

MENSTRUAL CYCLE AND FERTILITY

C.P.Y 605

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INTRODUCTION

► Female reproductive functions can be divided into two major phases:

1. Preparation of the female body for conception and pregnancy

2. The period of pregnancy itself

► Between the ages of menarche at approximately 12yr to about 46yr, the reproductive organs of normal women undergo a series of closely coordinated changes at approximately monthly intervals that together comprise the normal menstrual cycle.

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(A) MENSTRUAL CYCLE

- It is the expression of the coordinated interactions of the hypothalamic-pituitary-ovarian axis, with associated changes in the target tissues (endometrium, cervix, vagina) of the reproductive tract.
- The median menstrual cycle length is 28 days but differences may be due to diet, exercise, environment or serious emotional problem.
- The menstrual cycle can be divided into three distinct phases: *follicular, ovulatory and luteal*

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Female hormonal system

► It consists of three hierarchies of hormones as follows:

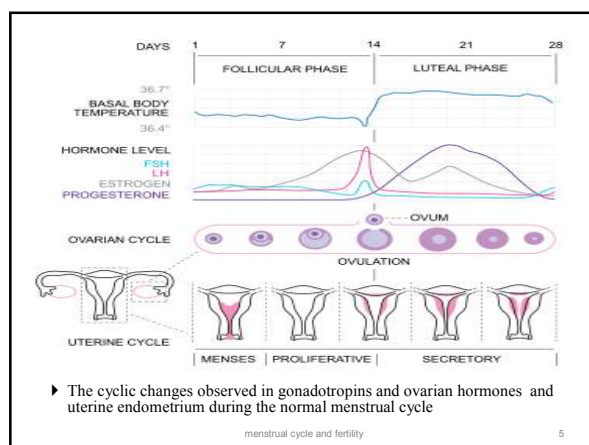
1) A hypothalamic releasing hormone, *gonadotropin-releasing hormone (GnRH)*

2) The anterior pituitary sex hormones, *follicle-stimulating hormone (FSH)* and *luteinizing hormone (LH)* both of which are secreted in response to the release of GnRH from the hypothalamus

3) The ovarian hormones, *estrogen* and *progesterone* which are secreted by the ovaries in response to the two sex hormones from the anterior pituitary gland

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a) The follicular phase

- It begins from the first day of menstrual bleeding and extends to the day prior to the preovulatory LH surge.
- This phase is initiated by a rise in FSH stimulated by reduced amount of plasma progesterone and estrogen in the late luteal phase of the previous menstrual cycle continuing into the early follicular phase stimulating accelerated growth and development of the granulosa cells of group of follicles.
- In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells to form the *theca* cells.

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cont'

- The mass of granulosa cells secretes a follicular fluid (contains high levels of estrogen) that accumulates causing antrum to appear within the mass of granulosa cells stimulated by FSH.
- This antral follicle then undergoes rapid growth to the vesicular follicle due to the estrogen secreted into the follicles causing the granulosa cells to increase the numbers of FSH receptors
- When the egg has nearly matured, levels of estrogen reach a threshold above which they stimulate production of LH

Cont'

- Increased levels of estrogen causes proliferation of the endometrium and increases LH secretion by a positive feed back mechanism leading to the LH surge
- These opposite responses of LH to estradiol may be enabled by the presence of two different estrogen receptors in the hypothalamus: **estrogen receptor alpha**, which is responsible for the negative feedback estradiol-LH loop, and **estrogen receptor beta**, which is responsible for the positive estradiol-LH relationship(Hu *et al.*,2008).

Cont'

- The LH then binds on surface receptors on the theca cells and through cAMP pathway leads to the production of androgens.
- The androgens are converted to estrogen through aromatase activity which is stimulated by FSH in the granulosa cells.
- The increasing estrogen stimulates more production of LH leading to preovulatory LH surge in this environment the following occurs:

- I. Rapid growth of follicle and weakening of its walls for ovulation
 - II. Diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion
 - III. Initiation of secretion of progesterone just before ovulation
- The increased estrogen and the hormone inhibit start inhibiting FSH

b) The ovulatory phase

- The release of LH matures the egg and weakens the wall of the follicle in the ovary, causing the fully developed follicle to release the ovum
- Which of the two ovaries—left or right—ovulates appears essentially random; no known left and right co-ordination exists. Occasionally, both ovaries will release an egg.
- Some women experience brief ,dull, unilateral pelvic pain near the time of ovulation, termed *mittelschmerz*. This may be due to the leakage of follicular fluid into the abdominal cavity at ovulation.

