

ENDOCRINE EVENTS AND LIFE STAGES OF WOMEN

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The sex of every baby is determined at the time of conception¹. If a "Y" carrying sperm fertilizes an ovum, the sex of the developing fetus will be male. If the ovum is fertilized by a sperm carrying X chromosome, the result will be a female embryo. On each side of the embryo, a primitive gonad arises from the genital ridge². The gonad develops a cortex and a medulla. Until the sixth week of development, these structures are identical in both sexes. In case of XY chromosomes, the medulla develops into a testis during the 7-8 weeks and the cortex regresses¹. Leydig cells appear next and small amount of testosterone is secreted for growing male sex organs of fetus². While in case of XX chromosomes, the cortex develops into an ovary and the medulla regresses. The embryonic ovary does not secrete hormones. Each of the embryonic ovaries is initially populated by about 1000 to 2000 primordial germ cells which through rapid proliferation give rise in each ovary to about three million oocytes¹. This number of oocyte is reduced through cell death to 1 million at birth and each of them is surrounded by a single layer of flattened epithelial cells, granulosa cells. The ovum remains inactive and is suspended in the prophase stage of meiotic division till puberty¹. After puberty in response to GnRH from hypothalamic pituitary glands produce gonadotrophic hormones. The responsibility of imprinting the fetal hypothalamus to produce a male or female pattern of gonadotrophin release has been ascribed to testosterone².

PUBERTY

Puberty means beginning of adult sexual life. In this process infantile state is transformed to adult state in an orderly pattern, starts in the head and works its way down.

The fetal hypothalamus contains GnRH and the pituitary gland contains gonadotrophin before mid-gestation³. Both these hormones increase and contains gonadotrophin before ovarian activity at this stage. After birth, placenta separates and the levels of sex steroids drop abruptly⁴. The negative feedback action of placental steroids is removed and gonadotrophin are released from the pituitary. In the newborn girls the levels of these hormones reach a maximum during first two months and then fall to baseline levels by 24 months.

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The hypothalamic- pituitary-ovarian(HPO) axis becomes quiescent and the low level of gonadotrophin and ovarian steroids are maintained up to 10 years of life². With these changes ovaries are fully developed during childhood and capable of being stimulated by gonadotrophin. If human menopausal gonadotrophin (hMG) are given to a prepubertal girl, ovulation can be induced²

The first endocrine event of puberty is an increase in the amplitude of gonadotrophin pulses at night due to increase pulsatile release of hypothalamic gonadotrophin releasing hormone (GnRH). With progress of puberty the surges of secretion of gonadotrophin occur whether the individual is asleep or awake. Physical events in this stage include thelarche, the development of breasts, followed by pubarche, the development of axillary and pubic hair and then menarche, the first menstrual period. Behavior and attitudes also change and the capacity for fertility is realized, with this increase of gonadotrophin and appearance of secondary sex characteristics, HPO axis reactivates. Estradiol level increases but cannot induce ovulation till about one year after menarche. The regular ovulatory cycle begins when rising estradiol level causes LH surge from the surge generator².

Menstrual period may start anytime between 11-16 years of age because of these changes. Some research workers reported 13-24 years mean age at menarche in Saudi's women³. They also noted that, those women who were born in the past 20 years matured more than half a year earlier than their mother's generation. Girls tend to have an early onset of menses if there is a family history of early menarche. Blind women also have early menarche probably due to reduce activities and melatonin secretion. Whereas diabetic girls are reported to have a later menarche than girls with normal carbohydrate metabolism. An increase upto 30% above ideal body weight is associated with early menarche while obesity of more than 30% delay menarche³. Nutrition, Rigorous exercise, rural living, climate, life style, higher altitudes are other factors affecting menarcheal age¹.

MENSTRUAL CYCLE

Menstrual cycle, of human female is approximately 28 days in length and is usually counted as beginning with day 1 of the menstruation. The follicular phase is the first half of the cycle. During follicular phase, after the beginning of menstruation the concentration of FSH and LH begins to increase. The levels of LH was between 3.9 to 36.4 mIU/ml and FSH 4.3 to 9.2 mIU/ml during follicular phase in our female

population⁶. FSH stimulates the growth of 6-12 follicles while LH in combination with FSH promotes the maturation of a single follicle¹. Granulosa cells proliferate forming thick layers of cells. Outside these cells other layers of spindle cells (theca cells) are also formed. During follicular growth granulosa cells secrete a fluid that contains a high concentration of estrogens.

