The Normal Menstrual Cycle:

Introduction: 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 & hypothalamus.

The Ovary:

Within the ovary the menstrual cycle can be divided into 3 phases:

1. Follicular phase
2. Ovulation
3. Luteal phase

The key event in the follicular phase is the development of the oocytes. The ovary contains thousands of primordial follicles that are in a continuous state of development from birth to the menopause. The initial stages of follicular development (up to the pre-antral stage) are independent of hormonal stimulation, however, development beyond the pre-antral stage is stimulated by the pituitary hormones LH & FSH which are the key regulators of oocyte development.

At the start of the menstrual cycle the FSH level increase as the pituitary is released from the negative feedback effect of progesterone, estrogen & inhibin.

Steroidogenesis: The basis of hormonal activity in the pre-antral to the pre-ovulatory follicles is described as the two cell, two gonadotrophin' hyothesis. Steroidogenesis occur in two cell types within the follicle, the theca & granulosa cells. The hypothesis states that these cells are responsive to gonadotrophins LH & FSH respectively. Within the theca cells, LH stimulate the release of androgen from cholesterol. Within the granulosa cells, FSH stimulate the conversion of thecally derived androgens to estrogens (aromatization). Both FSH & LH are required for normal follicular development, FSH alone

produce ovulatory follicles but with low estrogen production. Androgen production within the follicle also regulate the development of pre-antral follicle. Low level of androgen enhance aromatization & increase oestrogen production where as high androgen levels inhibit aromatization & produce follicular atresia. The ideal situation for the initial stages of follicular development is low LH & high FSH.

Selection of the dominant follicle: The developing follicles grow & produce steroid hormones under the influence of LH & FSH. Only one of these follicles is destined to grow to a pre-ovulatory follicle & be released at ovulation - the dominant follicle, it is the largest & most developed follicle in the ovary at the mid-follicular phase. Such a follicle has the highest concentration of FSH receptors & the most efficient aromatase activity. At the time of follicular selection, FSH levels are declining in response to the negative-feedback effect of oestrogen. The dominant follicle is therefore the only follicle that is capable of continued development in the face of falling FSH level.

Ovulation: As the dominant follicle develops further, follicular oestrogen production increases so that it reaches the threshold required to exert a positive-feedback effect on pituitary LH secretion which in turn 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 LH surge. Ovulation occur 36 hours after the onset of LH surge. Prior to release of the oocyte at the time of ovulation, LH surge stimulate the resumption of meiosis, a process which is completed after the sperm enters the egg. Also it stimulate the release of inflammatory mediators including prostaglandins which cause the follicle wall to break down, releasing the oocyte at ovulation. Inhibition of prostaglandin production may result in failure of release of the oocyte from the ovary, despite apparently normal steroidogenesis.

Luteal phase: The 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 & 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 accumulation of yellow pigment, lutein, from which the corpus luteum derives its name. The production of progesterone from the corpus luteum is dependent on continued pituitary LH secretion. Progesterone & estrogen production from the corpus luteum have negative feedback on the pituitary gonadotrophins & the low levels of gonadotrophins mean that the initiation of new follicular growth is inhibited for the duration of the luteal phase.

Luteolysis: The duration of the luteal phase is fairly constant, around 14 days in most women. In the absence of pregnancy & the production of human chorionic gonadotrophin (hCG) from the implanting embryo, the corpus luteum regresses at the end of the luteal phase, a process known as luteolysis. As the corpus luteum dies, oestrogen, progesterone & inhibin levels decline so that the pituitary is released from the negative feedback effect of these hormones & gonadotrophins particularly FSH start to rise. A cohort of follicles that happen to be at the pre-antral phase is rescued from atresia & a further menstrual cycle is initiated.

The pituitary Gland: The pituitary hormones LH & FSH, are the key regulators of folliculogenesis. The output of LH & FSH from the pituitary is stimulated by pulses of gonadotrophin-releasing hormone (GnRH) produced by the hypothalamus & transported to the pituitary in the portal circulation. The response of the pituitary is regulated by ovarian hormones. Low level of oestrogen has negative feedback on LH where as high level stimulate LH production (positive feedback). In contrast low level of progesterone has a positive feedback effect on LH

& FSH, while high level of progesterone as seen in the luteal phase inhibit pituitary gonadotrophins.