c) The luteal phase

- After ovulation the remaining granulosa and theca cells change rapidly into lutein cells called *corpus luteum* filled with lipid inclusions that give them a yellowish appearance.
- The corpus luteum maintains the endometrium of the uterus by the secretion of large amounts of progesterone and minor amounts of estrogen.
- The reduced amount of estrogen internally reduces the release of LH a negative feedback mechanism
- Inhibin, which is also secreted by the corpus luteum, contributes to FSH inhibition.
- After about 8 days after ovulation the corpus luteum begins to involute losing its secretory functions and yellowish colour and become the corpus albicans

Female reproductive cycle

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TABLE 22.4 Major Events in a Reproductive Cycle	
1.	The anterior pituitary gland secretes FSH and LH.
2.	FSH stimulates maturation of a follicle.
3.	Granulosa cells of the follicle produce and secrete estrogens. <ol style="list-style-type: none"> Estrogens maintain secondary sex traits. Estrogens cause the endometrium to thicken.
4.	The anterior pituitary gland releases a surge of LH, which stimulates ovulation.
5.	Follicular and thecal cells become corpus luteum cells, which secrete estrogens and progesterone. <ol style="list-style-type: none"> Estrogens continue to stimulate uterine wall development. Progesterone stimulates the endometrium to become more glandular and vascular. Estrogens and progesterone inhibit secretion of FSH and LH from the anterior pituitary gland.
6.	If the secondary oocyte is not fertilized, the corpus luteum degenerates and no longer secretes estrogens and progesterone.
7.	As the concentrations of luteal hormones decline, blood vessels in the endometrium constrict.
8.	The uterine lining disintegrates and sloughs off, producing a menstrual flow.
9.	The anterior pituitary gland is no longer inhibited and again secretes FSH and LH.
10.	The reproductive cycle repeats.

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Cyclic changes in target cells

- **Endometrium**-it undergoes remarkably histologic and cytologic changes during the menstrual cycle which culminates with menstrual flow as the corpus luteum ceases to secrete progesterone.
- The basal layer regenerates the superficial layer of compact epithelial cells and the intermediate layer of spongiosa
- Under the influence of estrogen, endometrial glands in this layer proliferate in the follicular phase so that the mucosa thickens.

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Cont,

- In the luteal phase the glands become coiled and secretory, with increased vascularity and oedema of the stroma due to the presence of progesterone
- As progesterone and estrogen decline in the late luteal phase, endometrial and blood vessel necrosis occurs, and endometrial bleeding ensues
- Local release of prostaglandin causes vasospasm and necrosis of endometrium as well as uterine contraction (dysmenorrhea)
- Fibrinolytic activity (by the enzyme plasmin) in the endometrium peaks up at menstruation accounting for the non coagulation of menstrual blood.

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- **Cervix and cervical mucus**-during the follicular phase, cervical vascularity and oedema increase under the influence of estrogen.
- The external cervical os opens in diameter of 3mm at ovulation.
- Cervical mucus increases in quantity and elasticity in the follicular phase
- Under the influence of progesterone in the luteal phase, the mucus becomes thicker, less watery and loses its elasticity.

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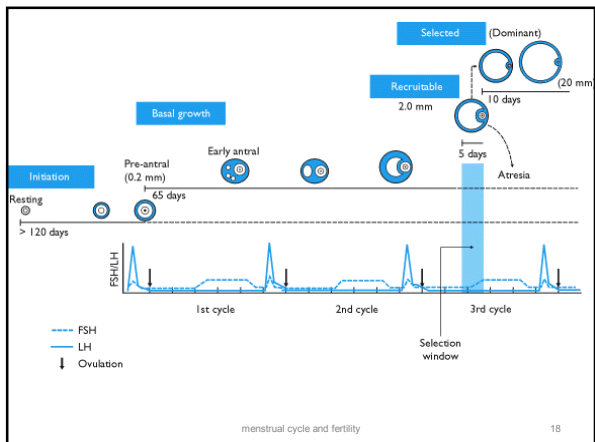
- **Vaginal**-in the early follicular phase when estrogen is low, the epithelium is pale and thin.
- In the follicular phase under the influence of estrogen the epithelium thickens and the number of mature cornified epithelial cells increases.
- **Ovaries**-changes in the ovaries due to hormonal stimulation is expressed through the process of folliculogenesis

Folliculogenesis

- It is the maturation of the ovarian follicle, a densely-packed shell of somatic cells that contains an immature oocyte. It describes the progression of a number of small primordial follicles into large preovulatory follicles that enter the menstrual cycle.