In our study, estradiol was found in the range of 19.4 to 256.6 Pg/ml during the proliferative phase and 33 to 201.8 Pg/ml during the secretory phase⁶. Estrogens cause the granulosa cells to form increasing number of FSH receptors and hence FSH secretion increases from the anterior pituitary gland by positive feedback mechanism. In combination with FSH, estrogens also promote LH receptors. Approximately two days before ovulation, the rate of secretion of LH increases six to ten fold (LH surge) which has specific effect on the granulosa and theca cells and converts most of them into progesterone secreting cells. Therefore, the rate of secretion of estrogen begins to fall approximately 1 day prior to ovulation, while small amounts of progesterone begin to be secreted'. Because of the rapid growth of follicle, decrease secretion of estrogens and beginning secretion of progesterone, ovulation occurs. Ovulation usually occurs at about 14th day of the cycle. After few hours of expulsion of the ovum from the follicle, the remaining granulosa cells change rapidly into lutein cells and become filled with lipid inclusions, forming yellowish colour mass, corpus luteum. As this process of luteinization is due to LH, hence LH has been given the name luteinizing hormone. In presence of LH, corpus luteum grows, maintains and secretes progesterone and estrogens but more progesterone. In our study the mean level of progesterone during the follicular phase was 0.84±0.35 ng/ml and luteal phase 10.03±5.26 ng/ml. In a study progesterone was found below 1 ng/ml prior to menstruation⁸. Some authors stated that circulating concentration of progesterone and estradiol could be elevated on the day bleeding begin and conversely the levels of these hormones could be low' for some days without menstruation occurring⁹. The estrogens in particular and progesterone to a lesser extent exert a negative effect on the hypothalamus and anterior pituitary resulting in a gradual lowering of LH and FSH levels. An author stated that estradiol initially inhibits gonadotrophin levels but prolong exposure (over 30 hours) to elevated estradiol level results in increased LH secretion¹⁰. On 26th day of the normal female sexual life due to loss of LH, corpus luteum degenerates completely. Now, the lack of secretion of the estrogen and progesterone by the CL removes the feedback inhibition of the anterior pituitary gland, and Gonadotrophin are secreted. These hormones initiate growth of new' follicles and new cycle is started.

Besides ovulation, the other purpose of the monthly cycle is to prepare uterine endometrium for implantation of zygote. Under the influence of estrogen secreted during follicular phase, the stromal cells and epithelial cells in the endometrium proliferate rapidly and growth of the endometrial glands and blood vessels occurs. After ovulation estrogens cause slight additional proliferation in the endometrium, whereas progesterone causes marked swelling and secretory development of the endometrium forming thick coiled structure. At the end of the secretory phase, the endometrium has a thickness of 5-6 mm with increase blood supply¹. In the last two days of cycle due to sudden reduction/withdrawal of estrogens and especially progesterone, necrosis of endometrial blood vessels occurs. Except basal layer all the outer layers of endometrium separate from the uterus. The mass of tissues and blood vessels in the uterine cavity and contractile effects of the prostaglandin, initiate uterine contractions that expel the uterine contents. This menstruation in most women takes 4 to 5 days. After menstruation, the endometrium regenerates from the residual basal layer during proliferative phase of the next cycle. Absence of menstruation at the age of 16 years is pathological condition in women. Such patients are required progesterone therapy. Failure to bleed after therapy indicates either estrogen deficiency or a uterine disorder. In a study it was demonstrated that uterine bleeding usually occurs with this therapy in patients having estradiol level more than 50 ng/ml¹¹. Estrogen deficiency can be excluded by administering estrogen prior to progesterone. The absence of withdrawal bleeding after this regimen suggests the presence of uterine disease.

