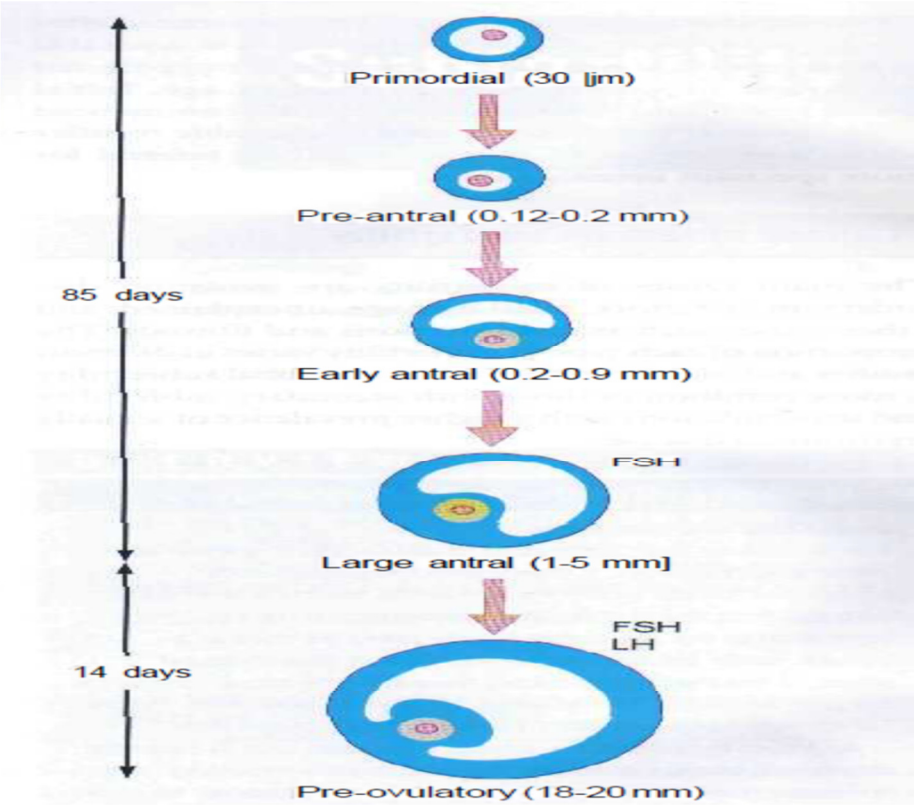
Physiology of female reproductive organs

Menstrual cycle in the female reflects the physiological change of her reproductive organs.The most obvious manifestation of the normal menstrual cycle is the presence of regular menstrual periods.These occur as the endometrium is shed following failure of implantation or fertilization of the oocyte.Menstruation is initiated in response to changes in steroids produced by the ovaries, which themselves are controlled by the pituitary and hypothalamus.

Oogenesis: The formation and maturation of an oocyte.It starts with the growth of a primordial follicle to form a pre-antral follicle and ends with the final maturation of a pre-ovulation follicle.The formation of the pre-antral follicle takes 85 days in a human. The final maturation stage (the follicular phase of the menstrual cycle) from the pre-antral follicle to the pre-ovulatory follicle takes 14 days to complete.

