle pool. In the absence of further gonadotrophin stimulation the secondary follicles undergo apoptosis and atresia.

This process of gonadotrophin-independent recruitment to secondary follicles and apoptosis in absence of gonadotrophins is continuous during intrauterine, pre-pubertal and reproductive life till depletion of the follicular pool at the age of menopause. Unlike spermatogenesis, the atretic follicles cannot be replenished; therefore the ovarian reserve of follicles is a finite pool. On average the number of primordial follicles is about 1–2 million at birth and decreases to about 400,000 at initiation of puberty and is less than 1000 by the age of menopause, with only about 500 oocytes destined to ovulate during a woman’s reproductive lifespan. The rate of loss of the primordial follicle pool is variable among individual females, with variable age of loss of fertility and menopause (40–55 years). It is believed that natural fertility is lost around 10 years earlier than the age of menopause (fixed-interval hypothesis). The duration of the gonadotrophin-independent phase is around 74–80 days.

Gonadotrophin-dependent phase

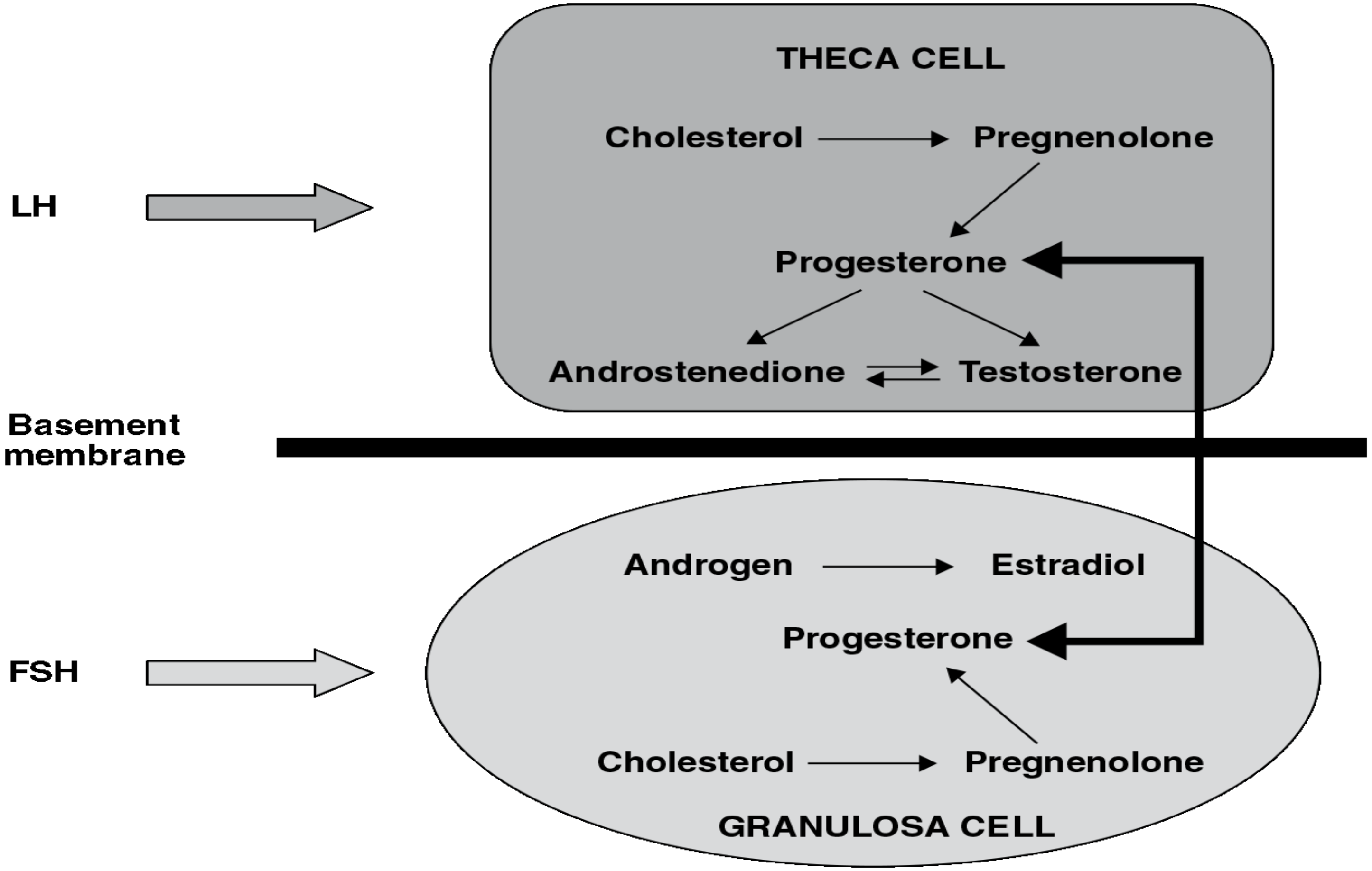
In the absence of pituitary gonadotrophins, the growing follicles in the ovary will be destined to atresia (apoptosis). The rise of pituitary gonadotrophins during the reproductive years, as a result of release of hypothalamic GnRH pulse center from pre-pubertal inhibitory signals, leads to rescue of the preantral/antral follicles.

