A review on haematological profile in menstruating, pre-menopausal and menopausal women

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Abstract

In females, the reproductive age is characterized by the onset of menstruation called menarche and ceases with the onset of menopause. The female reproductive cycles are controlled by various hormones and these hormones are known as female hormonal system. The female sexual cycle is the cycle of natural changes that occurs in the uterus and ovary as an essential part of making sexual reproduction possible. Its timing is governed by endogenous biological cycles. During the first few days of each monthly female sexual cycle, the concentrations of both FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month. Menstruation is the principal cause of iron loss in women. The menstrual period is associated to the rupture of blood vessels which irrigate the superficial layer of the endometrium. Platelets constitute the first haemostatic component that mobilizes in order to interrupt the bleeding as vascular injury occurs. During menstruation, tremendous numbers of leukocytes are released along with the necrotic materials and blood. This is probable as a result of some substances released by the endometrial necrosis which causes the outflow of leukocytes during menstruation. The paper reviewed haematological profile menstruating women, premenopause women and menopause women.

Keywords: Haematological profile, menstrual women, premenopause women, menopause women

Introduction

In females, the reproductive age is characterized by the onset of menstruation called ‘menarche’ and ceases with the onset of ‘menopause’ (Guyton and Hall, 2006; Sembuligam and Sembuligam, 2006). Reproduction begins with the development of ova in the ovaries. In the middle of each monthly sexual cycle, a single ovum is expelled from an ovarian follicle into the endometrial cavity near the open fimbriated ends of the two fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus; if it has been fertilized by a sperm, it implants in the uterus, where it develops into a foetus, a placenta, and foetal membranes- and eventually into a baby; if not fertilized by the sperm, the uterus sheds its inner lining of soft tissue and blood vessels which exits the body from the vagina in the form of menstrual fluid (Guyton and Hall, 2006; Sadiqua and Ashwini, 2012).

During all the reproductive years of adult life, between about 13 and 45 years of age, 400 to 500 of the primordial follicles develop enough to expel their ova-
one each month; the remainder degenerate (become atretic). At the end of each reproductive capability (i.e. menopause), only a few primordial follicles remain in the ovaries and even these ovaries degenerate soon thereafter (Sievert, 2013).

The female reproductive cycles are controlled by various hormones and these hormones are known as female hormonal system (Guyton and Hall, 2006). The female hormonal system, like that of the male, consists of three hierarchies of hormones as follows:

- A hypothalamic releasing hormone, gonadotropin releasing hormone (GnRH).
- 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.
- The ovarian hormones, estrogen and progesterone, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland.

These hormones and their interplay are collectively known as the hypothalamic-pituitary-ovarian (HPO) axis. These various hormones are secreted at drastically differing rates during different parts of the female monthly sexual cycle (Doufas and Mastorakos, 2000).

The female monthly sexual cycle

The female sexual cycle is the cycle of natural changes that occurs in the uterus and ovary as an essential part of making sexual reproduction possible. Its timing is governed by endogenous (internal) biological cycles. The sexual cycle is essential for the production of eggs, and for the preparation of the uterus for pregnancy. The cycle occurs only in fertile female humans and it occurs repeatedly between the ages of menarche when cycling begins, until menopause, when it ends (Koenig et al., 1998).

The length of a sexual cycle varies greatly among women (ranging from 21 to 35 days), with 28 days designated as the average length (Guyton and Hall, 2006). Each cycle is divided into phases based on events in the ovary (ovarian cycle) or in the uterus (uterine cycle) (Brodin et al., 2011). The ovarian cycle consists of the follicular phase, ovulation and luteal phase, whereas the uterine cycle is divided into proliferative phase (which occur simultaneously with the follicular phase), secretory phase (which occurs simultaneously with ovulation and the luteal phase) and menstruation.

The phases of the sexual cycle

The day count for sexual cycle begins on the first day of menstruation when blood starts to come out of the vagina to the day before the next menstruation. The entire duration of a female sexual cycle can be divided into four main phases:

- Menstrual phase (From day 1 to 5)
- Follicular phase (From day 1 to 13)
- Ovulation (Day 14), and
- Luteal phase (From day 15 to 28).

Fig. 1: Flowchart of the hormonal control of the menstrual cycle
The monthly ovarian cycle

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, secreted by the anterior pituitary gland (Hu et al., 2008). In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood when almost no pituitary gonadotropic hormones are secreted (Harlow et al., 2012). During each month of the female sexual cycle, there is a cyclical increase and decrease of both FSH and LH. These cyclical variations cause cyclical ovarian changes which are the:

- Follicular phase.
- Ovulation.
- Luteal phase.

Both FSH and LH stimulate their ovarian target cells by combining with highly specific FSH and LH receptors in the ovarian target cell membranes. In turn, the activated receptors increase the cells’ rate of secretion and usually the growth and proliferation of the cells as well. Almost all these stimulatory effects result from activation of the cyclic adenosine monophosphate second messenger system in the cell cytoplasm, which causes the formation of protein kinase and multiple phosphorylations of key enzymes that stimulate sex hormone synthesis (Hu et al., 2008).

The follicular phase of the ovarian cycle

This phase begins on the first day of menstruation and lasts till the 13th day of the sexual cycle.