The Hypothalamus: The hypothalamus, via the pulsatile secretion of gonadotrophins, stimulate pituitary LH & FSH secretion. GnRH is produced in a pulsatile manner to exert its effect. Drugs that are GnRH agonist cause a reduction in the pituitary LH & FSH secretion due to their long acting effect, continued exposure of the pituitary to moderately high levels of GnRH causes down-regulation & desensitization of the pituitary. LH & FSH levels are markedly reduced, ovarian steroidogenesis is suppressed, so that serum oestrogen & progesterone fall to postmenopausal levels.

The Endometrium:

Menstruation: As the corpus luteum dies at the end of the luteal phase, circulating levels of oestrogen & progesterone fall precipitously. In an ovulatory cycle, where the endometrium is exposed to oestrogen & then progesterone in an orderly manner, the endometrium become decidualized during the second half of the cycle to allow implantation of the embryo. Decidualization is an irreversible process & if implantation does not occur, programmed cell death (apoptosis) ensues. Menstruation is the shedding of the 'dead' endometrium & ceases as the endometrium regenerates. Menstruation is initiated by the withdrawal of oestrogen & progesterone. Withdrawal of progesterone has several main effects. First, intense spiral artery vasoconstriction is generated caused by locally produced prostaglandins, inflammatory mediators also produced which attract & activate neutrophil & macrophages. These events lead to ischaemia (particularly of the upper endometrium) & tissue damage, shedding of the functional endometrium (stratum compactum & stratum spongiosum) & bleeding from fragments of arterioles remaining in the basal endometrium. Menstruation ceases as the damaged spiral arteries vasoconstrict & the endometrium regenerates. Haemostasis in the endometrium differs from haemostasis elsewhere in a number of aspects. Normally, bleeding from a damaged vessel is stemmed by

platelet accumulation, fibrin deposition & platelet degranulation. Such events may lead to scarring which If occur in the endometrium would significantly inhibit function so an alternative system of haemostasis is required. Vasoconstriction is the mechanism by which haemostasis is initially secured in the endometrium. Scarring is minimized by enhanced fibrinolysis which break down blood clots. Later, repair of the endometrium & new vessel formation (angiogenesis) lead to complete cessation of bleeding within 5-7 days from the start of the menstrual cycle.

The proliferative / follicular phase: once endometrial repair is completed, around day 5-6 of the cycle, menstruation ceases & the remainder of the follicular phase is characterized by glandular & stromal growth, hence the name proliferative phase. The massive development taking place in the endometrium is reflected in the increased endometrial thickness, from 0.5 mm at menstruation to 3.5-5 mm at the end of the proliferative phase.

The secretory/ luteal phase: this is characterized by endometrial glandular secretory activity hence the name secretory phase. Under the action of progesterone, oestrogen-induced cellular proliferation is inhibited, & the depth of the endometrium remain fixed. Despite this some of the elements continue to grow, leading to increased tortousity of both the glands & spiral arteries in order to fit into the endometrial layer. Shortly after ovulation, vacuoles containing intracytoplasmic granules appear in the glandular cells they progress to the apex of the glandular cells & their contents are released into the endometrial cavity. Peak secretory activity occur at the time of implantation, 7 days after the gonadotrophin surge. Progesterone is important for the induction of the secretory changes which are seen only after ovulation. Within the stroma, oedema is induced. stromal cells display increased mitotic activity & nuclear enlargement. Immediately before menstruation, three distinct zones of the endometrium can be seen. The basalis is the basal 25% of the endometrium, which is retained during menstruation

& show few changes during the menstrual cycle. The mid-portion is the stratum spongiosum. The superficial portion (upper 25%) is the stratum compactum, with prominent decidualized stromal cells. The onset of menstruation heralds the end of one menstrual cycle & the beginning of the next.

Clinical features of normal menstrual cycle: Normal menstrual cycle range from 21 to 35 days with an average of 28 days. Menstrual cycles are longest immediately after puberty & in the 5 years leading up to menopause, corresponding to peak incidence of anovulatory cycles. The length of menstrual cycle is determined by the length of follicular phase. Once ovulation occurs, luteal phase is fixed at 14 days in almost all women. The duration of the menstrual flow varies from 2-8 days. The amount of menstrual flow peaks on the first or second day of menstruation.. The normal volume of menstrual loss is 35 mL per month, menstrual loss more than 80 mL is considered excessive.