NAME: MATTHEW OGHOGHO PRECIOUS

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1. **CYCLIC CHANGES IN THE CERVIX AND VAGINA**

**THE CERVIX**

The cervix is the lower constricted part of the uterus.it is divide into two parts; The Upper Supravaginal portion and The Lower vaginal portion.

* The Upper Supravaginal portion communicates with the body of the uterus through internal os(orifice) of cervix. Mucus membrane of this portion has glandular follicles, which secrete mucus. This portion is made of columnar epithelial cells.
* The lower vaginal portion which projects into the anterior wall of the vagina and it communicates with the vaginal through external os of cervix. Mucus membrane of this portion is formed by stratified squamous epithelium cells.

**THE VAGINA**

The vagina is a short tubular organ. It is lined by mucus membrane, which is formed by stratified epithelial cells.

The cyclic changes are grouped into 4. They are

1. Ovarian changes
2. Uterine changes
3. Vaginal changes
4. Cervical changes

**THE OVARY**

The ovary is the primary sex organ in females. Females have two ovaries which have two function. Thy are: Gametogenic and Endocrine functions.

* Gametogenic function is the production and release of eggs or ovum, which is the female reproductive cell.
* Endocrine function of ovaries is the secretion of female sex hormones.

These functions are further divided into 3. They are:

* Secretion of sex hormone
* Oogenesis
* Menstrual cycle

The ovary secretes the female sex hormone such as Estrogen and Progesterone.

**ESTROGEN**: in a normal non-pregnant woman, estrogen is secreted in large quantity by theca interna cells of ovarian follicles and in small quantity by corpus luteum of the ovaries.

**FUNCTIONS OF ESTROGEN**.

The major function of estrogen is to promote cellular proliferation and tissue growth in the sexual organs and in other tissues related to reproduction. In childhood, estrogen secretion is smaller than during puberty which results in changes in the sexual organs.

**Effects of Estrogen in Vagina**

1. Changes the vaginal epithelium from cuboidal to stratified epithelium which is more resistant to trauma and infection.
2. Increase the layers of the vaginal epithelium by proliferation.
3. Reduces the pH of vaginal, making it more acidic

All these changes are necessary for the prevention of certain common vaginal infections like gonorrheal vaginitis. Which can be cured by the administration of estrogen.

**PROGESTERONE**

In a non-pregnant woman, small quantity of progesterone is secreted by theca interna cells of ovaries during the first half of menstrual cycle. A large amount of progesterone is secreted during the latter half of each menstrual cycle.

**Functions of Progesterone**

Progesterone is concerned mainly with the final preparation of the uterus for pregnancy and the breast for lactation.

**Effects of Progesterone on the Cervix**

The progesterone increases the thickness of cervical mucosa and thereby inhibits the transport of sperm into the uterus. This effect is utilized in the contraceptive actions of minipills.

Menstrual cycle events take place in a rhythmic fashion during the reproductive period of a woman’s life.

During each menstrual cycle, series of changes occur in ovary and accessory reproductive organs e.g the cervix and the vagina.

**CHANGES IN CERVIX**

Mucus membrane of the cervix also show cyclic changes during different phases of menstrual cycle.

**Proliferative Phase**

During proliferative phase, the mucus membrane of cervix becomes thinner and more alkaline due to the influence of estrogen. It helps in the survival and motility of spermatozoa.

**Secretory Phase**

During secretory phase, the mucus membrane of the cervix becomes thicker and adhesive because of action of progesterone.

**VAGINAL CHANGES**

**Proliferative Phase**

Epithelial cells of vagina are cornified. Estrogen is responsible for this.

**Secretory Phase**

Vaginal epithelium proliferates due to the actions of progesterone. It is also infiltrated with leukocytes. These two changes increase the resistance of vagina for infection.

1. **MENSTRUAL CYCLE**

* DEFINITION

Menstrual cycle is defined as cyclic events that take place in a rhythmic fashion during the reproductive period of a woman’s life. The cycle starts at the age of 12 to 15 years, which marks the beginning of puberty. The beginning of the menstrual cycle is called the **MENARCHE.** Menstrual cycle ceases at the age of 45 to 50 years. Permanent cessation of menstrual cycle in old age is called **MENOPAUSE.**

* DURATION

The duration of menstrual cycle is usually 28 days. But, under physiological conditions, it may vary between 28 ± 7 days.

* CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, series of changes occur in the ovary and accessory sex organs. These changes are divided into 4 groups. They are

1. Ovarian changes
2. Uterine changes
3. Vaginal changes
4. Changes in the Cervix

All these changes take place simultaneously.

NOTE: changes also occur in the breast during menstrual cycle.

* **OVARIAN CHANGES**

The ovary is the primary sex organ in females. Females have two ovaries which have two function. Thy are: Gametogenic and Endocrine functions.

* Gametogenic function is the production and release of eggs or ovum, which is the female reproductive cell.
* Endocrine function of ovaries is the secretion of female sex hormones.

Ovaries are flattened ovoid bodies, with dimensions of 4 cm in length, 2 cm in width and 1 cm in thickness. Each ovary is attached at hilum to the broad ligament, by means of mesovarium and ovarian ligament.

Each ovary has two portions:

1. Medulla
2. Cortex.

Changes in the ovary during each menstrual cycle occur in two phases:

* Follicular phase
* Luteal phase.

Ovulation occurs in between these two phases

* **Follicular phase**

This phase starts from the 5th day of the cycle until the time of ovulation which takes place on the 14th day. Maturation of ovum with development of ovarian follicles takes place during this phase.

Ovarian Follicles

Ovarian follicles are glandular structures present in the cortex of ovary. Each follicle consists of the ovum surrounded by epithelial cells, namely granulosa cells. The follicles gradually grow into a matured follicle through various stages. These stages are of different follicles namely:

1. Primordial follicle
2. Primary follicle
3. Vesicular follicle
4. Matured follicle or graafian follicle

* Primordial Follicle

At the time of puberty, both the ovaries contain about 400,000 primordial follicles. Each primordial follicle has an ovum which is incompletely surrounded by the granulosa cells These cells provide nutrition to the ovum during childhood and also secrete the oocyte maturation inhibiting factor, which keeps ovum in the immature stage. All the ova present in the ovaries are formed before birth and after birth no new ovum is developed.

* Primary Follicle

Primordial follicle becomes the primary follicle when the ovum is completely surrounded by the granulosa cells.

During this stage, the follicle and the ovum increase in size. The follicle is not covered by a definite connective tissue capsule. Changes taking place during development of primary follicle

1. Proliferation of granulosa cells and increase in size of the follicle
2. Increase in size of the ovum
3. Onset of formation of connective tissue capsule around the follicle.

Primary follicles develop into vesicular follicles.

* Vesicular Follicle

Under the influence of FSH, about 6 to 12 primary follicles start growing and develop into vesicular follicles. Changes taking place during the development of vesicular follicle

1. Changes in granulosa cells
2. Changes in ovum
3. Formation of capsule

* Changes in granulosa cells

The proliferation of granulosa cells occurs then a cavity called follicular cavity or antrum is formed in between the granulosa cells. The Antrum is filled with a serous fluid called the liquor folliculi and with continuous proliferation of granulosa cells, the follicle increases in size. The Antrum with its fluid also increases in size which pushes the ovum to one side and it is surrounded by granulosa cells, which forms the germ hill.

* Changes in ovum

When the ovum increases in size, the nucleus becomes larger and vesicular. A thick membrane is formed around the ovum, which is called zona pellucida.

* Formation of capsule

Spindle cells from the stroma of ovarian cortex are modified and form a covering sheath around the follicle. The covering sheath is known as follicular sheath. The Theca folliculi divides into two layers:

a. Theca interna

b. Theca externa.

* The Theca interna is the inner vascular layer with loose connective tissue. This layer also contains special type of epithelial cells with lipid granules and some delicate collagen fibers. The epithelial cells become secretory in nature and start secreting the female sex hormones, especially estrogen and hormones are released into the fluid of antrum.
* Theca externa is the outer layer of follicular capsule and consists of thickly packed fibers and spindle shaped cells. After about 7th day of menstrual cycle, one of the vesicular follicles outgrows others and becomes the dominant follicle. It develops further to form graafian follicle and other vesicular follicles degenerate and become atretic by means of apoptosis.

