Physiology 4

Female reproductive cycle (uterine cycle):

The uterine cycle is composed of three phases (menstrual phase, proliferative phase and secretory phase).

- First: Menstrual phase:

At the end of the ovarian cycle, if there is no pregnancy, the level of progesterone and estrogen will become almost zero. What are the results of their withdrawal?

The blood supply to the endometrium decreases because the blood vessels become constricted and necrotic, no blood supply, degeneration and the sloughing of the endometrium occurs.

- Menstruation lasts usually 4-5 days. It can be as short as 1 day and as long as 8 days. The duration does not matter and there are no problems as long as it's fixed and regular.
- Blood amount is usually 30 ml, ranges from spots to 80 ml. If it exceeds 80 ml then it's abnormal.
- The amount and duration of menses is affected by some drugs and diseases.

- Second: Proliferative phase:

The uterus prepares itself for the implantation. Uterine glands elongate and spiral arteries grow to supply the thickened endometrium. The proliferative phase coincides with high concentration of estrogen therefore it's called the estrogen phase.

- Third: Secretory phase:

Coincides with the luteal phase, the changes which occur in the proliferative phase are further augmented here. The secretory phase coincides with high concentration of progesterone therefore it's called sometimes the progesterone phase.

These points are very important about the hormones and their production :

- In mammals removal of gonads results in decreased or absent sexual activity in both sexes.

- Injection of gonadal hormones in castrated animals revives sexual activity, (this is expected).

- Testosterone in male and Estrogen in the female have most marked effect (also this is expected), large doses of testosterone and other androgens in castrated females initiate female behavior and large doses of estrogens in castrated males trigger male mating responses, (this is the unexpected) but they explained that in the body these hormones are converted to the opposites sex hormones, testosterone into estrogen and vice versa.

- In women ovariectomy does not necessarily reduce libido, post-menopausal women continue to have sexual relations often without much change in frequency from the premenopausal pattern, however adrenal androgens are still present in these women.
- Testosterone for example increases libido in males and so does estrogen which is used to treat some diseases such as carcinoma of prostate.

- The behavioral pattern that was present before treatment is stimulated but not redirected; administration of testosterone to homosexuals intensified their homosexual drive but did not convert it to heterosexual drive.
- The day after ovulation the overall body temperature rises from 0.5-1.0 centigrade this is because of progesterone, and this indicates the presence of ovulation in the previous day (useful to prevent pregnancy).

- The dr. briefly mentioned some functions for estrogen and progesterone:
    - Effect of estrogen:
        - On bones, increases growth by osteoblasts.
        - Endocrine, increases progesterone responses.
        - Steroid binding, females are protected from high cholesterol because of high estrogen
        - Reproductive organs
    - Effects of progesterone:
        - On breast, growth of milk-producing glands.
        - Endometrial growth and secretions.
        - Increases internal temperature.

Time of development of the different physical manifestations of puberty in boys and girls:

- First sign of puberty in females is budding of the breasts → Thelarche. While in males the first sign is the increase in the size of testes.
- Within one year, appearance of pubic hair (Pubarche)
- 2 years after budding of breasts, first menstrual cycle occurs→Menarche (the reproductive life of the female begins) at about 13 years of age.

- Throughout childhood gonadotropin release is suppressed by two mechanisms that affect the hypothalamic GnRH pulse generator:
    1. The sex steroid dependent mechanism that renders the pulse generator extremely sensitive to the negative feedback by steroids
    2. Intrinsic CNS inhibition of GnRH pulse generator by substances; GABA and endogenous peptide in the CNS.

  That's why gonadotropins and GRH are low in childhood.
- But at the beginning of puberty the hormones are activated, this response involves decrease in the sensitivity of the pulse generator to sex steroids and reduction in intrinsic CNS inhibition over GnRH pulse generator.