PREGNANCY

When ovulation occurs, the ova along with attached granulosa cells are released into peritoneal cavity where they find their way into closely adherent uterine tubes, fallopian tubes. Fertilization of ovum by previously introduced spermatozoa during intercourse, takes place in the mid portion of the uterine tube. On the other side these tubes are connected to the upper lateral aspects of the uterus which is a thick walled, muscular organ that serves as site for fetal development. Ciliated mucosal cells of fallopian tubes beat toward the uterus and convey the zygote towards the uterus in 3-4 days¹. During this transport several stages of division occur, now called blastocyst, with about 100 cells². After reaching the uterus, the developing blastocyst usually remains in the uterine cavity for 2-4 days. Implantation occurs on about 7th day after ovulation due to trophoblast cells, develop over the surface of the blastocyst². With implantation trophoblast secretes Human Chorionic Gonadotrophin (HCG) which has same function as LH and thus maintains Corpus Luteum (CL) to secrete Progesterone and Estrogens'. These hormones cause

endometrium to continue growing and to secrete large amounts of nutrients. The levels of HCG rise very rapidly after implantation, doubling every 1.7 to 2.0 days and reach a serum concentration of 100 mIU/ml around 14 days after ovulation¹². Peak level (40000-60000 mIU/ml) occur at approximately 9 to 10 weeks of gestation, then falls and remains low (10000 mIU/ml) for the remainder of pregnancy¹³. Before implantation, the blastocyst obtains its nutrition from the endometrial secretions called the uterine milk. After that trophoblast and other sub lying cells proliferate rapidly forming a protective wall, placenta which produces hormones by utilizing either fetal or maternal precursors¹⁴. In addition, food stuffs diffuse through placenta from mother's blood into the fetal blood and excretory products from the fetus back into mother. A study documented that appetite of pregnant women is increased by progesterone by increasing the catabolism of protein¹⁵. If the corpus luteum is removed before 50 days of pregnancy, abortion will occur whereas its removal after that is without effect because placenta begins to secrete sufficient quantities of Progesterone and Estrogen to maintain pregnancy¹⁶. Progesterone replacement therapy is therefore, necessary whenever, the corpus luteum is removed surgically before completion of the seven week of gestation. Vaginal suppositories of 100 mg would be expected to give peak levels of 20 ng/ml, which should adequately supplement deficient endogenous secretion². However, there are substantial variation in absorption of the suppositories, progesterone levels should be measured in these patients.

In our study, progesterone levels were found constant in the first trimester (42.05JM3.76 ng/ml), then rose (126.0j24.76 ng/ml) and before term again decreased (109.33J24.08 ng/ml)⁶. A study gave information that mean serum progesterone in women with ectopic pregnancies were lower than those with intrauterine pregnancies¹⁷. Whereas, estradiol levels increased steadily with the progress of pregnancy⁶. The increased production of estradiol in the third trimester is due to prostaglandin synthesis before labour. While the constant level of progesterone may be due to gradual failure of secretion of the corpus luteum before the takeover by the trophoblast of progesterone production. The increased level of progesterone during second trimester is derived largely from placental extraction of maternal cholesterol with subsequent conversion in the placenta to progesteron¹⁸. In the last trimester more progesterone is converted into 20 alpha-dihydro progesterone. The fall in progesterone and rise in estrogen in the maternal plasma are considered as pre-requisites of parturition¹⁹. To explain the point that fall in progesterone level is necessary for delivery. Some scientists, for premature delivery, treated lamps with 3 beta-hydroxysteroid dehydrogenase inhibitor injection which resulted in progesterone withdrawal, increased PGF₂ alpha

secretion and uterine contractions²⁰. Gonadotrophin have no prominent role during pregnancy. This may be the reason that both these pituitary hormones were quite low in pregnant women⁶. However, prolactin levels were progressively increased during gestation most probably due to its role in future lactation⁶. A study documented that abortion of one out of three cases occurred decreased levels of prolactin during pregnancy²¹. Some research workers claimed that estrogens have a stimulating effect on the secretion of prolactin²². Another study showed that prolong lactational amenorrhea in women is associated with higher prolactin level²³. The high prolactin levels (1830 mIU/ml) in these patients were treated with gradually increasing doses of bromocriptine which reduce the levels to 350 mIU/ml²⁴.

PARTURITION

During pregnancy progesterone makes the endometrium secretory and inhibits uterine contractility while estrogens enlarge uterus and external genitalia and increase contractility of uterus. From the 7th month onward the level of progesterone decreases slightly. E2/P ratio increases which increase contraction of uterus²⁵. Due to the contraction of uterus fetus irritates or stretch uterine cervix of mother and cause her posterior pituitary gland to secrete increase oxytocin hormone². In addition, the fetal membranes secrete prostaglandin in high concentration during these contractions. These two hormones further increase the intensity of the uterine contractions. Besides hormonal factors, movements of fetus stretch uterus and cervix and resulting in uterine contraction. These contractions become stronger toward the end of pregnancy till the baby is expelled. The strong contractions that result in final parturition are called labour contractions.

