I. **Female Sex Hormones** - These hormones are primarily produced by the ovaries. There are two groups of female sex hormones

A. **Estrogens** - Estrogens promote proliferation and growth of specific cells in the body and are responsible for the development of most sexual characteristics of the female.

B. **Progesterones** - concerned almost entirely with the final preparation of the uterus for pregnancy and the breasts for lactation.

II. **Review of Reproduction** - As we begin our discussion of female sex hormones, we will first review a few aspects of reproduction.

A. **Reproduction begins with the development of ova (eggs) in the ovaries.**

1. A single ovum (egg) is expelled from an ovarian follicle in the middle of each monthly sexual cycle.
2. This ovum then passes through one of the fallopian tubes into the uterus, and if it is fertilized by a single sperm, it implants in the uterus where it develops into a fetus, a placenta, and fetal membranes.
3. During fetal development, the outer surface of the ovary is covered by a germinal epithelium.
4. As the fetus develops, primordial ova differentiate from this germinal epithelium and migrate into the ovarian cortex. These primordial ova carry with them a layer of epithelioid granulosa cells. The ovum, surrounded by a single layer of epithelioid cells, is called a primordial follicle. At birth, approximately 750,000 primordial follicles are present in the two ovaries combined. This number decreases rapidly, resulting in approximately 400,000 primordial follicles remaining at puberty.
   a. During all of the reproductive years of the female, only about 450 of these 400,000 primordial follicles develop enough to expel their ova. The remainder of these degenerate. Once these are gone, no more are produced and the female is at the end of her reproductive capability, which is referred to as menopause.

B. **The female hormonal system, like that of the male, consists of three levels of hormones**.

1. First is the hypothalamic releasing factor, Gonadotropin-Releasing Hormone (GnRH).
2. The second level of hormones are those that are produced by the adenohypophysis in response to this releasing factor.
   a. **FSH**
   b. **LH.**
3. These in turn stimulate the ovaries to produce estrogens and progesterones, which make up the third level.

III. The Hypothalamic-Pituitary-Ovarian Axis

In adult women, a tightly coordinated feedback system exists between the hypothalamus, anterior pituitary, and ovaries to orchestrate menstruation. This feedback system is illustrated in Figure 45-2, page 853 in Kaplan.

A. Cyclic ovarian function - depends on appropriately timed secretion of the anterior pituitary gonadotropins, FSH and LH, in response to hypothalamic GnRH.

1. Coordination of the menstrual cycle depends on the positive and negative feedback relationships between the ovarian hormones, estrogen and progesterone, and GnRH, FSH and LH secretion.
2. The release of pituitary FSH and LH requires constant pulsatile secretion of GnRH from the hypothalamus.
3. The gonadotropins are glycoproteins composed of two polypeptide chains, designated alpha and beta. The alpha chain is common to both, as well as other hormones previously discussed (e.g., TSH), whereas the beta chain is unique ensuring specific biological activity for each hormone.

The function of FSH and LH is to stimulate the gonads. FSH stimulates the growth of ovarian primordial follicles, and in the presence of LH, promotes secretion of estrogen by maturing follicles. LH causes the release of the ovum from the ovarian follicle whose maturation has been stimulated by FSH.

Following ovulation there is transformation of the ruptured follicle into the corpus luteum (i.e. luteinization), and secretion of progesterone by the corpus luteum occurs to prepare for pregnancy. This secretion of progesterone by the corpus luteum appears to also by somewhat under the control of LH (primarily) and FSH.

The release of FSH and LH is affected both positively and negatively by estrogen and progesterone. Whether estrogen or progesterone stimulate or inhibit gonadotropin secretion depends on the concentration of the hormone and the duration of exposure of the pituitary. Estrogen exerts its inhibitory effect on both the hypothalamus and pituitary. Some inhibition of FSH and LH release occurs at low levels of estrogen, but it is more complete at high levels. Progesterone in high concentrations inhibits gonadotropin secretion by suppression of hypothalamic GnRH release. In addition to these negative feedback effects, female gonadal steroids also have a positive effect on pituitary gonadotropin secretion. The positive feedback is triggered by a sharply rising plasma level of estrogen that is maintained for approximately 48 hours and is critical in promoting the LH surge required to initiate ovulation.

FSH is basically controlled by a negative feedback system. LH regulation is more complex. LH may be controlled by a negative feedback system under certain circumstances and controlled by a positive feedback system under other circumstances. First, low levels of estrogen, such as what occurs in the follicular phase of the menstrual cycle, stimulates the negative feedback center. Therefore, estrogen levels increase causing a decreased level of LH. Second, high levels of estrogen, such as seen at mid-cycle, triggers the positive feedback center. Therefore, these increased estrogen levels will lead to an increased LH level. In the luteal phase of the menstrual cycle, progesterone starts to come into play. In this phase, estrogen and progesterone stimulate the negative feedback center, therefore decreasing LH.