The factors involved in the initiation (timing) of puberty:

1. Genetics.
2. Nutritional.
3. Climatic.
4. Geographic.
   Those are the main factors that determine timing, other factors:
5. Leptin: permissive effect on initiation of puberty providing signals to the CNS that there is sufficient energy stores to support reproduction, When this hormone is deficient the puberty is delayed.
6. Distance from the equator (خط الاستواء)
7. Obesity and heavy exercise delay puberty, while overweight makes puberty early.

Age of puberty has declined over the last 150 years by 2-3 months per decade, this correlates with the improvement in nutrition and general health all over the world.

- Normal pubertal growth spurt requires concerted action of sex steroids, growth hormone (GH) and insulin like growth factors (ILGF).

Fertilization:

- Sperms remain in the female reproductive system for two days capable of fertilizing the ovum.
- The woman is considered pregnant at the time of fertilization.
  The duration of pregnancy is 38 weeks (from the time of ovulation) or 40 weeks from the first day of the last menstrual cycle).
- Oviducts or fallopian tubes transport the sperms from uterus to fertilization site, and transports fertilized ovum from fertilization site to uterus, this requires coordination between smooth muscle contractions, ciliary movement and peristaltic movement (for the ovum) and fluid secretion, all are under hormonal and neural control.

- The female sex response facilitates sperm transport through the female reproductive tract.
  1. Uterine and cervical activity increased by the spinal reflexes during orgasm.
  2. The cervix dilates during orgasm.
  3. Oxytocin release at the time of orgasm increases uterine contractility.
  4. The mucus of the cervical canal increases the movement of the sperm under estrogen dominance and orgasm.
  5. Activity and fluid flow in the oviduct assists transport.

- The peristaltic activity in the uterine tube: another important point about the movement of the zygote towards the uterus; is that it is in a one way direction → behind the zygote are contractions and in front of it relaxation.

- Capacitation occurs in the female reproductive system by which the sperm acquires the capacity to fertilize the ovum.
  - So fertilization only occurs in the female reproductive system.
  - Upon reaching the ovum, they bind to glycoprotein receptors, these receptors are species specific.
  - The ovum recognizes the sperm of the same species.

- The embryo is enclosed by the zona pellucida, this is necessary for the transport of the embryo, protection against mechanical damage, adhesion to the oviduct's walls and prevention of immunological rejection by the mother.
- In implantation, placenta is formed, ovarian cycles are suspended and hCG is

released, because of this hormone corpus luteum continues to grow, secreting more estrogen and progesterone until the end of the forth month, when placenta takes over.

- The hCG hormone is tested for in the mother after two weeks in the urine or in plasma.
  - ✓ In urine → after 3 weeks.
  - ✓ In plasma → after 2 weeks.

- There are glycoprotein receptors on the sperms to prevent the fertilization of nonspecific ovum (from another species), which might happen between animals from different species, where in that case the sperms won't be able to fertilize the ovum because of its glycoprotein receptors.

Substances secreted by the blastocyst (Table 55-2):

1- Immunosuppressive agents
2-Metalloproteases.
From these the most important one is hCG, its actions: immunosuppressant, growth promoting activity and acts as an autocrine growth factor that promotes trophoblast growth and placental development.

Hormones made by the placenta (Table 55-4):

1-Peptide hormones and neuropeptides.
2-Steroid hormones.

- You will know these hormone with time but we want the most important one from the placenta which is also hCG.
- Other hormones are *human chorionic somatomammotropins (hCS) 1 and 2* (hCS is also known as *human placental lactogen, hPL*). Those hormones (1 and 2) are polypeptides that are structurally related to growth hormone, placental-variant growth hormone and prolactin. They are important in conversion of glucose to fatty acids and ketones, thus coordinating the fuel economy of the feto-placental unit. The fetus and placenta use fatty acids and ketones as energy sources and store them as fuels in preparation for the early neonatal period; when a considerable reservoir of energy is necessary for the transition from intrauterine life to life outside uterus. They also promote the development of maternal mammary glands during pregnancy.