When a female child is born, each ovum is surrounded by a single layer of granulosa cells; the ovum, with this granulosa cell sheath, is called a primordial follicle. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an oocyte maturation-inhibition factor that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division. Then, after puberty, when FSH and LH from the anterior pituitary gland begin to be secreted in significant quantities, the ovaries, together with some of the follicles within them, begin to grow. The first stage of follicular growth is moderate enlargement of the ovum itself, which increases in diameter twofold to threefold. Then follows growth of additional layers of granulosa cells in some of the follicles; these follicles are known as primary follicles.

During the first few days of each monthly female sexual cycle, the concentrations of both FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month.

The initial effect of FSH is rapid proliferation of the granulosa cells, giving rise to many more layers of these cells. In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells called the theca. The theca is divided into two layers, the theca interna and the theca externa. In the theca interna, the cells take an epithelioid characteristic similar to those of the granulosa cells and develop the ability to secrete additional steroid sex hormones known as estrogen and progesterone. The outer layer (theca externa) develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle. After the early proliferative phase of growth, lasting for a few days, the mass of granulosa cells secretes a follicular fluid that contains a high concentration of estrogen. Accumulation of this fluid causes an antrum to appear within the mass of granulosa cells. The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone. Then greatly accelerated growth occurs, leading to still larger follicles called vesicular follicle (Guyton and Hall, 2006). This accelerated growth is caused by the following:

- Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors; this causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH.
- The pituitary FSH and the estrogen combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even rapid increase in follicle secretion.
- The increasing estrogen from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion as well.

As the follicle enlarges, the ovum remains embedded in a mass of granulosa cells located at one pole of the follicle. After a week or more of growth—but before ovulation occurs—one of the follicles begins to outgrow all the others; the remaining 5 to 11 developing follicles are said to become atretic (Silverthorn, 2013).
The cause of the atresia is unknown, but it has been postulated to be the following: the large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute. This single follicle that outgrows others and reaches a diameter of 1 to 1.5 centimetres at the time of ovulation is called the mature follicle.

Ovulation

Ovulation in a woman who has a normal 28-day sexual cycle occurs 14 days after the onset of menstruation (Guyton and Hall, 2006).

About two days before ovulation, the rate of secretion of LH by the anterior pituitary gland increases markedly, rising 6-10 fold and peaking about 16 hours before ovulation. FSH also increases about twofold to threefold at the same time, and the FSH and LH act synergistically to cause rapid swelling of the follicle during the last few days of ovulation. The LH also has a specific effect on the granulosa and the theca cells, converting them mainly to progesterone-secreting cells. Therefore, the rate of secretion of estrogen begins to fall about one day before ovulation, while increasing amounts of progesterone begin to be secreted (Ecochard et al., 2000). It is the environment of (1) rapid growth of the follicle, (2) diminishing estrogen secretion after a prolonged phases of excessive estrogen secretion and (3) initiation of secretion of progesterone that ovulation occurs.

Initial pre-ovulatory surge of LH is needed for ovulation to occur. LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are responsible for ovulation:

- The theca externa begins to release proteolytic enzymes from lysomes, and these cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma.
- Simultaneously, there is a rapid growth of new blood vessels into the follicle wall, and at the same time prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues.

These two effects cause plasma transudation into the follicle, which contributes to follicle swelling. Finally, the combination of the follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum (Guyton and Hall, 2006).

Luteal phase

This phase begins immediately after the day of ovulation (usually on the 15th day of the onset of menstruation in an average woman).

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into lutein cells. They enlarge in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance. This process is called luteinisation, and the total mass of cells together is called the corpus luteum. A well developed vascular supply also grows into the corpus luteum. The granulosa cells in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of female sex hormones-estrogen and progesterone. The corpus luteum normally grows to about 1.5 centimetres in diameter, reaching this stage of development 7 to 8 days after ovulation. Then it begins to involute and eventually loses its secretory function and its yellowish, lipid characteristics about 12 days after ovulation, becoming the corpus albicans (Kalantaridou et al., 2012).

The change of granulosa and theca interna cells into luteum cells is dependent mainly on LH secreted by the anterior pituitary gland. This function gives LH its name—“luteinizing”, for “yellowing”. Luteinisation also depends on extrusion of the ovum from the follicle. A local hormone in the follicular fluid, called luteinisation-inhibiting factor, seems to hold the luteinisation process in check until after ovulation (Guyton and Hall, 2006). The corpus luteum formed during this phase is a highly secretory organ, secreting large amounts of both progesterone and estrogen (Guyton and Hall, 2006). Once LH (mainly that secreted during the ovulatory surge) has acted on the granulosa and theca cells to cause luteinisation, the newly formed lutein cells seem to be programmed to go through a preordained sequence of (1) proliferation, (2) enlargement, and (3) secretion, followed by (4) degeneration. All these occur in about 12 days. Estrogen in particular and progesterone in lesser extent, secreted by the corpus luteum during the luteal phase of the ovarian cycle, have strong feedback
effects on the anterior pituitary gland to maintain low secretory rates of both FSH and LH. In addition, the lutein cells secrete small amounts of the hormone inhibin which inhibits secretion by the anterior pituitary gland, especially FSH secretion. Low blood concentration of both FSH and LH result and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called involution of the corpus luteum. Final involution normally occurs at the end of almost exactly 12 days of corpus luteum life, which is around the 26th day of an average female sexual cycle-two days before menstruation begins. At this time, the sudden cessation of secretion of estrogen, progesterone and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH initiate the growth of new follicles, beginning a new ovarian cycle. The paucity of secretion of progesterone and estrogen at this time also leads to menstruation by the uterus.

