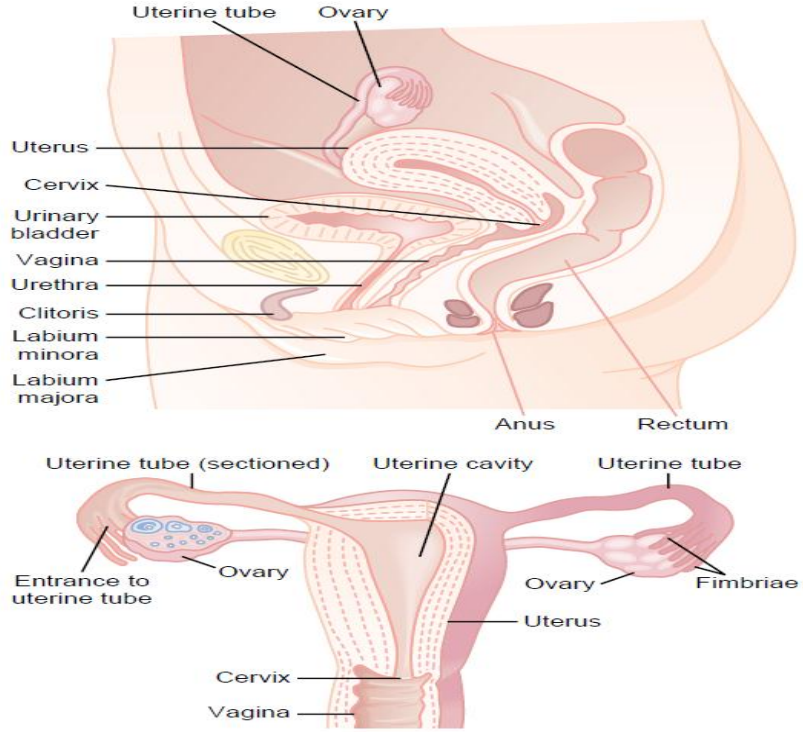
Lecture No.9

Female Physiology Before Pregnancy and Female Hormones

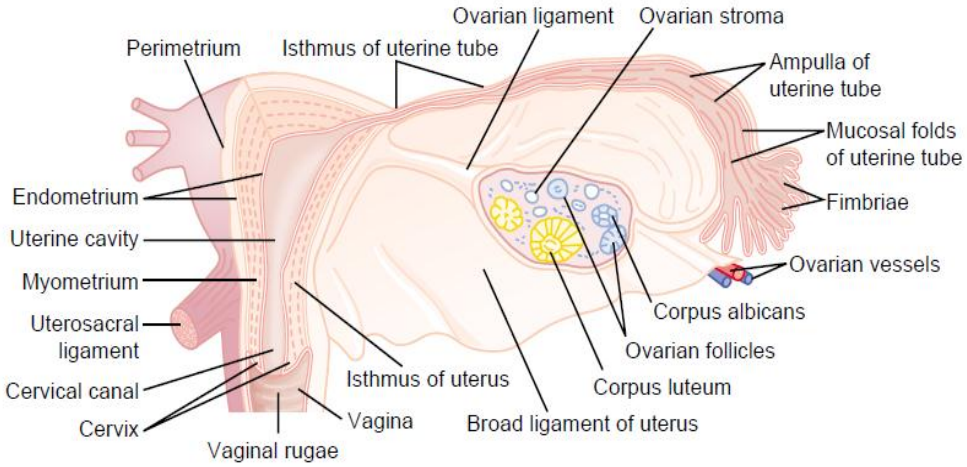


Female reproductive functions can be divided into two major phases: (1) preparation of the female body for conception and pregnancy, and (2) the period of pregnancy itself.