1. Graafia Follicle

The Graafian follicle is the matured ovarian follicle with maturing ovum. It is named after the Dutch physician and anatomist, Regnier De Graaf. During the development of graafian follicle the following changes occur:

1. Size of the follicle increases to about 10 to 12 mm which extends through the entire thickness of ovarian cortex
2. At one point, the follicle encroaches upon tunica albuginea and protrudes upon surface of the ovary. This protrusion is called stigma. At the stigma, the tunica albuginea becomes thin
3. Follicular cavity becomes larger and distended with fluid
4. Ovum attains maximum size
5. Zona pellucida becomes thick
6. Corona radiata becomes prominent
7. Small spaces filled with fluid appear between the cells of germ hill, outside the corona radiata. These spaces weaken the attachment of the ovum to the follicular wall
8. Theca interna becomes prominent. Its thickness becomes double with the formation of rich capillary network
9. On the 14th day of menstrual cycle, graafian follicle is ready for the process of ovulation.

**OVULATION**

Ovulation is the process by which the graafian follicle ruptures with consequent discharge of ovum into the abdominal cavity. It is influenced by LH. Ovulation occurs on 14th day of menstrual cycle in a normal cycle of 28 days where the ovum enters the fallopian tube.

The process of ovulation mechanism is not clearly known. Ovulation occurs in different stages which are as follows:

1. Rupture of graafian follicles takes place at the stigma
2. Follicular fluid oozes out
3. Germ hillock is freed from wall
4. Ovum is expelled out into the abdominal cavity along with some amount of fluid and granulosa cells
5. From abdominal cavity, the ovum enters the fallopian tube through the fimbriated end.

Ovum becomes haploid before or during ovulation by the formation of polar bodies. After ovulation, the ovum is viable only for 24 to 48 hours. So it must be fertilized within that time.

A fertilized ovum is called Zygote. The zygote moves from fallopian tube and reaches the uterus on 3rd day after ovulation. It is implanted in the uterine wall on 6th or 7th day and if fertilization does not occur, the ovum degenerates.

* LUTEAL PHASE

The Luteal phase extends between 15th and 28th day of menstrual cycle. During this phase, corpus luteum is developed and hence this phase is called luteal phase.

**Corpus Luteum**

Corpus luteum is a glandular yellow body, developed from the ruptured graafian follicle after the release of ovum and can also be called yellow body.

**Development of Corpus Luteum**

Soon after the rupture of graafian follicle and release of ovum, the follicle is filled with blood and as such is called corpus hemorrhagicum. The blood clots slowly. Corpus hemorrhagicum does not degenerate immediately. It is transformed into corpus luteum. Follicular cavity closes gradually by the healing of the wound. Blood clot is gradually replaced by a serous fluid containing fibrin. Corpus luteum obtains a diameter of 15 mm and remains in the ovary till the end of the cycle.

Structure of Corpus Luteum

In the corpus luteum, granulosa cells and theca interna cells are transformed into lutein cells called granulosa lutein cells and theca lutein cells. The process which transforms the granulosa and theca cells into lutein cells is called luteinization.

Functions of Corpus Luteum

1. Secretion of hormones Corpus luteum acts as a temporary endocrine gland. It secretes large quantity of progesterone and small amount of estrogen.
2. Maintenance of pregnancy If pregnancy occurs, corpus luteum remains active for about 3 months, i.e. until placenta develops. Hormones secreted by corpus luteum during this period maintain the pregnancy. Abortion occurs if corpus luteum becomes inactive or removed before third month of pregnancy.

* **UTERINE CHANGES DURING MENSTRUAL CYCLE**

The Uterus is otherwise known as womb. It lies in the pelvic cavity, in between the rectum and urinary bladder. Uterus is a hollow muscular organ with a thick wall. It has a central cavity, which opens into vagina through cervix. On either side at its upper part, the fallopian tubes open.

Uterus communicates with peritoneal cavity through fallopian tubes. Virgin uterus is pyriform in shape and is flattened anteroposteriorly. It measures about 7.5 cm in length, 5 cm in breadth at its upper part and about 2.5 cm in thickness. There is a constriction almost at the middle of uterus called isthmus.