The number of rescued and recruited follicles depends on the pool of secondary follicles available at the time of the rise of FSH, which is indirectly related to the total pool of primordial follicles in the ovary (ovarian reserve). It also depends on the level of FSH and duration of rise (**selection window**).

A critical step of this rescue process is the induction of aromatase enzyme activity in the granulosa cells which converts the androgens synthesised in the theca cells into oestrogen under the effect of LH.

Therefore the two gonadotrophins, FSH and LH, act preferentially on the two main steroid-producing cells (granulosa and theca cells) in the ovary. The main effect of FSH is the rescue of granulosa cells (and oocytes) from atresia and induction of aromatase activity. The main role of LH is the stimulation of steroidogenesis by acting on theca cells to synthesise androgenic substrates that are converted into oestrogens in the granulosa cells. This is called **the two cell, two gonadotrophins theory**. The effect of this synchronised action of FSH and LH is conversion of the microenvironment of the secondary pre-antral follicles from one dominated by androgens into one dominated by oestrogens.

The two cell, two gonadotrophins theory



The effect of the latter is further proliferation of the granulosa and theca cells with accelerated production of oestrogen and peptide hormones (inhibins, activin, follistatin) and formation of a cavity (antrum) in which the oocyte is surrounded by a few layers of granulosa cells projecting into the cavity.The follicular cavity fluid contains a myriad of growth factors and signalling molecules involved in bidirectional communication between the oocyte and surrounding granulosa.