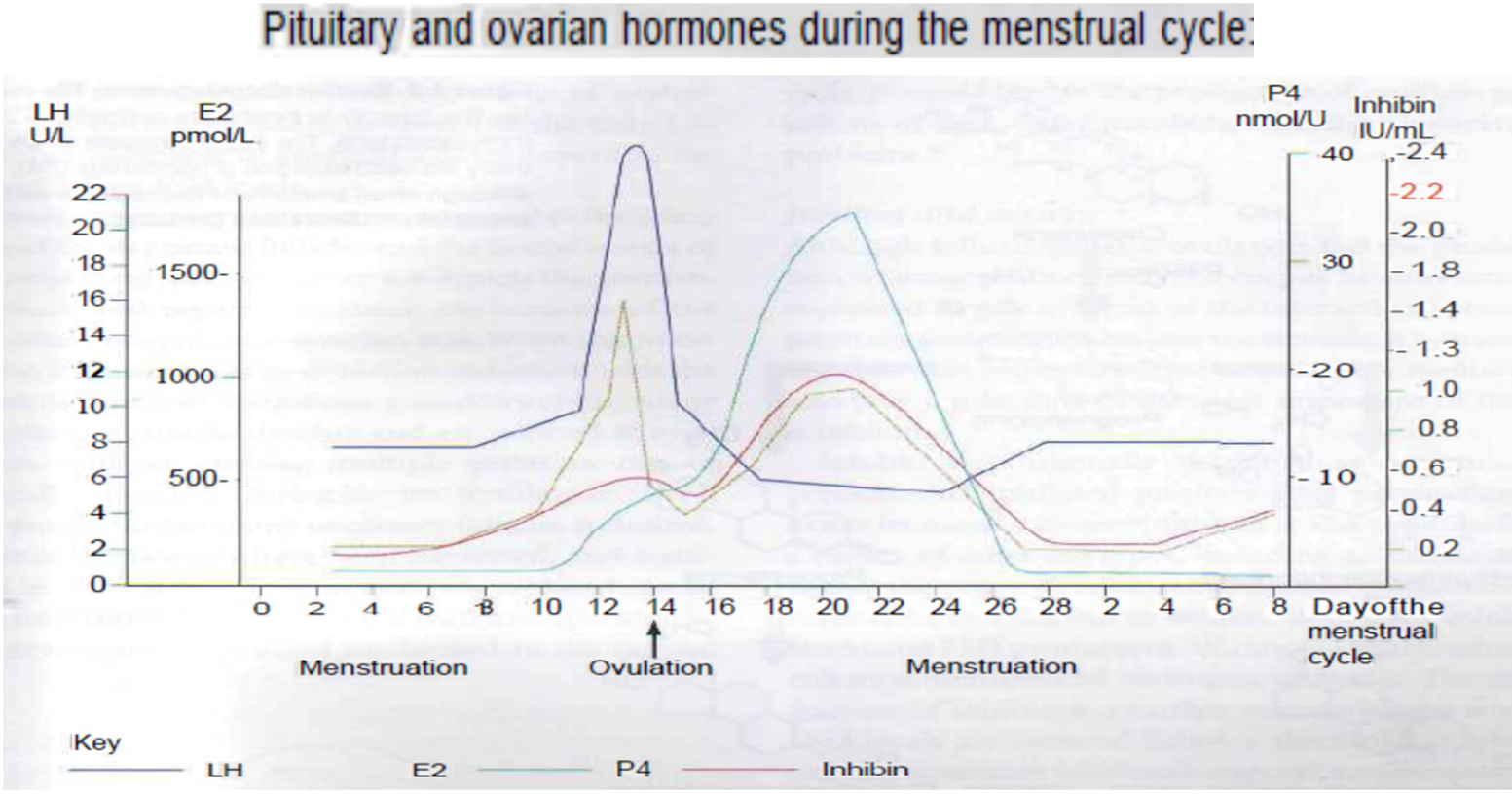


Ovarian folliciilogenesis

The physiological changes of the ovaries:

Within the ovary, the menstrual cycle can be dividedinto three phases:

1. the follicular phase 2. ovulation 3. the luteal phase.



1-Follicular phase:

The development of the oocyte is the key event.The ovary contains thousands of primordial follicles that are in a continuous state of development from birth, through periods of anovulation, such as pregnancy, to the menopause. These initial stages of follicular development are independent of hormonal stimulation. In the absence

of the correct hormonal stimulus, however, follicular development fails at the pre-antral stage, with ensuing follicular atresia.Development beyond the pre-antral stage is stimulated by the pituitary hormones (luteinizing hormone [LH] and follicle stimulating hormone [FSH]), which can be considered as key regulators of oocyte development.At the start of the menstrual cycle, FSH levels begin to rise as the pituitary is released from the negative feedback effects of progesterone, oestrogen and inhibin.Rising FSH levels rescue a cohort of follicles from atresia, and initiate steroidogenesis

Steroidogenesis

The basis of hormonal activity in pre-antral to pre-ovulatory follicles is described as the 'two cell,two gonadotrophin' hypothesis. Steroidogenesis is compartmentalized in the two cell types within the follicle: the theca and granulosa cells; these cells are responsive to the gonadotrophins LH and FSH respectively.Within the theca cells, LH stimulates the production of androgens from cholesterol. Within the granulosa cells, FSH stimulates the conversion of thecally derived androgens to oestrogens (aromatization) .FSH is also responsible for the proliferation of granulosa cells.