The monthly endometrial cycle

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that operates through the following stages: (1) proliferation of the uterus endometrium; (2) development of secretory changes of the endometrium; and (3) desquamation of the endometrium, which is known as menstruation (Gruber et al., 2002).

Proliferative phase of the endometrial cycle, occurring before ovulation

At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation (Guyton and Hall, 2006). After menstruation, only a thin layer of endometrial stroma remains and the only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium. Under the influence of estrogens, secreted in increasing quantities by the ovary during the follicular phase, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is re-epithelialized within 4 to 7 days after the beginning of menstruation. Then, during the next week and a half, before ovulation occurs, the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells and to progressive growth of the endometrial glands and new blood vessels into the endometrium (Guyton and Hall, 2006). At the time of ovulation, the endometrium is 3 to 5 millimetres thick.

Secretory phase of the endometrial cycle, occurring after ovulation

After ovulation has occurred and corpus luteum formed, progesterone and estrogen together are secreted in large quantities by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity; an excess of secretory substances accumulates in the glandular epithelial cells. Also, the cytoplasm of the stromal cells increases; lipid and glycogen deposits increase greatly in the stromal cells; and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeter. The whole purpose of the endometrial changes is to produce a highly secretory endometrium that contains large amount of stored nutrients (example, lipids and glycogen) to provide appropriate conditions for implantation of a fertilized ovum during the latter half of the monthly cycle (if fertilization occurs).
**Menstrual phase**

If the ovum is not fertilized, about two days before the end of the monthly cycle, the corpus luteum in the ovary suddenly involutes and the ovarian hormones (estrogen and progesterone) decrease to low levels of secretion (Patrick et al., 2012). Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle (Guyton and Hall, 2006). The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium itself to about 65 percent of its previous thickness. Then, during the 24 hours preceding the onset of menstruation, the tortuous blood vessels leading to the mucosal layers of the endometrium become vasospastic, presumably because of some effect of involution, such as release of a vasoconstrictor material—possibly one of the vasoconstrictor types of prostaglandins that are present in abundance at this time (Jabbour et al., 2006).

The vasospasm, the decrease in nutrients to the endometrium, and the loss of hormonal stimulation initiates necrosis in the endometrium, especially of the blood vessels. As a result, blood at first seeps into the vascular layer of the endometrium and the haemorrhagic areas grow rapidly over a period of 24 to 36 hours. Gradually, the necrotic outer layers of the endometrium separate from the uterus at the sites of the haemorrhages until, about 48 hours after the onset of menstruation, all the superficial layers of the endometrium have desquamated. The mass of desquamated tissue and blood in the uterine cavity, plus contractile effects of prostaglandins or other substances in the decaying desquamate, all acting together, initiates uterine contractions that expel the uterine contents (Laufer et al., 2001). Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized. During menstruation, tremendous numbers of leukocytes are released along with the necrotic material and blood. It is probable that some substances liberated by the endometrial necrosis causes this outflow of leukocytes. As a result of these leukocytes, the uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded (Guyton and Hall, 2006).
The ovarian hormones: estradiol and progesterone

The two types of ovarian sex hormones are the estrogens and the progestins. By far the most important of the estrogens is the hormone estradiol, and by far the most important progestin is progesterone (Guyton and Hall, 2006). The estrogens mainly promote proliferation and growth of specific cells in the body that are responsible for the development of most secondary sexual characteristics of the female. The progestins function mainly to prepare the uterus for pregnancy and the breasts for lactation.

Chemistry of the sex hormone-estrogen

In a normal non-pregnant female, estrogens are secreted in significant quantities only by the ovaries, although minute amounts are also secreted by the adrenal cortices (Gruber et al., 2002). During pregnancy, tremendous quantities of estrogens are also secreted by the placenta (Guyton and Hall, 2006).

Types of estrogen

The three major naturally occurring estrogens in the plasma of the human females are estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity. During menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen in terms of serum levels. Though estriol is the most plentiful of the three estrogens, it is also the weakest, whereas estradiol is the strongest with a potency of approximately 80 times that of estriol (LaMarca and Rosen, 2008).

ESTRONE (E1) is considered a weaker form of estrogen. Estrone has a chemical name of 3-hydroxy-estra-1, 3, 5(10)-triene-17-one with the chemical formula C_{18}H_{22}O_{2}. Estrone is the least abundant of the three hormones. Small amounts of estrone are made throughout the body in most tissues, especially fat and muscles. Estrone is the major estrogenic form found in naturally-menopausal women who are not taking hormone replacement therapy (HRT). It is the only estrogen present in women after menopause.

ESTRADIOL (E2) is the most potent form of estrogenic steroids produced by ovaries. Estradiol has a chemical name of estr-1, 3, 5(10)-triene-3,17 beta-diol and the molecular formula of C_{18}H_{22}O_{2}. Estradiol is the estrogen capable of the fullest range of estrogen effects. It goes out to the different body tissues and sockets into the estrogen receptors (ERs) and cause estrogen effect. In addition to being produced by ovaries, estradiol can also be produced by conversion from a number of precursors in the adrenal glands and the placenta.

ESTRIOL (E3) is a metabolic waste product of estradiol metabolism that can still have some effects upon a limited number of ERs. Estriol has a chemical name of estra-1, 3, 5(10)-triene-3, 16 alpha, 17 beta-triol and a molecular formula of C_{18}H_{24}O_{3}. Estriol only produced in significant quantities during pregnancy. Estriol is made by the placenta from 16-hydroxydehydrogensterone sulfate (16-OH DHEAS), which is an androgen steroid made in the fetal liver and adrenal glands and is 8 percent as potent as estradiol and 14 percent as potent as estrone.