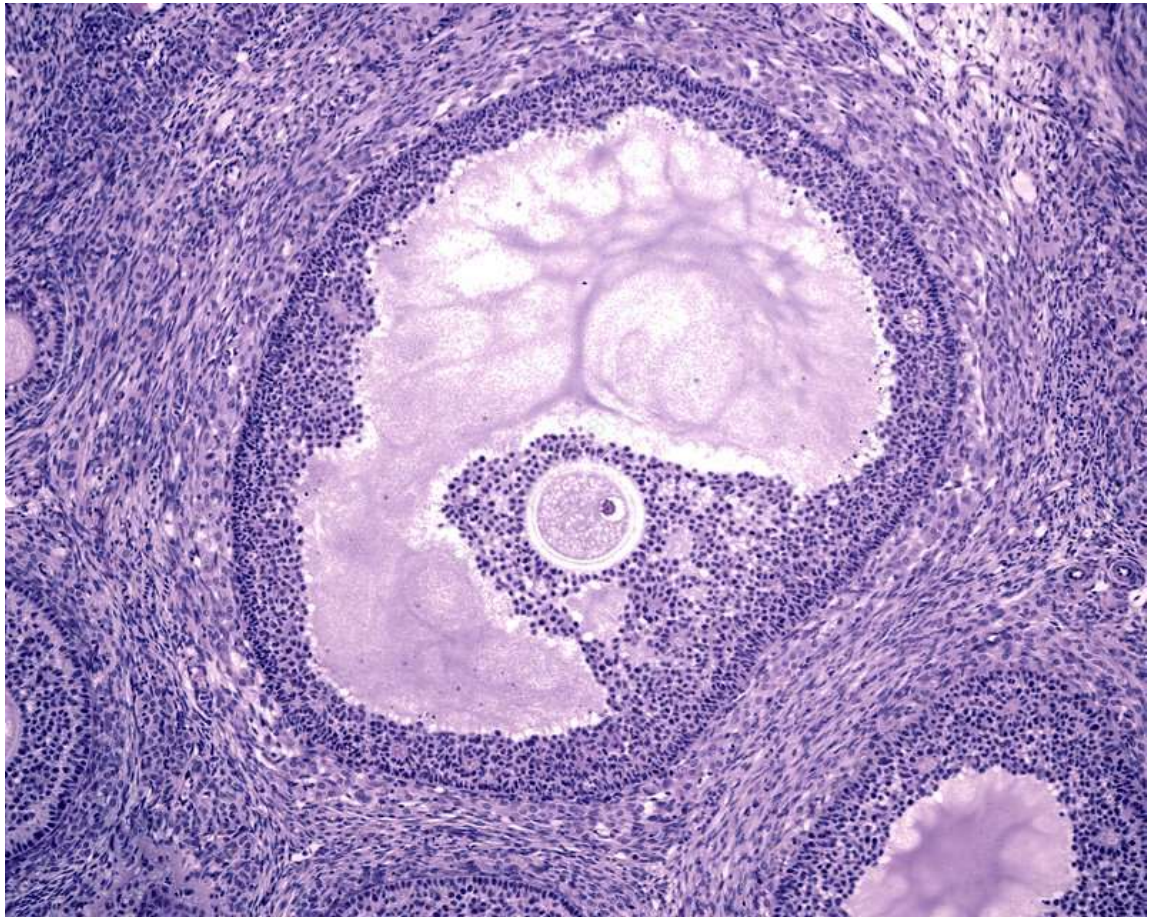
The dominant follicle

In the mid-follicular phase (usually on day 7–8 of a 28-day cycle) selection of a dominant follicle (which is usually over 10 mm in diameter at that stage) occurs by the effect of rising oestrogen and inhibin A levels produced by actively growing follicles. This results in a negative feedback effect on the pituitary gonadotrophin (FSH/LH) secretion, and starvation of most of the follicles of the necessary FSH to support granulosa cell proliferation and aromatase activity. The dominant follicle expands in size with an exponential rise of oestradiol levels.

This further accentuates the decline in FSH levels and leads to atresia of the rest of the follicles. In natural cycles selection of a single dominant follicle and monofollicular ovulation is the rule, whilst in ovarian stimulation cycles the prolonged exogenous FSH stimulation leads to support and survival of more than one follicle.

The dominant follicle accumulates more fluid in the follicular cavity and its granulosa cells become organized into three compartments: mural granulosa cells surrounding the antrum; cumulus oophorus (which is a stalk of granulosa cells connecting the oocyte to the mural granulosa); and corona radiata (which is a layer of granulosa cells in direct contact with the oocyte). The oocyte with its surrounding corona radiata and cumulus oophorus are bathed within follicular cavity fluid. The latter separates it from the mural granulosa and outer theca cells. The follicle is now is known as the pre-ovulatory or Graafian follicle. The Graafian follicle continues to produce oestrogen, independent of FSH stimulation, and has the highest number of granulosa cells and oestradiol levels with the lowest androgen-to-oestrogen ratio. This follicle also develops LH receptors in the granulosa cells, which helps with maturation of the oocyte and prepares the follicle for the ovulatory stimulus of the LH surge. The LH receptors also ensure adequate progesterone production by the luteinised granulosa cells from the corpus luteum after ovulation.

Light micrograph of a section through a mature Graafian follicle.



Ovulation

When the estradiol (E2) levels peak to 300–400 pg/ml (500–900 pmol/L) (which usually coincides with a follicle size of 18–20 mm), the pituitary gland responds by a surge of LH levels to about 15–30 IU/L. This leads to a cascade of changes in the Graafian follicle and leads to ovulation within 36 hours (34–39 hours) of the onset of the LH surge.

The LH surge initiates the following changes in the Graafian follicle and ovary:

1 Resumption of meiosis in the oocyte with extrusion of the first polar body (the oocyte becomes haploid), and the oocyte becomes arrested into the metaphase of the second meiotic division which is completed at fertilisation with extrusion of second polar body.

2 Induction of angiogenesis and increased vascularity and capillary permeability in the theca cell layers with increased production of follicular fluid and increase in intrafollicular pressure.

3 Synthesis and secretion of various prostaglandins that help increase blood flow in the follicular wall and stimulate smooth muscle cells within the ovarian stroma that help expel the oocyte.

4 Activation of matrix metalloproteinases and other proteolytic enzymes that digest the follicular wall and ovarian capsule at the site of the follicle to facilitate follicular rupture and oocyte release the i.e. ovulation.

5 LH stimulates progesterone synthesis by the granulosa and theca cells shortly before ovulation. This further accentuates the LH surge and ensures adequate luteinisation of the theca and granulosa cells and adequate corpus luteum function later.