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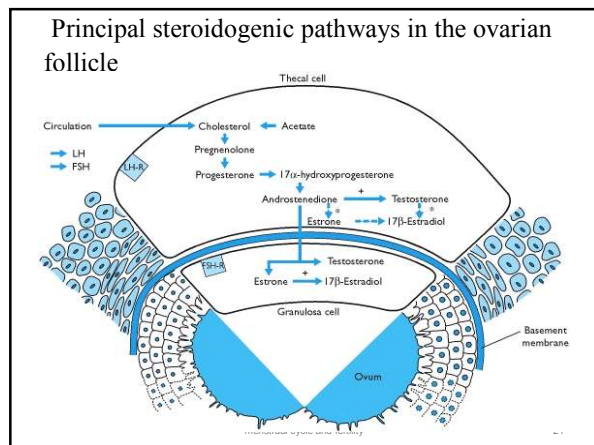
Stage	Description	size
primordial	Dormant, small, only one layer of flat granulosa cells	Primordial follicles are about 0.03-0.05 mm in diameter.
primary	Mitotic cells, cuboidal granulosa cells develop receptors to FSH at this time, but they are gonadotropin-independent	Almost 0.1mm in diameter
secondary	Presence of theca cells, multiple layers of granulosa cells	The follicle is now 0.2mm in diameter
Early tertiary (antral or graafian)	Formation of an antrum. gonadotropin-dependent	The early tertiary follicle is arbitrarily divided into five classes. Class 1 follicles are 0.2 mm, class 2, 0.4 mm, class 3, 0.9 mm, class 4, 2 mm, and class 5 about 5 mm.
Late tertiary	Fully formed antrum, no further cytodifferentiation, no novel progress	Class 6 follicles are about 10 mm in diameter, class 7 about 16 mm, and class 8 about 20 mm.
preovulatory	Building growth in estrogen concentration, all other follicles atretic or dead	

Chemistry of female sex hormones

- They are synthesized in the ovaries from cholesterol derived from blood.
- During synthesis, mainly progesterone and testosterone are produced first; then during the follicular phase the two hormones are converted to estrogen by granulosa cells.
- During the luteal phase far more progesterone is formed for it to be converted .
- Also about one-fifteenth of the testosterone may be secreted in blood

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- Three estrogens — β -estradiol —₁₂— estrone —₆₈— estriol.
- Progestins — progesterone and little 17- α -hydroxyprogesterone
- **Degradation**
- The liver conjugates estrogen to form glucuronides and sulphates with one fifth excreted in bile and the rest in urine
- Progesterone is degraded into another steroid (pregnenediol) which has no progesteronal effect. It is together with progesterone excreted in urine

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Regulation of the hypothalamic-pituitary-ovarian system.

A) postovulatory regulation (between ovulation and menstruation)

- Large quantities of progesterone and estrogen from the corpus luteum as well as inhibin have a combined negative feedback effect on the anterior pituitary and hypothalamus causing the suppression of both FH and LH

B) Follicular growth phase

2-3 days before menstruation, the corpus luteum has regressed, and this releases the negative feedback of the anterior pituitary leading to FSH secretion and several days after menstruation LH secretion increases slightly leading to the production of estrogen.

The presence of this estrogen slightly decreases the secretion of FSH and LH because of the negative feedback effect just before the preovulatory surge.

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C) Preovulatory surge

- About 2 days before ovulation the decline in secretion of LH and FSH comes to a halt.
- High levels of estrogen at this time causes a positive feedback stimulatory effect on the anterior pituitary leading to terrific surge of LH (which leads to ovulation and subsequent development of and secretion by the corpus luteum) and to a lesser extent FSH.

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Functions of ovarian hormones

- **Estrogen**

➤ its primary function is to cause cellular proliferation and growth of the tissues of sex organs and tissues related to reproduction.

A) Uterus and External Female Sex Organs.

✓ It changes the vaginal epithelium from the cuboidal to a more resistant to trauma and infection stratified form.

✓ It causes marked proliferation of the endometrial stroma and development of endometrial glands. The size of the endometrium increases twofold

B) Fallopian tubes

✓ Cause the glandular tissues of this lining to proliferate and cause an increase in the number of ciliated epithelium that line the fallopian tube

C) Breast

✓ initiates growth of breast by causing the development of the stroma tissue of the breast, growth of extensive ductile system, and deposition of fats.

C) Skeleton

✓ Stimulates bone growth by inhibiting osteoclastic activity.

✓ It also causes the uniting of the epiphyses with the shaft of long bones causing growth to cease earlier in female than male.

D) Fat deposition and body metabolism

✓ Increases the whole body metabolism slightly and deposition of increased quantity of fat in subcutaneous tissues, buttocks and thighs

E) Hair distribution

✓ It does not greatly affect hair distribution but hair develops in the pubic and axillae in response to androgens from adrenal gland

✓ F) skin

➤ Causes the skin to develop a texture that is soft and usually smooth and thickened

- **Progesterone**

A) Effect on the uterus

✓ Promotes secretory changes in the uterine endometrium during the latter half of the female menstrual cycle.