Although scientifically there are various estrogens, the usage of the word “estrogen” refers specifically to the steroidal estrogen estradiol (E2). This explains why “estrogen” is generally said to have its highest levels in females of reproductive age, which is true of estradiol.

Chemistry of the sex hormone-progestin

By far the most important of the progestins is progesterone. However, small amounts of another progestin, 17-alpha-hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects (Guyton and Hall, 2006). In the normal non-pregnant female, progesterone is secreted in significant amounts only during the luteal phase of each ovarian cycle, when it is secreted by the corpus luteum. During pregnancy, large amounts of progesterone are also secreted by the placenta.

Biosynthesis of estrogens and progestins

Estrogen and progesterone is both steroid hormone which are derived from the same precursor compound cholesterol. They are synthesized in the ovaries, mainly from the blood but also to a slight extent from acetyl coenzyme A, multiple molecules of which can combine to form the appropriate steroid nucleus (Jabbour et al., 2006). During synthesis, mainly progesterone and androgen (testosterone and androstenedione) are synthesized first; then, during the follicular phase of the ovarian cycle stimulated by the FSH, before these two initial hormones can leave the ovaries, almost all the androgens and much of the
progesterone are converted into estrogens by the enzyme aromatase in the granulosa cells. The conversion of androstenedione to testosterone is catalyzed by 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD), whereas the conversion of androstenedione and testosterone into estrone and estradiol, respectively is catalyzed by aromatase, enzymes which are both expressed in granulosa cells. In contrast, granulosa cells lack 17 alpha-hydroxylase and 17, 20-lyase, whereas theca cells express these enzymes and 17 beta-HSD but lack aromatase. Because the theca cells lack the aromatase, they cannot convert androgens to estrogens. However, androgen diffuse out of the theca cells to enter granulosa cells, where they are converted to estrogen by aromatase (the activity of which is stimulated by FSH). Hence, both granulosa and theca cells are essential for the production of estrogen in the ovaries (Guyton and Hall, 2006).

During the luteal phase of the ovarian cycle, far too much progesterone is formed for all of it to be converted, which accounts for the large secretion of progesterone into the circulating blood at this time.

Both estrogens and progesterone are transported in the blood bound mainly with plasma albumin and with specific estrogen- and progesterone-binding globulins. The binding between these hormones and the plasma proteins is loose enough that they are rapidly released to the tissues over a period of 30 minutes or so (Spat and Hunyady, 2004).

Functions of the liver in sex hormones degradation

Fate of Estrogen: The liver conjugates the estrogens to form glucuronides and sulfates, and about one fifth of these conjugated products is excreted in the bile; most of the remainder is excreted in the urine. Also, the liver converts the potent estrogens estradiol and estrone into the almost important estrogen estriol. Therefore, diminished liver function actually increases the activity of estrogens in the body sometimes causing hyperestrinism (Feder, 2001).

Fate of Progesterone: Within a few minutes after secretion, almost all the progesterone is degraded to other steroids that have no progestational effect (Levin, 2008). As with the estrogens, the liver is especially important for this metabolic degradation. The major end product of progesterone degradation is pregnanediol. About 10 percent of the original progesterone is excreted in the urine in this form.

Therefore, one can estimate the rate of progesterone formation in the body from the rate of this excretion.

Mechanism of action of estrogen receptor

Estrogens are steroid hormones that regulate growth, differentiation, and function in a broad range of target tissues in the human body (Norman and Litwack, 2005).

Estrogens have an effect on target tissues by binding to fractions of cells called estrogen receptors (ERs). These receptors are protein molecules found inside those cells that are targets for estrogen action. Only estrogens (or closely related molecules) are able to bind to these receptors (Carlstedt-Duke et al., 2011). The target tissues affected by estrogen molecules all contain estrogen receptors other organs and tissues in the body do not have therefore, when estrogen molecules circulate in the bloodstream and move throughout the body, they exert effects only on cells that contain ERs.

Estrogen receptors exist in the cell’s nucleus, together with deoxyribonucleic acid (DNA) molecules. In the absence of estrogen molecules, these estrogen receptors are inactive and have no influence on DNA (which contains the cell’s genes). But when an estrogen molecule enters a cell and passes into the nucleus, the estrogen binds to its receptor, in doing do causing the shape of the receptor to change. This estrogen-receptor complex then binds to specific DNA sites called estrogen response elements (EREs) located near genes that are controlled by estrogen. After attachment to EREs in DNA, this estrogen-receptor complex binds to co-activator proteins and more nearby genes become active. The active genes produce molecules of messenger ribonucleic acid (RNA), which guide the synthesis of specific proteins. These proteins can then influence cell behavior in different ways, depending on the cell type involved (Carlstedt-Duke et al., 2011).

Estrogens exert some of their effects through the actions of ERs on gene expression, but a number of other effects of estrogens are so rapid that they cannot depend on the activation of RNA and protein synthesis. These actions are known as nongenomic actions and are believed to be mediated through membrane-associated ERs. Their actions are frequently associated with the activation of various protein-kinase cascades (Karavolas and Hodges, 2000). However, nongenomic actions of estrogens may indirectly influence gene expression through the activation of signal transduction pathways that
void of estrogen production secreted by the ovaries. This estrogen contain EREs (Carlstedt-Duke et al., 2011), therefore there are nongenomic actions of estrogens. This signaling pathway can be referred to as nongenomic-to-genomic signaling, and it provides for a mechanism distinct from protein-protein interactions in the nucleus, by which ERs can modulate the functions of transcription factors, and thus regulate the expression of genes that do not contain EREs (Carlstedt-Duke et al., 2011).