The resulting effect of these changes is follicular wall rupture with release of follicular fluid and the oocyte and its surrounding cumulus cells. This is usually picked up by the fimbrial end of the tube, and is transported to the ampullary part of the fallopian tube where fertilisation may occur.

In a regular 28-day cycle the gonadotrophin-dependent phase (follicular phase of the ovarian cycle) lasts about 14 days. However, this is variable amongst individuals and leads to variable lengths of the follicular phase and subsequent variable menstrual cycle lengths as the corpus luteum lifespan is nearly fixed at about 14 days. The timing of ovulation is therefore difficult to predict prospectively; however a fertile period when ovulation is likely to occur can be predicted using the woman's menstrual history and cycle lengths.[3,]

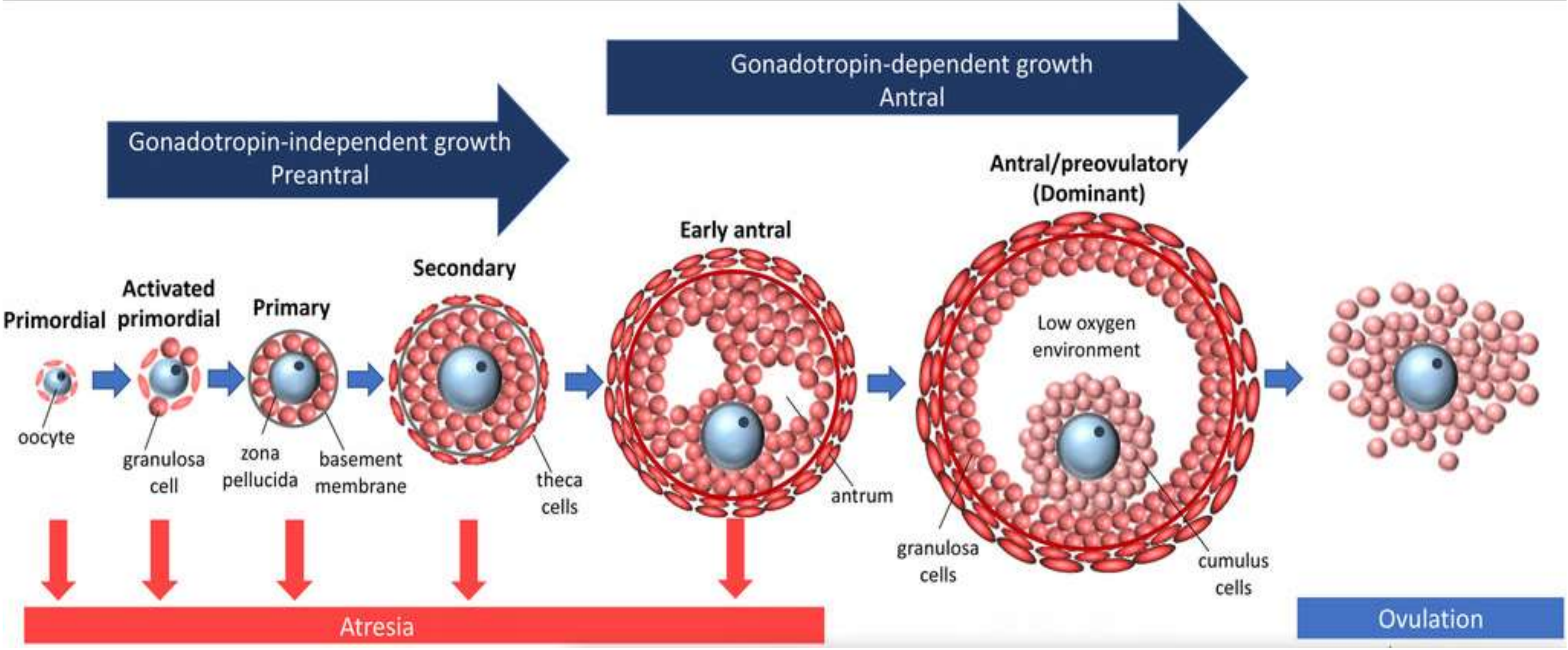
The luteal phase

After the release of the oocyte–cumulus complex the follicular antrum is filled with blood and new blood vessels forms. The theca–lutein cells become full of cholesterol (luteinised) and the resulting structure is called a corpus luteum. The corpus luteum produces oestrogen, progesterone (P4) and inhibin A in response to LH pulses. These in turn suppress FSH and LH secretion by the pituitary. In the face of declining FSH and LH levels the corpus luteum functions for only about 10 days, with peak activity at about 7 days after ovulation (mid-luteal peak of progesterone on day 21 of a 28-day cycle).