Divisions of uterus

Uterus is divided into three portions:

1. Fundus (above the entrance points of fallopian tubes)
2. Body (between fundus and isthmus)
3. Cervix (below isthmus).

Structure of uterus

Uterus is made up of three layers:

1. Serous or outer layer
2. Myometrium or middle muscular layer
3. Endometrium or inner mucus layer

During each menstrual cycle, along with ovarian changes, uterine changes also occur simultaneously. Uterine changes occur in three phases:

1. Menstrual phase
2. Proliferative phase
3. Secretory phase.

* MENSTRUAL PHASE

After ovulation, if pregnancy does not occur, the thickened endometrium is shed. This desquamated endometrium is passed out through the vagina along with blood and tissue fluid. The process of shedding and exit of uterine lining along with blood and fluid is called menstruation and lasts for about 4 to 5 days. This period is called menstrual phase or menstrual period.

The day when bleeding starts is considered as the first day of the menstrual cycle. Two days before the onset of bleeding, that is on 26th or 27th day of the previous cycle, there is a sudden reduction in the release of estrogen and progesterone from the ovary which results to Menstruation.

Changes in Endometrium during Menstrual Phase

1. Lack of estrogen and progesterone causes sudden involution of endometrium
2. It leads to reduction in the thickness of endometrium, up to 65% of original thickness
3. During the next 24 hours, the tortuous blood vessels in the endometrium undergo severe constriction because:
4. Involution of endometrium
5. Actions of vasoconstrictor substances like prosta glandin released from tissues of involuted endometrium
6. Sudden lack of estrogen and progesterone (which are vasodilators)
7. Vasoconstriction leads to hypoxia, which results in necrosis of the endometrium
8. Necrosis causes rupture of blood vessels and oozing of blood
9. The outer layer of the necrotic endometrium is separated and is passed out along with blood
10. This process is continued for about 24 to 36 hours
11. Within 48 hours after the reduction in the secretion of estrogen and progesterone, the superficial layers of endometrium are completely desquamated
12. Desquamated tissues and the blood in the endometrial cavity initiate the contraction of uterus.
13. Uterine contractions expel the blood along with desquamated uterine tissues to the exterior through the vagina.

During normal menstruation, about 35 mL of blood along with 35 mL of serous fluid is expelled. The blood clots as soon as it oozes into the uterine cavity. Fibrinolysin causes lysis of clot in uterine cavity itself, so that the expelled menstrual fluid does not clot. However, in the pathological conditions involving uterus, the lysis of blood clot does not occur. So, the menstrual fluid comes out with blood clot.

Menstruation stops between 3rd and 7th day of menstrual cycle. At the end of menstrual phase, the thickness of endometrium is only about 1 mm. This is followed by proliferative phase.

* PROLIFERATIVE PHASE

Proliferative phase extends usually from 5th to 14th day of menstruation, i.e. between the day when menstruation stops and the day of ovulation. It corresponds to the follicular phase of ovarian cycle.

At the end of menstrual phase, only a thin layer of endometrium remains, as most of the endometrial stroma is desquamated.

Changes in Endometrium during Proliferative Phase

1. Endometrial cells proliferate rapidly
2. Epithelium reappears on the surface of endometrium within the first 4 to 7 days
3. Uterine glands start developing within the endometrial stroma
4. Blood vessels appear in the stroma
5. Proliferation of endometrial cells occurs continuously, so that the endometrium reaches the thickness of 3 to 4 mm at the end of proliferative phase.

These uterine changes during proliferative phase occur due to the influence of estrogen released from ovary. On 14th day, ovulation occurs under the influence of LH. This is followed by secretory phase.

* SECRETORY PHASE

Secretory phase extends between 15th and 28th day of the menstrual cycle, i.e. between the day of ovulation and the day when menstruation of next cycle commences.

After ovulation, corpus luteum is developed in the ovary. It secretes a large quantity of progesterone along with a small amount of estrogen. Estrogen causes further proliferation of cells in uterus, so that the endometrium becomes thicker. Progesterone causes further enlargement of endometrial stroma and further growth of glands.

Under the influence of progesterone, the endometrial glands commence their secretory function. Many changes occur in the endometrium before commencing the secretory function. These changes include:

1. Endometrial glands become more tortuous. Because of increase in size, the glands become tortuous to get accommodated within the endometrium
2. Cytoplasm of stromal cells increases because of the deposition of glycogen and lipids
3. Many new blood vessels appear within endometrial stroma. Blood vessels also become tortuous
4. Blood supply to endometrium increases
5. Thickness of endometrium increases up to 6 mm.