**Functions of estrogen**

A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.

1. **Effect of Estrogens on the Uterus and External Female Sex Organs:** During childhood, estrogens are secreted only in minute quantities, but at puberty, the quantity secreted in the female under the influence of the pituitary gonadotropic hormones increases 20-fold or more. At this time, the female sex organs change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus, and vagina all increase several times in size. Also, the external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and enlargement of the labia minora. In addition, estrogens change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection than is the prepubertal cuboidal cell epithelium. Vaginal infections in children can often be cured by the administration of estrogens simply because of the resulting increased resistance of the vaginal epithelium (Guyton and Hall, 2006). During the first few years after puberty, the size of the uterus increases twofold to threefold, but more important than the increase in uterus size are the changes that take place in the uterine endometrium under the influence of estrogens. Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands, which will later aid in providing nutrition to the implanted ovum.

2. **Effect of Estrogens on the Fallopian Tubes:** The estrogens’ effect on the mucosal lining of the fallopian tubes is similar to that on the uterine endometrium. They cause the glandular tissues of this lining to proliferate; especially important, they cause the number of ciliated epithelial cells that line the fallopian tubes to increase. Also, activity of the cilia is considerably enhanced. These cilia always beat toward the uterus, which helps propel the fertilized ovum in that direction.

3. **Effect of Estrogens on the Breasts:** The primordial breasts of females and males are exactly alike. In fact, under the influence of appropriate hormones, the masculine breast during the first 2 decades of life can develop sufficiently to produce milk in the same manner as the female breast. Estrogens cause (1) development of the stromal tissues of the breasts, (2) growth of an extensive ductile system, and (3) deposition of fat in the breasts. The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin that cause the ultimate determinative growth and function of these structures. In summary, the estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, they do not complete the job of converting the breasts into milk-producing organs.

4. **Effect of Estrogens on the Skeleton:** Estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth. At puberty, when the female enters her reproductive years, her growth in height becomes rapid for several years. However, estrogens have another potent effect on skeletal growth: They cause uniting of the epiphyses with the shafts of the long bones. This effect of estrogen in the female is much stronger than the similar effect of testosterone in the male. As a result, growth of the female usually ceases several years earlier than growth of the male. A female eunuch who is devoid of estrogen production usually grows several inches taller than a normal mature female because her epiphyses do not unite at the normal time.

Osteoporosis of the Bones Caused by Estrogen Deficiency in Old Age: After menopause, almost no estrogens are secreted by the ovaries. This estrogen deficiency leads to (1) increased osteoclastic activity in the bones, (2) decreased bone matrix, and (3) decreased deposition of bone calcium and phosphate. In some women, this effect is extremely severe, and the resulting condition is osteoporosis. Because this can greatly weaken the bones and lead to bone fracture, especially fracture of the vertebrae, a large share of postmenopausal women is treated prophylactically with estrogen replacement to prevent the osteoporotic effects.
5. Effect of Estrogens on Protein Deposition: Estrogens cause a slight increase in total body protein, which is evidenced by a slight positive nitrogen balance when estrogens are administered. This mainly results from the growth-promoting effect of estrogen on the sexual organs, the bones, and a few other tissues of the body.

6. Effect of Estrogens on Body Metabolism and Fat Deposition: Estrogens increase the whole-body metabolic rate slightly, but only about one third as much as the increase caused by the male sex hormone testosterone. They also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in the female body is considerably greater than that in the male body, which contains more protein. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause the deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure.

7. Effect of Estrogens on the Skin: Estrogens cause the skin to develop a texture that is soft and usually smooth, but even so, the skin of a woman is thicker than that of a child or a castrated female. Also, estrogens cause the skin to become more vascular; this is often associated with increased warmth of the skin and also promotes greater bleeding of cut surfaces than is observed in men.

8. Effect of Estrogens on Electrolyte Balance: The chemical similarity of estrogenic hormones to adrenocortical hormones has been pointed out. Estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. This effect of estrogens is normally slight and rarely of significance, but during pregnancy, the tremendous formation of estrogens by the placenta may contribute to body fluid retention causing haemodilution (Guyton and Hall, 2006).

9. Effect of Estrogen on Haematopoietic Tissue: Estrogen increases haematopoietic stem and progenitor cells independent of its actions on bone. Estrogen has been discovered to have some effect on stem cells. It is discovered that blood-forming cells divide more frequently in females than in males due to higher estrogen level in females (Daisuke et al., 2014). This explains the fact why with the monthly loss of blood in menstruating women that red blood cell count is slightly different from that of men, while no difference is experienced in platelet and white blood cell count (Daisuke et al., 2014). This discovery also explains how red blood cell production is augmented during pregnancy (Morrison, 2014). Therefore, females at the reproductive age with normal sexual cycle are believed to have adequate number of blood cells due to the effect of estrogen on the haematopoietic tissues in the bone marrow cavity.