It then enters into an apoptosis and regression phase of about 4 days if pregnancy does not occur. In the absence of pregnancy, the corpus luteum has a fairly predictable life span of 14 days. The falling oestradiol and progesterone levels lead to apoptosis and shedding of the endometrium. The falling ovarian steroid levels release the hypothalamus and pituitary from the negative feedback effect, with a subsequent increase in FSH levels and ensuring a new cycle of recruitment of secondary follicles. The luteo-follicular transition phase is characterised by increasing FSH levels, low oestradiol and progesterone levels and high inhibin B secreted by the granulosa cells of recruited follicles.

[3,4]

If pregnancy occurs the hCG produced by the trophoblast of the implanting embryo rescues the corpus luteum from apoptosis and atresia, enabling the corpus luteum to function and produce progesterone till 10–12 weeks' gestation when the placenta takes over this function.


Gonadotropin-independent growth
Preantral
Gonadotropin-dependent growth
Antral
Primordial
Activated primordial
Primary
Secondary
Early antral
Antral/preovulatory (Dominant)
oocyte
granulosa cell
zona pellucida
basement membrane
theca cells
antrum
Low oxygen environment
granulosa cells
cumulus cells
Atresia
Ovulation

THE MENSTRUAL CYCLE

The endometrium undergoes cyclic changes which mirror the effect of the hormones produced by the growing follicles and corpus luteum in the ovary.

In the early follicular phase the endometrium is rebuilt from the basalis layer after its superficial layer has been shed in the menses of the previous cycle. The prevailing oestradiol secreted from the ovary leads to active mitosis and proliferation of the endometrial glands and stroma. This leads to an increase in the thickness of the endometrium from 2–3 mm to about 6–8 mm by the end of this **proliferative phase**.

Following ovulation the prevailing progesterone hormone leads to more functional maturation of the endometrial glands and decidualisation of the endometrial stroma. Histologically these changes are reflected in enlarged tortuous endometrial glands that are full of secretions; hence this phase is called the **secretory phase**. The stroma appears oedematous with an increased number and coiling of the spiral arteries and pericapillary leukocytic and cellular infiltrates, a process called decidualisation. The effect of the epithelial changes is secretion of adhesion molecules, such as integrins and glycodelins, which mediate the attachment of the blastocyst (in the case of successful fertilisation) that initiates the implantation process.