- Although hCG and human placental lactogens (1, 2) are produced by the same cells, it seems that the pattern of secretion is different indicating the possibility of different regulatory mechanisms.
- Morning sickness is most probably caused by the high concentrations of thyroxin and hCG (since during this period these two hormones are relatively high).
- From the second week hCG increases drastically and it reaches the highest concentration between week 10 and 13.

The fetoplacental unit and steroidogenesis (Figure 38.7):

- Placenta produces steroid hormones, progesterone, estrone- estradiol but mainly estriol.
- The levels of estriol in plasma, amniotic fluid and urine are used as an index for fetal well-being. Low levels of estriol would indicate potential fetal distress, although rare inherited sulfatase deficiencies can also lead to low estriol.
- There is cooperation between these three compartments to produce androgens and estrogens; to produce the androgens and estrogens the placenta needs the substrates form both maternal and fetal compartments.

Fetal endocrine system:

- The fetal nervous and immune systems develop slowly but the fetal endocrine system plays a vital role in fetal growth, development and homeostasis.
- Fetal hormones perform the same functions in the adults, but also have unique processes such as sexual differentiation and initiation of labor.
- Adrenal glands are unique in size, structure and function. At about the forth month of gestation the size of the adrenal glands in the fetus is larger than the size of its kidneys.
  - The fetal adrenal gland (adrenal cortex) produces androgens, aldosterone and cortisol; cortisol is essential for the growth and maturation of the lungs, pancreas, hepatic enzymes and GIT cytodifferentiation.
  - The adrenal medulla functions properly and begins to produce catecholamines after week 10.

- Fetal growth is gradual, but during the last 3 months of pregnancy it increases significantly under the effect of insulin, not growth hormone.

- The most important factor in the fetus as far as the growth is concerned is insulin. Fetal insulin is the most important hormone in regulating fetal growth. Glucose is the main metabolic fuel for the fetus.
- Fetal insulin is produced by the pancreas by week 12 of gestation. It regulates tissue glucose use, controls liver glycogen storage, and facilitates fat development. It doesn't control the supply of glucose; this is determined by the maternal gluconeogenesis and placental glucose transport. The release of insulin in the fetus is relatively constant.

Initiation of labor

- During pregnancy the uterus is inactive under the effect of progesterone and relaxin. During the last month of pregnancy, weak and irregular uterine contractions occur, these contractions end in rhythmic forceful contractions that last for hours-one day or even more, and these forceful contractions end in delivery.

- Not all the pathways leading to delivery are known but endocrine, paracrine and mechanical stretching of the uterus all play a role. Once labor is initiated it is sustained by a series of positive feedback mechanisms.

- The last theory of initiation of labor is that labor is initiated by hormones released from fetus. Fetal pituitary ACTH is the initiator of labor, it affects fetal adrenals, and DHEA-S (dehydroepiandrosterone sulfate) is produced, this affects the placenta which leads to an increase in local estrogen and progesterone ratio which in turn increases local prostaglandins. Fetal adrenals also produce cortisol.

- Oxytocin (from the maternal pituitary), the high local estrogen progesterone ratio, local prostaglandins (both of these from the fetus) and catecholamines (both maternal and fetal) contribute in the contractions of the uterus for labor to occur.

Breastfeeding:

- After delivery prolactin is needed for milk, prolactin needs estradiol which moderates prolactin secretion by two means:
    1. Increases the sensitivity of Lactotrophs for stimulation by PRH.
    2. Decreases the sensitivity of the Lactotrophs for inhibition by Dopamine.

- If the mother doesn't nurse her baby within 2 weeks, Prolactin secretion decreases and returns to the levels of a non-pregnant woman. If the mother nurses her baby, prolactin secretion will be maintained as long as there is suckling.
- Lactation inhibits ovarian cycles; suckling reduces the release of GnRH from the hypothalamus. However if the mother continues to nurse her infant for a long period, the cycle eventually resumes.
- A study that was conducted about "Breast feeding in Bangladesh women" shows that the average period of un-ovulation is 18-24 months.
- If the mother doesn't nurse the infant the cycle will resume 8-10 weeks after delivery up to 18 week.
- Oxytocin causes the ejection of milk.