**Menopause**

Menopause, also known as the climacteric, is the time in most women's lives when menstrual periods stop permanently, and the woman is no longer able to have children (Monterrosa-Castro et al., 2012). The cause of menopause is “burning out” of the ovaries. Throughout a woman’s reproductive life, about 400 of the primordial follicles grow into mature follicles and ovulate, and hundreds of thousands of ova degenerate. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH, and the production of estrogens by the ovaries decreases as the number of primordial follicles approaches zero. When estrogen production falls below a critical value, the estrogens can no longer inhibit the production of the gonadotropins FSH and LH. Instead, the gonadotropins FSH and LH (mainly FSH) are produced after menopause in large and continuous quantities, but as the remaining primordial follicles become atretic, the production of estrogens by the ovaries falls virtually to zero.

The loss of estrogens often causes marked physiological changes in the function of the body, including (1) “hot flushes” characterized by extreme flushing of the skin, (2) psychic sensations of dyspnea, (3) irritability, (4) fatigue, (5) anxiety, (6) occasionally various psychotic states, and (7) decreased strength and calcification of bones throughout the body; other symptoms may include vaginal dryness, trouble sleeping, and mood changes (Warren et al., 2009). These symptoms are of sufficient magnitude in about 15 per cent of women to warrant treatment. If counselling fails, daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women can likely avoid severe symptoms.

Menopause is usually a natural change. It can occur earlier in those who smoke tobacco, those who undergo surgery that removes both ovaries; and in some types of chemotherapy. At the physiological level, menopause happens because of a decrease in the ovaries' production of the hormones estrogen and progesterone.

**Signs and symptoms**

During early menopause transition, the menstrual cycles remain regular but the interval between cycles
begins to lengthen. Hormone levels begin to fluctuate. Ovulation may not occur with each cycle. The date of the final menstrual period is usually taken as the point in time when menopause has occurred (Hoffman and Barbara, 2012). During menopausal transition and after menopause, women can experience a wide range of symptoms which include:

- **Transition symptoms**
  Menstrual patterns can show shorter cycling (by 2–7 days); longer cycles remain possible; irregular bleeding (lighter, heavier, spotting).
- **Physical symptoms**
  Physical symptoms include: lack of energy, joint soreness, stiffness, back pain, breast enlargement, breast pain, heart palpitations, headache, dizziness, dry and itchy skin, thinning, tingling skin, weight gain, urinary incontinence, urinary urgency, interrupted sleeping patterns, heavy night sweats, hot flashes.
- **Psychological symptoms**
  Psychological symptoms include: anxiety, poor memory, inability to concentrate, depressive mood, irritability, mood swings.
- **Sexuality**
  Sexual changes include: painful intercourse, vaginal dryness, less interest in sexual activity.
  Other symptoms include:
  - Increased risk of osteopenia and osteoporosis,
  - Possible but contentious increased risk of atherosclerosis,
  - Migraine,
  - Dysfunctional uterine bleeding as part of menstruation. Women approaching menopause often experience this due to the hormonal changes that accompany the menopause transition. In post-menopausal women however, any genital bleeding is an alarming symptom that requires an appropriate study to rule out the possibility of malignant diseases. However, spotting or bleeding may simply be related to vaginal atrophy, a benign sore (polyp or lesion) or may be a functional endometrial response.
  - Atrophic vaginitis - Thinning of the membranes of the vulva, the vagina, the cervix, and also the outer urinary tract, along with considerable shrinking and loss in elasticity of all of the outer and inner genital areas.
  - Increased susceptibility to inflammation and infection, for example vaginal candidiasis, and urinary tract infections.
  The risk of acute myocardial infarction and other cardiovascular diseases rises sharply after menopause, but the risk can be reduced by managing risk factors, such as tobacco smoking, hypertension, increased blood lipids and body weight (Llaneza *et al*., 2012).

### Causes of menopause

- **Age**
  In the Western world, the typical age of menopause (last period from natural causes) is between 40 and 61, and the average age for last period is 51 years (Kato *et al*., 2010). The average age of natural menopause in women is 51.7 years (Treloar *et al*., 2013). In India and the Philippines, the median age of natural menopause is considerably earlier, at 44 years (Ringer 2000).

  In rare cases, a woman's ovaries stop working at a very early age, ranging anywhere from the age of puberty to age 40, and this is known as premature ovarian failure (POF). Spontaneous premature ovarian failure affects 1% of women by age 40, and 0.1% of women by age 30 (Soules *et al*., 2001).

  Women who have undergone hysterectomy with ovary conservation go through menopause on average 3.7 years earlier than the expected age. Other factors which can promote an earlier onset of menopause (usually 1 to 3 years early) are: smoking cigarettes, or being extremely thin (Kalantaridou *et al*., 2012).

- **Premature ovarian failure**
  Premature ovarian failure (POF) is diagnosed or confirmed by high blood levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) on at least 3 occasions at least 4 weeks apart (Kalantaridou *et al*., 2012). Known causes of premature ovarian failure include autoimmune disorders, thyroid disease, diabetes mellitus, chemotherapy, being a carrier of the fragile X syndrome gene, and radiotherapy. However, in the majority of spontaneous cases of premature ovarian failure, the cause is unknown, i.e. it is generally idiopathic. Women who have some sort of functional disorder affecting the reproductive system (e.g., endometriosis, polycystic ovary syndrome, cancer of the reproductive organs) can go into menopause at a younger age than the normal timeframe. The functional disorders often significantly speed up the menopausal process. An early menopause can be related to cigarette smoking, higher body mass index, racial and ethnic factors, illnesses, and
the surgical removal of the ovaries, with or without the removal of the uterus (Bucher et al., 2012).