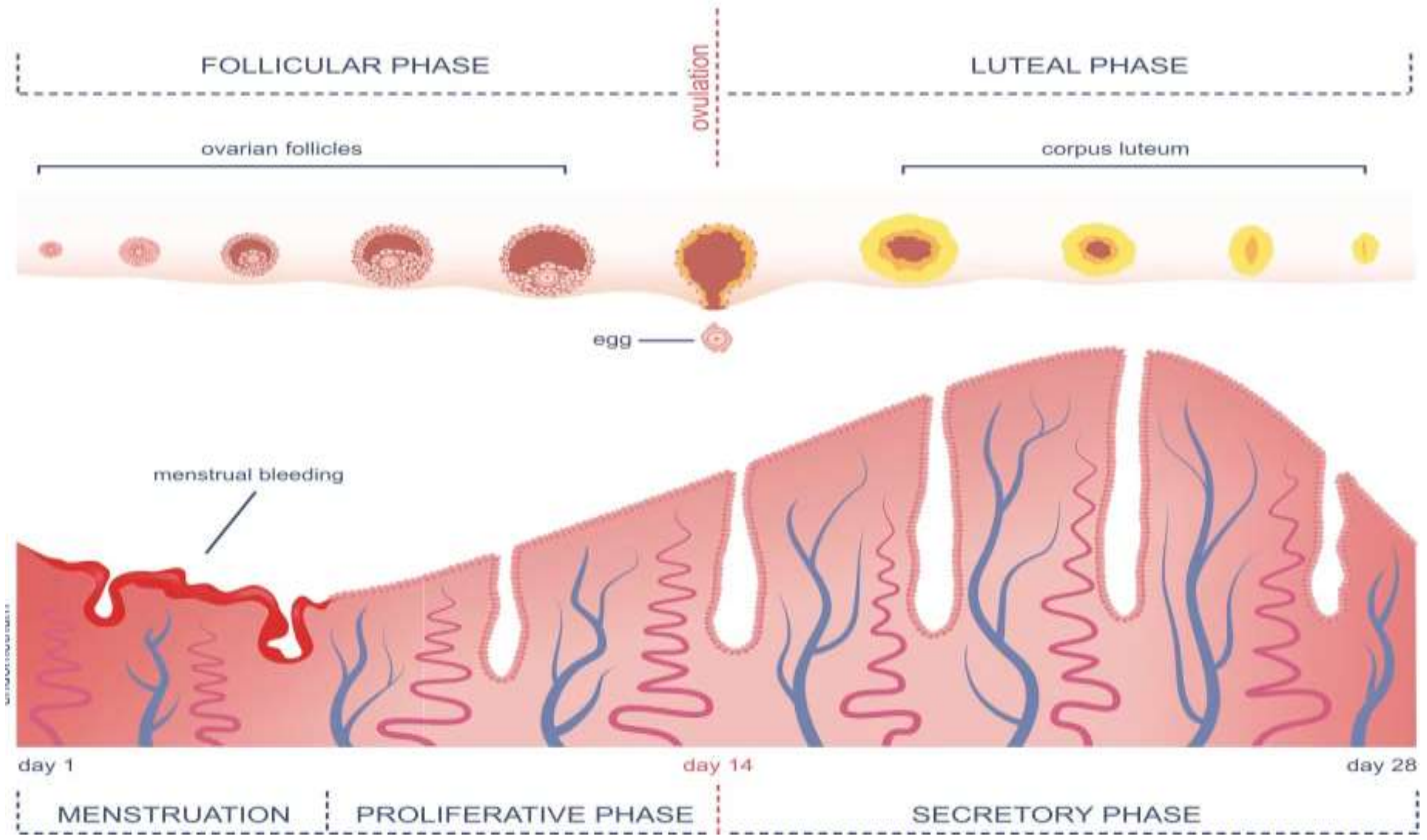
The effect of stromal decidualisation is recruitment of immunological cells (natural killer cells, dendritic cells) that help regulate the trophoblastic invasion and effect changes in the spiral arteries that lead to the development of the early placenta. The peak of secretory changes in the endometrium is 7–9 days after ovulation when the endometrium is most receptive to implantation of the blastocyst, the so called **implantation window**.

If fertilisation occurs and a blastocyst successfully implants in the endometrium the trophoblast of the implanting embryo secretes hCG which rescues the corpus luteum.

This prolongs the lifespan of the corpus luteum and maintains progesterone secretion till about 10 weeks' gestation when the developing placenta takes over the hormonal production (luteo-placental shift). As a result of maintenance of oestrogen and progesterone production and stability of the decidua, pregnant women will experience the physiological amenorrhoea of pregnancy.

If there was no fertilisation or a blastocyst could not successfully implant then the declining corpus luteum function (starting around day 10–12 after ovulation and almost complete by day 14) is associated with falling oestrogen and progesterone levels. This in turn initiates apoptosis in the endometrium with release of prostaglandins and lysosomal enzymes from the cells, setting waves of vasoconstriction leading to ischaemia.

There is further breakdown of blood vessels and cells followed by vasodilatation, with escape of blood cells (erythrocytes, leukocytes, platelets) as well as various proteolytic enzymes (metalloproteinases, enkephalinases, fibrinolysins) into the endometrial stroma. The effect of these waves of vasoconstriction and vasodilatation with apoptosis and proteolysis culminates into endometrial sloughing at the junction of superficial and basal layers forming the menstrual bleeding. In concert with these changes the released prostaglandins from the endometrium, as well as the myometrial cells under the effect of falling progesterone levels, lead to myometrial contractions. This leads to expulsion of the menstrual blood from the uterus.


FOLLICULAR PHASE
ovulation
LUTEAL PHASE
ovarian follicles
corpus luteum
egg
menstrual bleeding
day 1
day 14
day 28
MENSTRUATION
PROLIFERATIVE PHASE
SECRETORY PHASE

A normal menstrual phase is expected to last 2–6 days and the amount of bleeding is generally 20–80 ml. The rising oestradiol level caused by the recruited follicles leads to rapid repair and rebuilding of the endometrium and the end of the menstrual phase.

Menstrual bleeding in ovulatory cycles (oestrogen/ progesterone withdrawal bleeding) is characterised by being synchronised and less prolonged and associated with menstrual cramps due to higher levels of prostaglandins, while in anovulatory dysfunctional menses are usually prolonged, erratic, heavy and painless.

Thank you