Secretory phase is the preparatory period, during which the uterus is prepared for implantation of ovum. All these uterine changes during secretory phase occur due to the influence of estrogen and progesterone. Estrogen is responsible for repair of damaged endometrium and growth of the glands. Progesterone is responsible for further growth of these structures and secretory activities in the endometrium.

If a fertilized ovum is implanted during this phase and if the implanted ovum starts developing into a fetus, then further changes occur in the uterus for the survival of the developing fetus. If the implanted ovum is unfertilized or if pregnancy does not occur, menstruation occurs after this phase and a new cycle begins.

CHANGES IN CERVIX AND VAGINA DURING MENSTRUAL CYCLE

CHANGES IN THE CERVIX

Mucus membrane of the cervix also shows cyclic changes during different phases of menstrual cycle.

Proliferative Phase: During proliferative phase, the mucus membrane of cervix becomes thinner and more alkaline due to the influence of estrogen. It helps in the survival and motility of spermatozoa.

Secretory Phase: During secretory phase, the mucus membrane of cervix becomes more thick and adhesive because of actions of progesterone.

VAGINAL CHANGES DURING MENSTRUAL CYCLE

Proliferative Phase: Epithelial cells of vagina are cornified. Estrogen is responsible for this.

Secretory Phase: Vaginal epithelium proliferates due to the actions of progesterone. It is also infiltrated with leukocytes.

These two changes increase the resistance of vagina for infection.

* **REGULATION OF MENSTRUAL CYCLE**

Regulation of menstrual cycle is a complex process that is carried out by a well-organized regulatory system. The regulatory system is a highly integrated system, which includes hypothalamus, anterior pituitary and ovary with its growing follicle which plays a vital role.

* HORMONES INVOLVED IN REGULATION

The regulatory system functions through the hormones of hypothalamo-pituitary-ovarian axis. Hormones involved in the regulation of menstrual cycle are:

1. Hypothalamic hormone: GnRH
2. Anterior pituitary hormones: FSH and LH
3. Ovarian hormones: Estrogen and progesterone.

* Hypothalamic Hormone – GnRH

GnRH triggers the cyclic changes during menstrual cycle by stimulating secretion of FSH and LH from anterior pituitary. GnRH secretion depends upon two factors:

1. External factors like psychosocial events, which act on hypothalamus
2. Feedback effects of ovarian changes

* Anterior Pituitary Hormones – FSH and LH

FSH and LH modulate the ovarian and uterine changes by acting directly and/or indirectly via ovarian hormones. FSH stimulates the recruitment and growth of immature ovarian follicles. LH triggers ovulation and sustains corpus luteum. Secretion of FSH and LH is under the influence of GnRH.

* Ovarian Hormones – Estrogen and Progesterone

Estrogen and progesterone which are secreted by follicle and corpus luteum, show many activities during menstrual cycle. Ovarian follicle secretes large quantity of estrogen and corpus luteum secretes large quantity of progesterone. Estrogen secretion reaches the peak twice in each cycle; once during follicular phase just before ovulation and another one during luteal phase.

On the other hand, progesterone is virtually absent during follicular phase till prior to ovulation. But it plays a critical role during luteal phase. Estrogen is responsible for the growth of follicles. Both the steroids act together to produce the changes in uterus, cervix and vagina. Both ovarian hormones are under the influence of GnRH, which acts via FSH and LH.

* REGULATION OF OVARIAN CHANGES

Follicular Phase

Estrogen is responsible for development and growth of graafian follicle. It also stimulates the secretory activities of theca cells

Initially, when estrogen secretion is moderate, it exerts a negative feedback control on GnRH so that GnRH secretion is inhibited and this leads to decrease in secretion of FSH and LH (negative feedback).

During later period of follicular phase, when a large amount of estrogen is secreted by the maturing follicle, it exerts a positive feedback effect on GnRH secretion. Now, GnRH secretion is increased, resulting in secretion of large quantity of FSH and LH. This in turn, facilitates the growth of graafian

* Luteal Phase

Role of LH Ovarian changes during luteal phase depend mainly on LH.