- Surgical menopause

Menopause can be surgically induced by bilateral oophorectomy (removal of ovaries), which is often, but not always, done in conjunction with removal of the Fallopian tubes (salpingo-oophorectomy) and uterus (hysterectomy). Cessation of menses as a result of removal of the ovaries is called "surgical menopause". The sudden and complete drop in hormone levels usually produces extreme withdrawal symptoms such as hot flashes, etc. Removal of the uterus without removal of the ovaries does not directly cause menopause, although pelvic surgery of this type can often precipitate a somewhat earlier menopause, perhaps because of a compromised blood supply to the ovaries.

Mechanism

Bone loss due to menopause occurs due to changes in a woman's hormone levels. The menopause transition, and post-menopause itself, is a natural life change, not usually a disease state or a disorder. The transition itself has a variable degree of effects (Soules et al., 2001). The stages of the menopause transition have been classified according to a woman's reported bleeding pattern, supported by changes in the pituitary follicle-stimulating hormone (FSH) levels. In younger women, during a normal menstrual cycle the ovaries produce estradiol, testosterone and progesterone in a cyclical pattern under the control of FSH and luteinizing hormone (LH) which are both produced by the pituitary gland. Blood estradiol levels remain relatively unchanged, or may increase approaching the menopause, but are usually well preserved until the late perimenopause. This is presumed to be in response to elevated FSH levels (Burger 1994). However, the menopause transition is characterized by marked, and often dramatic, variations in FSH and estradiol levels, and because of this, measurements of these hormones are not considered to be reliable guides to a woman's exact menopausal status (Burger, 1994). Menopause occurs because of the natural or surgical cessation of estradiol and progesterone production by the ovaries, which are a part of the body's endocrine system of hormone production. In this case, this hormone which makes reproduction possible and influence sexual behaviour is reduced or rather is ceased. After menopause, estrogen continues to be produced in other tissues, notably the ovaries, but also in bone, blood vessels and even in the brain (Simpson and Davis, 2001). However, the dramatic fall in circulating estradiol levels at menopause impacts many tissues, from brain to skin. In contrast to the sudden fall in estradiol during menopause, the levels of total and free testosterone, as well as dehydroepiandrosterone sulfate (DHEAS) and androstenedione appear to decline more or less steadily with age. Thus specific tissue effects of natural menopause cannot be attributed to loss of androgenic hormone production.
Natural or physiological menopause occurs as a part of a woman's normal aging process. It is the result of the eventual depletion of almost all of the oocytes and ovarian follicles in the ovaries (Cheung, 2012). This causes an increase in circulating follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels because there are a decreased number of oocytes and follicles responding to these hormones and producing estrogen. This decrease in the production of estrogen leads to the perimenopausal symptoms of hot flashes, insomnia and mood changes. Long-term effects may include osteoporosis and vaginal atrophy.

**Stages of menopause**

There are three stages of menopause, and they include:

- **Premenopause**

Premenopause is the first stage of menopause. It starts when a woman enters the reproductive years, and finishes with the first signs that menopause is getting closer (Kato et al., 2010). The beginning of Premenopause can be identified with the first menstrual cycle (i.e. menarche): in contrast, the end is not as clear, as it manifests variably in the late 30s or 40s with the first discomforts of menopause, such as hot flashes, mood swings, etc.

- **Perimenopause**

The term “Perimenopause”, which literally means “around the menopause”, refers to the menopause transition years, a span of time both before and after the date of the final episode of flow (Jerilynn and Prior, 2013). During perimenopause, there are fluctuations of hormones. These fluctuations cause many of the physical changes during perimenopause as well as menopause (Chichester et al., 2011). Some of these changes are hot flashes, night sweats, difficulty sleeping, vaginal dryness or atrophy, incontinence, osteoporosis, and heart disease. During this period, fertility diminishes, but is not considered to reach zero until the official date of menopause. The official date is determined retroactively, once 12 months have passed after the last appearance of menstrual blood. Signs and effects of the menopause transition can begin as early as age 35, although most women become aware of the transition in their mid to late 40s, which is often many years after the actual beginning of the perimenopausal window. The duration of perimenopause with noticeable bodily effects can be as brief as a few years, but it is not unusual for the duration to last ten or more years. The actual duration and severity of perimenopause effects for any individual woman currently cannot be predicted in advance. Even though the process, or the course, of perimenopause or menopause can be difficult to predict, the age of onset is somewhat predictable: women will often, but not always, start these transitions (perimenopause and menopause) about the same time as their mother (kessenich and Cathy, 2013).

In some women, menopause may bring about a sense of loss related to the end of fertility. In addition this change often occurs when other stressors may be present in a woman's life:

- Caring for, and/or the death of, elderly parent;
- Empty-nest syndrome when children leave home;
- The birth of grandchildren, which places people of "middle age" into a new category of "older people" (especially in cultures where being older is a state that is looked down on).

- **Post-menopause**

The term "postmenopausal" describes women who have not experienced any menstrual flow for a minimum of 12 months, assuming that they do still have a uterus, and are not pregnant or lactating (Harlow et al., 2012). In women without a uterus, menopause or post-menopause can be identified by a blood test showing a very high FSH level. Thus post-menopause is all of the time in a woman's life that take place after her last period, or more accurately, all of the time that follows the point when her ovaries become inactive.