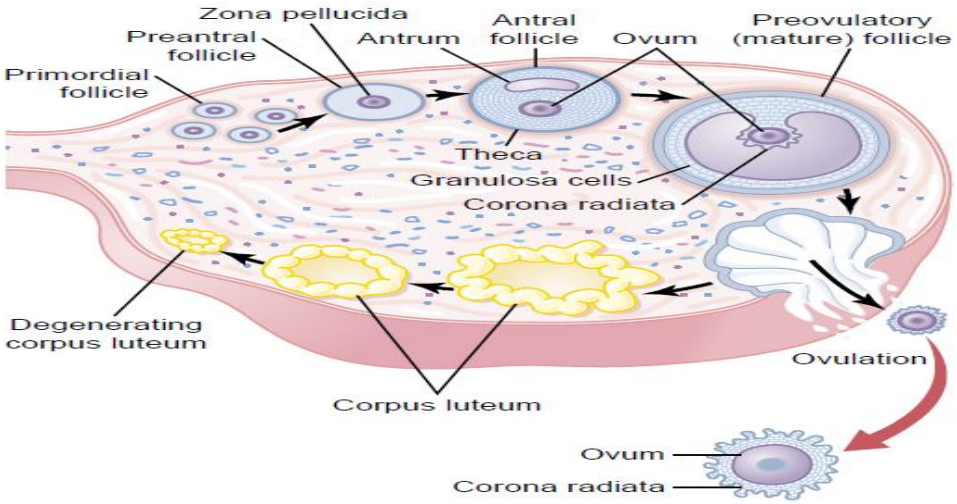
Physiologic Anatomy of the Female Sexual Organs

The figure above and the figure below show the principal organs of the human female reproductive tract, the most important of which are the *ovaries, fallopian tubes, uterus,* and *vagina.* 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 abdominal 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 fetus, a placenta, and fetal membranes—and eventually into a baby. During fetal life, the outer surface of the ovary is covered by a *germinal epithelium,* which embryologically is derived from the epithelium of the germinal ridges. As the female fetus develops, *primordial ova* differentiate from this germinal epithelium and migrate into the substance of the ovarian cortex. Each ovum then collects around it a layer of spindle cells from the ovarian *stroma* (the supporting tissue of the ovary) and causes them to take on epithelioid characteristics; they

are then called *granulosa cells.* The ovum surrounded by a single layer of granulosa cells is called a *primordial follicle.* The ovum itself at this stage is still immature, requiring two more cell divisions before it can be fertilized by a sperm. At this time, the ovum is called a *primary oocyte.*
During all the reproductive years of adult life, between about 13 and 46 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 reproductive capability (at *menopause*), only a few primordial follicles remain in the ovaries, and even these degenerate soon thereafter.



Ovarian Follicle Growth—"Follicular" Phase of the Ovarian Cycle
The figure below shows the progressive stages of follicular growth in the ovaries. 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*, as shown in the figure. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an *oocyte maturation-inhibiting 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.*

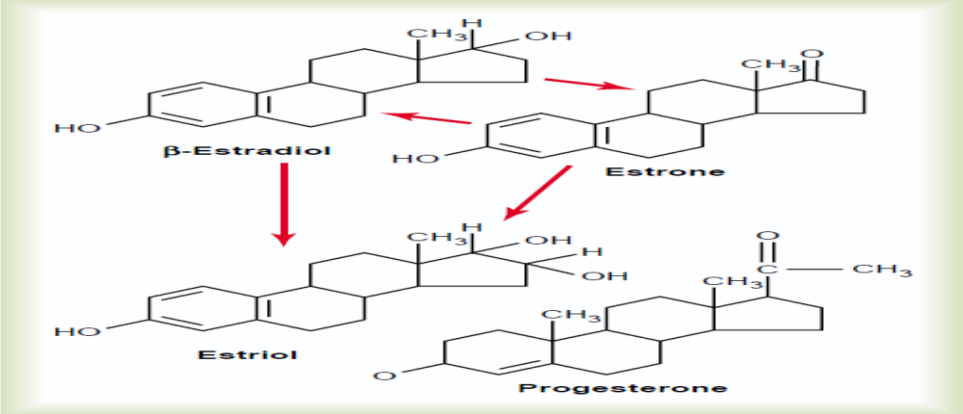


Functions of the Ovarian Hormones—Estradiol and Progesterone

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.* 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 Hormones