B) Effect on the fallopian tube

✓ It promotes increased secretion by the mucosal lining of the fallopian tubes which is necessary for the developing fertilized and dividing ovum

C) Effect on breast

✓ It promotes the development of the lobules and alveoli of the breast causing the alveoli to become secretory in nature. This also causes the breast to swell

Abnormalities of the menstrual cycle

- **Dysmenorrhoea**-painful menstruation of which they are two kinds;

➤ **Primary(spasmodic)**-usually affects the youth with cramping lower abdominal pains starting just before or with the menstrual flow associated with nausea, headache and vomiting due to prostaglandins.

➤ **Secondary(congestive)**-usually affects older women with the abdominal cramps associated with a pathologic cause e.g endometriosis, pelvic inflammatory disease

➤ **Premenstrual syndrome(PMS)**

- A group of syndromes experienced in varying degrees by women of reproductive age in a week before menstruation .this includes altered mental stability, fatigue, breast tenderness, weight gain, depression and headaches. The cause is unknown.

➤ **Dysfunctional uterine bleeding**

- Abnormal uterine bleeding with no demonstrable organic genital or extragenital cause.

➤ **Amenorrhoea** –it is the absence of menstruation for 3 or more months in women with past menses(secondary amenorrhoea) or the absence of menarche by 16 years of age (primary amenorrhoea). It is physiologic in prepubertal girls, during pregnancy and early lactation

- primary amenorrhoea may be caused by lack of ovaries or uterus or genetic disorder(turner syndrome)
- Secondary amenorrhoea may be caused by failure of the hypothalamic-pituitary-ovarian axis to produce the necessary hormones

- **Anovulation**-not associated with the development and release of a female ovum in the ovary. This may be due to inappropriate feedback signals to the hypothalamic-pituitary-ovarian axis

- **Luteinized unruptured follicle syndrome.** It describes the development of a dominant follicle without its subsequent disruption and release of ovum

- **Luteal phase dysfunction.**progesterone secretion in the luteal phase may be reduced in duration or in amount or the rarely the endometrium may be unable to respond to the secreted progesterone due to absence of progesterone receptors.

fertility

•Fertility is the natural capability of giving life. As a measure, "fertility rate" is the number of children born per couple, person or population.

Human fertility depends on factors of nutrition, sexual behavior, culture, instinct, endocrinology, timing, economics, way of life, and emotions.

•Women's fertility peaks between the ages of 22 to 26,because about 60% of the ovarian reserve is present and often declines after 30: a typical 30 year old woman has 12% of the ovarian reserve she was born with, and has only 3% at age 40. With a rise in women postponing pregnancy, this can create an infertility problem

- The requirements for pregnancy to occur

- the male must produce adequate number of normal motile spermatozoa

- the male must be able to ejaculate the sperm through the ductal system and unobstructed through the female tract

- the female must ovulate and release an ovum and the sperm must be able to fertilize the ovum

- the fertilized ovum must be capable of developing and implanting in appropriate prepared endometrium

INFERTILITY

- it is defined as the involuntary inability to conceive or in a male to induce conception while sterility is the total inability to reproduce.

- In about 60% of the cases it is due to female infertility.

• Causes of infertility

- **A) female factors**

- Amenorrhoea and anovulation

- Fallopian tube pathology

- Pelvic inflammatory disease

- Congenital abnormalities

- Endometriosis-the presence of tissue similar to the lining of the uterus at other sites in the pelvis.

- Immunologic factors

- sperm-immobilizing antibodies

- sperm-agglutinating antibodies

- Vaginal factors

- congenital absence of vagina

- vaginismus(sudden and painful contraction of the muscles of the vagina when touched leading to impeding sexual intercourse)

- vaginitis(inflammation of the vagina which may be caused by infection *Trichomonas vaginalis*)

- Cervical or uterine factors
 - Uterine abnormalities
 - Leiomyoma
 - Asherman's syndrome-a condition in which amenorrhoea and infertility follow a major haemorrhage in pregnancy.
- **2) male factors**
- Decrease production of spermatozoa
 - Testicular failure
 - Endocrine disorders
 - cryptorchidism

- Ductal obstruction
 - Epididymal
 - Congenital absence of vas deferens
 - Ejaculatory duct
- Abnormal semen
 - Infection
 - Abnormal volume
 - Abnormal viscosity

references

- Hu L, Gustafson RL, Feng H, et al. (October 2008). "Converse regulatory functions of estrogen receptor-alpha and -beta subtypes expressed in hypothalamic gonadotropin-releasing hormone neurons". *Mol. Endocrinol.* 22 (10): 2250-9. doi:10.1210/me.2008-0192. PMID 18701637.