Luteinizing hormone:

1. Induces development of corpus luteum from the follicle (devoid of ovum) by converting the granulosa cells into lutein cells.
2. Stimulates corpus luteum to secrete progesterone and estrogen which is necessary for the maintenance of corpus luteum.

Role of FSH

FSH also plays a role during luteal phase.

1. Maintains the secretory activity of corpus luteum.
2. Stimulates lutein cells to secrete inhibin, which in turn inhibits FSH secretion.

If the ovum is not fertilized or if implantation of ovum does not take place

REGULATION OF UTERINE CHANGES

Uterine changes during menstrual cycle are influenced by estrogen and progesterone.

* Proliferative Phase

During proliferative stage, the repair of the damaged endometrium occurs mainly by estrogen. Estrogen stimulates:

1. Proliferation of cells in endometrial stroma
2. Development of uterine glands and appearance of blood vessels in the endometrial stroma.

* Secretory Phase

Secretory phase of uterine changes, coincides with luteal phase of ovarian cycle. Under the influence of FSH and LH from anterior pituitary, the corpus luteum secretes large amount of progesterone and small amount of estrogen. Progesterone is responsible for endometrial changes along with estrogen during this phase. Progesterone stimulates:

1. Growth of endometrial glands and makes them more tortuous
2. Growth of blood vessels and makes them also tortuous, leading to increase in blood flow to endometrium
3. Secretory activities of endometrial glands. Thus, during the secretory phase, the structure, blood flow and secretory functions of uterus are influenced by estrogen and progesterone secreted by corpus luteum.

Menstrual Phase

If pregnancy does not occur, menstrual phase occurs:

1. During the last two days of secretory phase, i.e. two days prior to onset of menstruation, the secretion of large quantity of progesterone and estrogen from corpus luteum inhibits the secretion of FSH and LH from anterior pituitary, by negative feedback
2. In the absence of LH and FSH, the corpus luteum becomes inactive and starts regressing
3. Sudden withdrawal (absence) of ovarian hormones progesterone and estrogen occurs
4. It leads to menstrual bleeding. Lack of ovarian hormones causes the release of gonadotropins once again from anterior pituitary.

It results in the onset of development of new follicles in ovary and the cycle repeats.

* MENSTRUAL SYMPTOMS

Menstrual symptoms are the unpleasant symptoms with discomfort, which appear in many women during menstruation. These symptoms are due to hormonal withdrawal, leading to cramps in uterine muscle before or during menstruation.

Common Menstrual Symptoms

1. Abdominal pain
2. Dysmenorrhea (menstrual pain)
3. Headache
4. Occasional nausea and vomiting
5. Irritability
6. Depression
7. Migraine (neurological disorder, characterized by intense headache causing disability).

* PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is the symptom of stress that appears before the beginning of menstruation. It is also called premenstrual stress syndrome. It lasts for about 4 to 5 days prior to menstruation. Symptoms appear due to salt and water retention caused by estrogen.

Common Features

1. Mood swings
2. Anxiety
3. Irritability
4. Emotional instability
5. Headache
6. Depression
7. Constipation
8. Abdominal cramping
9. Bloating (abdominal swelling).

* ABNORMAL MENSTRUATION

1. Amenorrhea: Absence of menstruation
2. Hypomenorrhea: Decreased menstrual bleeding
3. Menorrhagia: Excess menstrual bleeding
4. Oligomenorrhea: Decreased frequency of menstrual bleeding
5. Polymenorrhea: Increased frequency of menstruation
6. Dysmenorrhea: Menstruation with pain
7. Metrorrhagia: Uterine bleeding in between menstruations.

* ANOVULATORY CYCLE

Anovulatory cycle is the menstrual cycle in which ovulation does not occur. The menstrual bleeding occurs but the release of ovum does not occur. It is common during puberty and few years before menopause. When it occurs before menopause, it is called perimenopause and if it occurs very often during childbearing years, it leads to infertility.

Common Causes of Anovulatory cycle

1. Hormonal imbalance
2. Prolonged strenuous exercise program
3. Eating disorders
4. Hypothalamic dysfunctions
5. Tumors in pituitary gland, ovary or adrenal gland
6. Long-term use of drugs like steroidal oral contraceptives.