Selection of the dominant follicle:

Is the result of complex signalling between the ovary and the pituitary.The dominant follicle is the largest and most developed follicle in the ovary at the mid-follicular phase.Such a follicle has the most efficient aromatase activity and the highest concentration of FSH-

induced LH receptors.Therefore produces the greatest amount of oestradiol and inhibin. Inhibin further amplifies LH-induced androgen synthesis, which is used as a substrate for oestradiolsynthesis.These features mean that the largest follicle therefore requires the lowest levels of FSH (and LH) for continued development.

Inhibin: was originally described as a testicular product that inhibited pituitary FSH production hence its name.However, inhibin is also produced by a variety of other cell types, including granulosa cells within the ovary; production is stimulated by FSH . In women, as in men, inhibin attenuates FSH production. Within the ovary, inhibin enhances LH-induced androgen synthesis. The production of inhibin is a further mechanism by which FSH levels are reduced below a threshold at which only the dominant follicle can respond, ensuring atresia of the remaining follicles.

Activin :is a peptide that that is structurally related to inhibin.It is produced both by the granulosa cells of antral follicles and by the pituitary gland.The action is almost directly opposite to that of inhibin in that it augments pituitary FSH secretion and increases FSH binding to granulosa cells. Granulosa cell activin production therefore appears to amplify the effects of FSH within the ovarian follicle.

Insulin-like growth factors (IGF):(IGF-1 and IGF-II) act as paracrine regulators.Follicular fluid levels increase towards ovulation, with the highest level found in the dominant follicle.In the follicular phase, IGF-1 is produced by theca cells under the action of LH.Within the theca &granulosa cells, IGF-I augments LH-induced steroidogenesis, stimulatory effects of FSH on mitosis, aromatase activity and inhibin production. In the pre-ovulatory follicle, IGF-I enhances LH-induced

progesterone production from granulosa cells. Following ovulation, IGF-II is produced from luteinized granulosacells,acts in an autocrine manner to augment LH-induced proliferation of granulosa cells.

2-Ovulation:

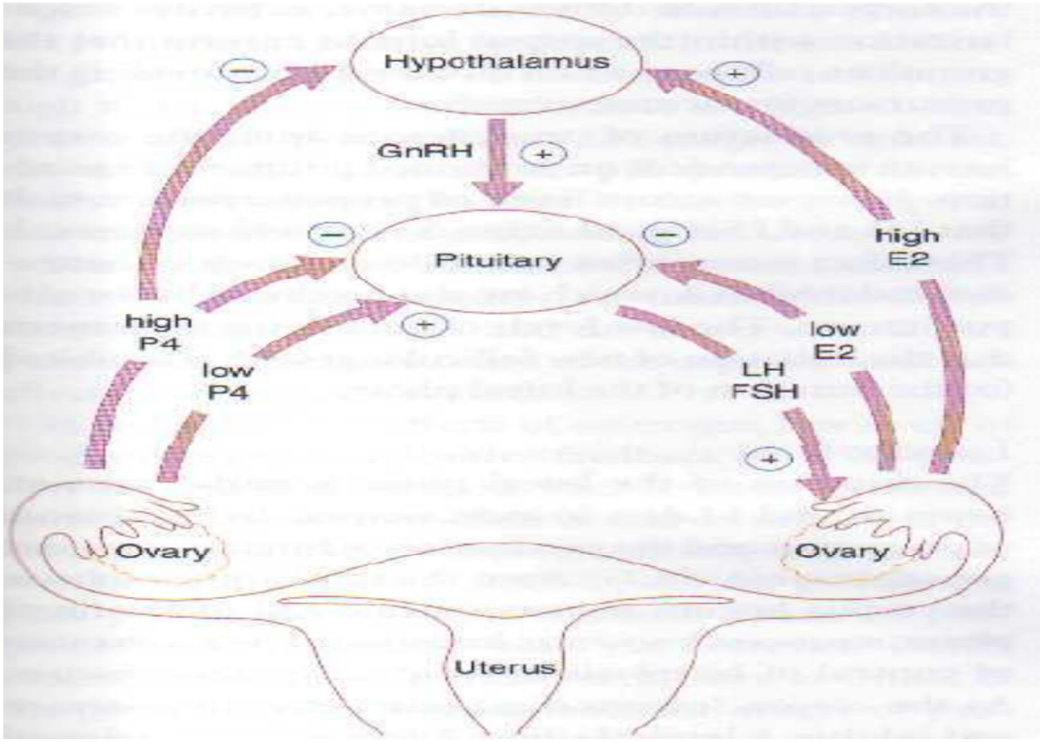
Late in the follicular phase, FSH induces LH receptors on granulosa cells.Oestrogen is an obligatory co-factor in this effect. As the dominant follicle develops further, follicular oestrogen production increases. Thus the production of oestrogen is sufficient for it to reach the threshold required to exert a positive-feedback effect on pituitary LH secretion. LH levels increase, at first quite slowly (day 8 to day 12 of the menstrual cycle) and then more rapidly (day 12 onwards).During this time, LH induces luteinization of granulosa cells in the dominant follicle, so that progesterone is produced. Progesterone further amplifies the positive-feedback effect of oestrogen on pituitary LH secretion, leading to a surge of LH.Ovulation occurs 36 hours after the onset of the LH surge. The peri-ovulatory FSH surge is probably induced by the positive-feedback effects of progesterone.In addition to the rise in LH, FSH and oestrogen that occurs around ovulation, a rise in serum androgcn levels also occurs.

3-Luteal phase:

Is characterized by the production of progesterone from the corpus luteum within the ovary.The corpus luteum is derived both from the granulosa cells that remain after ovulation and from some of the theca

cells that differentiate to become theca lutein cells.The granulosa cells of the corpus luteum have a vacuolated appearance associated with the accumulation of a yellow pigment, lutein, from where the corpus luteum derives its name.The production of progesterone from the corpus luteum is dependent on continued pituitary LH secretion.However, serum levels of progesterone are such that LH and FSH production is relatively suppressed.This effect is amplified by moderate levels of oestradiol and inhibin A, which are also produced by the corpusluteum. The low levels of gonadotrophins mean that the initiation of new follicular growth is inhibited for the duration of the luteal phase.The duration of the luteal phase is fairly constant, being around 14 days in most women.At the end of the luteal phase, in the absence of pregnancy, the corpus luteum regresses (luteolysis) that is controled by an obscure mechanism.

Hypothalamo-pituitary-ovanan axis showing positive and negative feedback of hormones



The hypothalamo-pituitary-ovarian axis:

The ovary, pitutary&the hypothlamus act in concerntto ensure the growth and development of (ideally) one ovarian follicle, and to maintain hormonal support of the endometrium to allow implantation.The output of LH and FSH from the pituitary gland is stimulated by pulses of gonadotrophin-releasing hormone (GnRH) produced by the hypothalamus and transported to the pituitary in the portal circulation.Production of GnRH has an effect alterations in the amplitude and frequency of GnRH pulsation throughout the cycle that are responsible for some fine tuning of gonadotrophin production.When GnRH production is suppressed as in anorexia nervosa and excessive exrecise there will anovulation &amenorrhea.The response of the pituitary is not constant, but is modulated by ovarian hormones, particularly oestrogen and progesterone.Low levels of oestrogen have an inhibitor effect on LH (negative feedback), whereas high levels of oestrogen actually stimulate pituitary LH production (positive feedback).In the late follicular phase, serum levels of oestrogen are sufficiently high that a positive-feedback effect is triggered, thus generating the peri-ovulatory LH surge.The mechanism of action of the positive-feedback effect of oestrogen involves an increase in GnRH receptor concentrations and an increase in GnRH production.The mechanism of the negative-feedback effect of oestrogen is uncertain.Low levels of progesterone prior to ovulation have a positive-feedback effect on pitutary LH and FSH secretion and contribute to the LH surge. High levels of progesterone (luteal phase) inhibit pituitary gonadotrophin production.Negative-feedback effects of progesterone are generated both via decreased GnRH production and via decreased sensitivity to GnRH at the pituitary