The reason for this delay in declaring post-menopause is because periods are usually erratic at this time of life, and therefore a reasonably long stretch of time is necessary to be sure that the cycling has actually ceased completely. At this point a woman is considered infertile; however, the possibility of becoming pregnant has usually been very low (but not quite zero) for a number of years before this point is reached. A woman's reproductive hormone levels continue to drop and fluctuate for some time into post-menopause, so hormone withdrawal effects such as hot flashes may take several years to disappear.
Management

Perimenopause is a natural stage of life. It is not a disease or a disorder, and therefore it does not automatically require any kind of medical treatment. However, in those cases where the physical, mental, and emotional effects of perimenopause are strong enough that they significantly disrupt the everyday life of the woman experiencing them, palliative medical therapy may sometimes be appropriate.

Hormone replacement therapy

In the context of the menopause, hormone replacement therapy (HRT) is the use of estrogen, plus progestin in women who have an intact uterus and estrogen alone in those without a uterus (WHO, 2010). HRT may be reasonable for the treatment of menopausal symptoms such as hot flashes. Its use appears to increase the risk of strokes and blood clots. When used for menopausal symptoms it should be used for the shortest time possible and at the lowest dose possible. The response to HRT in each postmenopausal woman may not be the same. Genetic polymorphism in estrogen receptors appears to be associated with inter-individual variability in metabolic response to HRT in postmenopausal women. It also appears effective for preventing bone loss and osteoporotic fracture.

Effects of menstruation on the number and distribution of blood cells

The regular monthly discharge of blood through the female genital tract give rise to the mere thought that there might be an effect on the population of blood cells in the body. Menstruation occurs primarily in humans and close evolutionary relatives such as Chimpanzees (Strassmann, 1996). Menstruation is defined as the shedding of the uterine lining (endometrium) accompanied by the discharge of blood from the endometrial arteries. Normally, blood loss during menstruation ranges from 10 to 80ml (David, 2004).

Effect of menstruation on red blood cells

The need to transport oxygen and remove carbon dioxide from animal tissue is a fundamental requirement of life, independent of age or sex. The role of iron in humans and many other mammals is central to this process. Iron is needed for a number of highly complex processes that continuously take place on a molecular level and that are indispensable to human life. Iron is required for the production of red blood cells (a process known as erythropoiesis), and it is also part of haemoglobin, binding to the oxygen and thus facilitating its transport from the lungs via the arteries to all cells throughout the body. Once the oxygen is delivered, the iron binds the carbon dioxide which is then transported back to the lungs from where it gets exhaled. Iron is also involved in the conversion of blood sugar to energy.

Menstruation is the principal cause of iron loss in women (Guyton and Hall, 2006). Due to this loss, normal haemoglobin production slows down leading to decreased haemoglobin concentration in menstruating women. The effect of menstruation on iron-status indicators was examined in 1712 women aged 18-44 years from the Second National Health and Nutrition Examination Survey (NHANES II) after adjusting for potential confounders. Adjusted mean values of haemoglobin, transferring saturation and serum ferritin were lowest for women whose blood was drawn during menstruation and highest for women examined in luteal or late luteal phase of the menstrual cycle (Chapman and Hall, 1994).

Effects of menstruation on platelet counts

The menstrual period is associated to the rupture of blood vessels which irrigate the superficial layer of the endometrium. Platelets constitute the first haemostatic component that mobilizes in order to interrupt the bleeding as vascular injury occurs. Exacerbated platelet activation may result in a platelet consumption transcending the capacity of reposition by bone marrow. Previous researches carried out by Dusse et al in 2002 shows that there is a significant decrease in the platelet number at the first day of menstruation compared to the medium day of the menstrual period. From the second day of menstruation, platelet counts are found to be increased as a result of the body’s response to decreased platelet number in the peripheral blood (Dusse et al., 2002).

Effects of menstruation on leukocyte counts

During menstruation, tremendous numbers of leukocytes are released along with the necrotic materials and blood. This is probable as a result of some substances released by the endometrial necrosis which causes the outflow of leukocytes during menstruation. As a result of these leukocytes, the
uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded (Guyton and Hall, 2006). In order to retain this resistance to infection during menstruation, the body produces more leukocytes during this period.

Previous researches carried out by Agoreyo and Asowata in 2010 shows that there is a significant increase in the total leukocyte and granulocyte count. However, the agranulocyte counts are reported to show only a minute increase during menstruation which was not statistically significant.

Effects of menopause on haematological profile

As previously stated, menopause is permanent cessation of menstrual cycles, and the loss of estrogen function. Menopausal women no longer menstruate; therefore the monthly loss of iron during menstruation is decreased.

Previous studies carried out by Mirand and Gordon, 1966; Bodis et al., 2003 and Horiguchi et al., 2005 indicated an increase in the haemoglobin of menopausal women. But the studies carried out by Achie and Olorunshola in 2011 suggested a decrease in the haemoglobin level of menopausal women as compared to their control. However Achie and Olorunshola suggested that the decrease in the haemoglobin level of these menopausal women may be as a result of the effect of nutrition in their subjects, as some of them were retirees (being older), widows and also unemployed.

Studies by Bain, 2006 and Vazquez et al., 2009 suggested an increase in the red cell indices of menopausal women; however, there were no significant difference in the haematocrit (PCV) between premenopausal and menopausal women.

Conclusion

During menstruation, tremendous numbers of leukocytes are released along with the necrotic materials and blood. This is probable as a result of some substances released by the endometrial necrosis which causes the outflow of leukocytes during menstruation.

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