Estrogens. In the normal *nonpregnant* female, estrogens are secreted in significant quantities only by the ovaries, although minute amounts are also secreted by the adrenal cortices. During *pregnancy*, tremendous quantities of estrogens are also secreted by the placenta. Only three estrogens are present in significant quantities in the plasma of the human female: *β-estradiol*, *estrone*, and *estriol*, the formulas for which are shown in figure below. The principal estrogen secreted by the ovaries is β-estradiol. Small amounts of estrone are also secreted, but most of this is formed in the peripheral tissues from androgens secreted by the adrenal cortices and by ovarian thecal cells. Estriol is a weak estrogen; it is an oxidative product derived from both estradiol and estrone, with the conversion occurring mainly in the liver. The estrogenic potency of β-estradiol is 12 times that of estrone and 80 times that of estriol. Considering these relative potencies, one can see that the total estrogenic effect of β-estradiol is usually many times that of the other two together. For this reason, β-estradiol is considered the major estrogen, although the estrogenic effects of estrone are not negligible.



Progestins. By far the most important of the progestins is progesterone. However, small amounts of another progestin, 17-a-hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects.Yet, for practical purposes, it is usually reasonable to consider progesterone the only important progestin. In the normal nonpregnant female, progesterone is secreted in significant amounts only during the latter half of each ovarian cycle, when it is secreted by the corpus luteum. As we shall see a large amounts of progesterone are also secreted by the placenta during pregnancy, especially after the fourth month of gestation.

Estrogens and Progesterone Are Transported in the Blood Bound to Plasma Proteins. 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.

Functions of the Liver in Estrogen Degradation.

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 totally impotent estrogen estriol. Therefore, diminished liver function actually *increases* the activity of estrogens in the body, sometimes causing *hyperestrinism*

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.

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.

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.

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.

Effect of Estrogens on Hair Distribution.

Estrogens do not greatly affect hair distribution. However, hair does develop in the pubic region and in the axillae after puberty. Androgens formed in increased quantities by the female adrenal glands after puberty are mainly responsible for this.

Effect of Estrogens on the Skin.

Estrogens cause the skinto 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.

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.

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 are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

Effect of Progesterone on the Uterus.

By far the most important function of progesterone is *to promote secretory changes in the uterine endometrium* during the latter half of the monthly female sexual cycle, thus preparing the uterus for implantation of the fertilized ovum. In addition to this effect on the endometrium, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.

Effect of Progesterone on the Fallopian Tubes.

Progesterone also promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube before implantation.

Effect of Progesterone on the Breasts.

Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. However, progesterone does not cause the alveoli to secrete milk, milk is secreted only after the prepared breast is further stimulated by *prolactin* from the anterior pituitary gland. Progesterone also causes the breasts to swell. Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the subcutaneous tissue.

Hormone Inhibin from the Corpus Luteum Inhibits FSH and LH Secretion.

In addition to the feedback effects of estrogen and progesterone, other hormones seem to be involved, especially *inhibin*, which is secreted along with the steroid sex hormones by the granulosa cells of the ovarian corpus luteum in the same way that Sertoli cells secrete inhibin in the male testes. This hormone has the same effect in the female as in the male—inhibiting the secretion of FSH and, to a lesser extent, LH by the anterior

pituitary gland. Therefore, it is believed that inhibin might be especially important in causing the decrease in secretion of FSH and LH at the end of the monthly female sexual cycle.

Negative Feedback Effects of Estrogen and Progesterone in Decreasing Both LH and FSH Secretion

Estrogen in small amounts has a strong effect to inhibit the production of both LH and FSH. Also, when progesterone is available, the inhibitory effect of estrogen is multiplied, even though progesterone by itself has little effect. These feedback effects seem to operate mainly on the anterior pituitary gland directly, but they also operate to a lesser extent on the hypothalamus to decrease secretion of GnRH, especially by altering thefrequency of the GnRH pulses.