level.Positive-feedback effects of progeteroneoperate at the pituitary level only and involve increased sensitivity to GnRH.

The physiological changes in the endometrium:

1-Menstruation:

As the corpus luteum dies at the end of the luteal phase, circulating levels of oestrogen and progesterone fall precipitously.In an ovulatory cycle, where the endumetrium is exposed to oestrogen and then progesterone in an orderly manner, the endometrium becomes 'decidualized' during the second half of the cycle to allow implantation of the embryo.Decidualizalion is an irreversible process, and if implantation does not occur, programmed cell death (apoptosis) ensues.Menstruation is the shedding of the 'dead' endometrium and ceases as the endometrium regenerates.

Withdrawal of progesterone has several main effects:-

1-intense endometrial spiral artery vasoconstriction is generated indirectly and generated by locally produced prostaglandins, endothelins and angiotensin II.

2- production of pro-inflammatory cytokines such as MCP-1, IL-8 and cyclo-oxygenase-2 (which produces prostaglandins).

The above events lead to:

1-ischaemia (particularly of the upper endometrium) and tissue damage

2- shedding of the functional endometrium (the stratum compactum and stratum spongiosum)

3- bleeding from fragments of arterioles remaining in the basal endometrium.

Menstruation ceases as the damaged spiral arteries vasoconstrict and the endometrium regenerates. Vasoconstriction is the mechanism by which haemostasis is initially secured in the endometrium .Normally, bleeding from a damaged vessel is stemmed by platelet accumulation, fibrin deposition and platelet degranulation that lead to scarring in the endometrium, scarring would significantly inhibit function (as seen in Asherman's syndrome).Scarring is minimized by enhanced fibrinolysis, which breaks down blood dots. Later, repair of the endometrium and new blood vessel formation (angiogenesis) lead to the complete cessation of bleeding within 5-7 days from the start of the menstrual cycle.Endometrial repair involves both glandular and stromal regeneration and angiogenesis.

Proliferative/follicular phase:

Once endometrial repair is completed, usually at around day 5-6 of the cycle, menstruation ceases.Within the endometrium, the remainder of the follicular phase is characterized by glandular and stromal growth - hence the name the proliferative phase.The epithelium lining the endometrial glands changes from a single layer of low columnar cells to pseudostratiffed epithelium withfrequent mitoses.The endometrial thickness increase from 0.5mm at menstruation to 3.5-5 mm at the end of the proliferative phase.

The secretory/luteal phase:

Is characterized by endometrial glandular secretory activity - hence the name the secretory phase. Under the action of progesterone, oestrogen-induced cellular proliferation is inhibited, and the depth of the endometrium remains fixed. Some elements continue to grow, leading to increased tortuosity of both the glands and spiral arteries in order to fit into the endometrial layer. Peak secretory activity' occurs at the time of implantation, 7 days after the gonadotrophin surge.Progesterone is essential for the induction of endometrial secretory changes and these changes are only seen after ovulation in the absence of exogenous steroid therapy.In the late secretory phase, progesterone inducts irreversible decidualization of the stroma. Histologically, decidualization is initiated around blood vessels.The surrounding stromal cells display increased mitotic activity and nuclear enlargement and a basement membrane is generated.Immediately prior to menstruation, three distinct zones of the endometriurn can be seen:

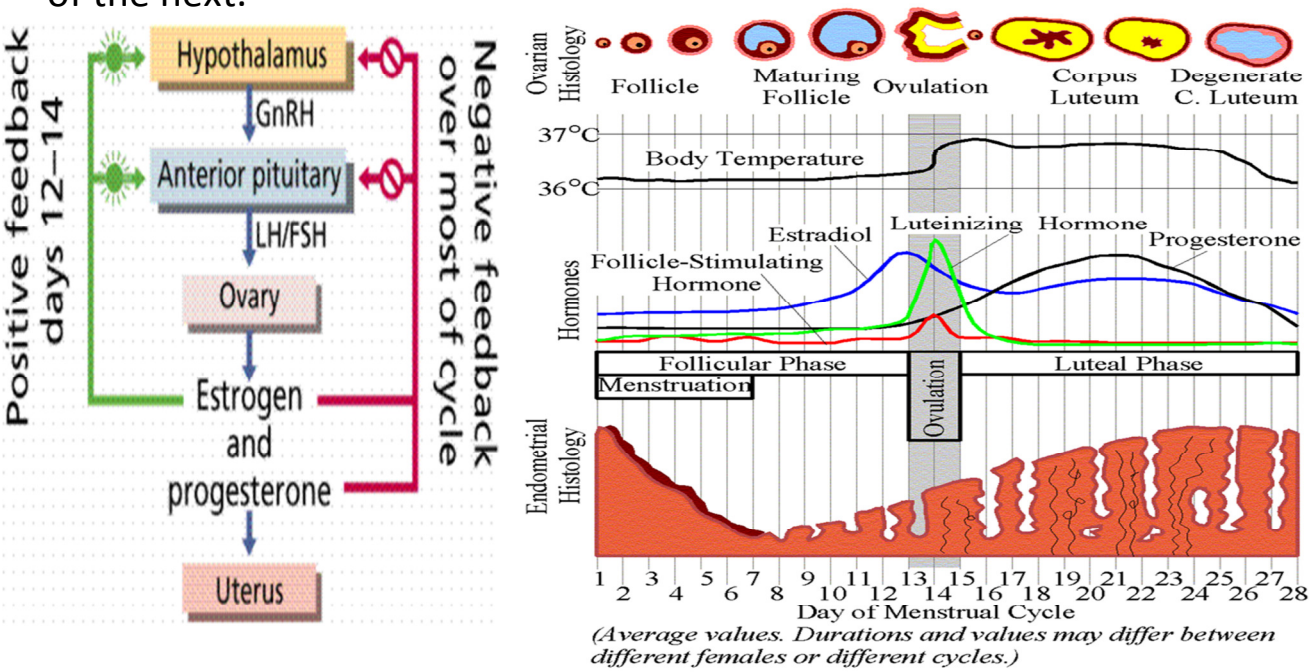
1-The basalis 2-Stratum spongiosum 3-Stratum compactum

The basalis is the basal 25 per cent of the endometriurn, which is retained during menstruation and shows few changes during the menstrual cycle.

Stratum spongiosumis is the mid-portion, with oedematousstroma and exhausted glands.

Stratum compactum the superficial portion (the uppermost 25 per cent) is the, with prominent decidualized stromal cells.The withdrawal of oestrogen and progesterone leads to collapse of the decidualized

endometrium, repeated vasoconstriction and relaxation of the spiral arteritiles, and consequent shedding of the endometrium.The onset of menstruation heralds the end of one menstrual cycle and the beginning of the next.



Hormonal Regulation of the Menstrual Cycle and Ovarian Cycle

The normal menstrual cycleis 28 days long (from the start of one cycle to the start of"the next) . In fact, only 15 per cent of women have a perfect 28-day cycle.Any cycle of between 21 and 35 days long can be regarded as normal.The length of the menstrual cycle is determined by the length of the follicular phase. Once ovulation occurs, luteal phase length is fairly fixed at 14 days in almost all women.The duration of menstrual flow also varies among women from 2 to 8 day; peaks on the first or second day of menstrnation. The normal volume of menstrual loss is 35 mL per month.