This stage in women's life of equal interest as many of the changes over the nine month of pregnancy are reversed in hours. In our study, we found decreased progesterone level (44.04^6.5 ng/ml) and increased estradiol level (2340.0+' 208.4 Pg/ml) before labour⁶. Some scientists reported a value of 5 in serum progesterone/estradiol ratio to precede the term labour²⁵. Other investigators established the hypothesis that a relative decrease in fetal membrane progesterone levels would result in the release of phospholipase A2 from lysosomes²⁶. This enzyme then would cleave arachidonic acid from phospholipid and the labour would initiate prostaglandin synthesis in fetal membranes and decidua. Prostaglandin E2 and F2 alpha thus synthesized would then cause cervical ripening and uterine contractions. In a study exogenous progesterone in high doses (200 ng/day) inhibited parturition²⁷. In addition, we found that the levels of both estradiol (1271 j+141.8 Pg/ml) and progesterone (11.64^2.3 ng/ml) completely declined after 1-2 days postpartum⁶. The reason may be that

placenta, the main source of progesterone and important producer of estradiol is expelled. Similar results were reported by others²⁸.

LACTATION

During gestation estrogens cause the ductal system of the breasts to grow and to branch. Once the ductal system has developed, progesterone makes it secretory in function. But both these hormones inhibit actual secretion of milk. There is another hormone prolactin, the concentration of which rises steadily from 5th week of pregnancy till birth. This hormone promotes the secretion of milk. In addition, placenta secretes human chorionic somatomammotrophin which also has mild lactogenic properties². After parturition progesterone and estrogens are suddenly decreased and actual milk secretion is thus started. The elevated levels of prolactin also fall to non-pregnant level. However, at the time the mother nurses her baby, nervous signals from the nipples of breasts to the hypothalamus cause a 10 to 20-fold surge in prolactin secretion². Crying of baby also give such signals to hypothalamus for milk secretion. In about half of nursing mothers, these signals inhibit secretion of GnRH and intern Gonadotrophin (Lactational Amenorrhea). Some research workers reported that in long term lactational amenorrhea, basal serum prolactin levels were significantly higher in a group of amenorrheic nursing mothers than they were in menstruating nursing mother²⁹. Physiological status associated with elevated prolactin levels include physical and emotional stress, sleep and hypoglycemia³⁰.

MENOPAUSE

The menopause is defined as permanent cessation of menstruation, is derived from the Greek Word "men" (gen. menos) meaning month, moon and "pauin" to stop. The mean age of menopause in the United States is about 51 years, with a normal distribution curve and 95% confidence limits between ages 45 and 55 years³¹. At this age only a few primordial follicles are left and hence production of estrogens by the ovary decreases. The small amount of estrogens cannot cause surge of LH and FSH essential for ovulation. When ovulation does not occur, corpus luteum is not formed and there is no secretion of estrogens and progesterone. Due to weak negative feedback effect of estrogens and lack of feedback effect of progesterone, production of LH and FSH increases and hence sexual cycles disappear (Menopause).

In our study we found that steroid hormones (Estradiol 23.84 ± 3.8 Pg/ml and progesterone 0.7 ± 0.1 ng/ml) decreased and Gonadotrophin (LH 27.7 ± 2.2 mIU/ml and FSH 38.1 ± 3.4 mIU/ml) increased after menopause⁶. These findings are important from the diagnostic point of view. In a study a 42 years' women stated that she had been in menopause from last 12

years but her investigation showed low levels of gonadotrophin consistent with hypothalamic amenorrhoea³². Besides, it was demonstrated that the hormonal changes begin about 5 years before the actual menopause³³.

These changes account for the fact, that some women will have hot flushes, vaginal atrophy, depression, anxiety, memory loss and nervousness³⁴. Estrogen replacement therapy relieve these symptoms and allowing the patients to sleep better³⁵. The same therapy had some risk like breast discomfort, headache, fluid retention and sometime endometrial cancer. Its cancer risk can be minimized with the addition of progesterone³⁶ but progesterone induces monthly withdrawal bleeding which many women consider inconvenient.

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