Hypothalamic-pituitary regulation of ovarian function is also influenced by neural stimuli from the central nervous system. The hypothalamus receives both neural and hormonal signals, which can affect GnRH

secretion and the menstrual cycle. This type of input can disrupt the pattern of GnRH secretion and lead to anovulation and amenorrhea.

While considering the hypothalamic-pituitary axis, there is another hormone to introduce at this point. This hormone is the luteotropic hormone (LTH) or prolactin (PRL). This is a protein hormone, not a steroid, which plays a role in the menstrual cycle. Prolactin is produced by the adenohypophysis and has two primary functions:

1. It acts synergistically with estrogen promoting hyperplasia of alveoli cells and mammary glands.
2. It maintains progesterone production by the corpus luteum in order to prepare the endometrium of the uterus for implantation.

Prolactin secretion is controlled in the following way. Typically the hypothalamus releases prolactin inhibitory factor (PIF) which blocks the production and release of prolactin from the anterior pituitary.

The significance of prolactin will become apparent during the discussion of the menstrual cycle. Briefly considering its function (which would begin in the luteal phase of the menstrual cycle):

↓ progesterone → ↑ LH → ↑ estrogens → ↓ GnRH → ↓ PIF → ↑ prolactin → ↑ progesterone

Estrogens

Estrogens are C18 steroid hormones, the smallest of the steroids. Estrogens are primarily produced by the ovarian follicles but they are also produced in very small amounts by the testes and the adrenal cortex.

There are three major estrogens present in the body. These are estradiol (more specifically known as 17β-estradiol, also abbreviated E_2, a hydroxy group at 17 instead of ketones), estrone (E_1), and estriol (E_3). . Of the three major estrogens, estradiol is the most potent. Estradiol is derived almost exclusively from the ovaries.

Estrogens in the female are responsible for the development and maintenance of the female sex organs and sex characteristics. During pre-puberty years, there is very little effect on the primary sexual characteristics because the ovary is almost dormant because of a sensitivity negative feedback system very similar to that seen in males. At puberty, in females, the same type of change occurs as with males. Specifically, the hypothalamus undergoes a change or a physiological maturation, and is all of a sudden less sensitive to the negative feedback system that is keeping the production of FSH at a minimum. In the female, it now takes more estrogen to regulate the production of FSH resulting in the establishment of a new equilibrium as seen with males. Therefore, FSH is increased, leading to increased follicular development, and increased estrogen production.

During the pre-puberty years, primordial follicles differentiate into proliferative primordial follicles. However, since there is not sufficient FSH, these follicles undergo atresia (degeneration due to lack of an adequate supply of FSH).

FSH stimulation of the ovaries will cause the production and release of estrogens. The synthetic pathway

is believed to be essentially the same as that seen in the adrenal cortex where acetate, cholesterol, progesterone and testosterone can all serve as precursors to estrogens. The normal ovary produces all three classes of sex steroids, estrogens, progesterones, and androgens. However, estradiol and progesterone (considered below) are its primary secretory products. Unlike the testes, the ovary possesses a highly active aromatase system that rapidly converts androgens such as testosterone to estrogens. Also, unlike the adrenal cortex, the ovary lacks 21-hydroylase and 11β-hydroxylase enzymes and can therefore not produce glucocortiosteroids nor mineralocorticosteroids.

Estrogens are not stored to any great extent by the ovary. Once released into the blood stream, estradiol is about 38% is bound to sex hormone binding globulin (SHBG), 60% bound to albumin, and 2-3% free.

Following post-puberty increases in estrogens, the following changes associated with primary female sex characteristics will occur:

1. The thickness of the vaginal lining will increase (this is why estrogens may sometimes be used in the treatment of vaginal gonorrhea).
2. The uterus will undergo the following changes:
    a. endometrial mitosis
    b. increased vascularity within the endometrium
    c. increased glandular development within the endometrium
    d increased excitability of myometrial smooth muscles
3. The ovaducts will undergo the following changes:
    a. glandular development
    b. promotion of ciliary activity - ciliated cells form currents in the ovaduct which provides sperm orientation but not sperm movement
4. Mammary gland development will include:
    a. development of mammary gland ductile components (there is no effect on alveolar components by estrogens)
    b. movement of adipose tissue to the mammary glands

Estrogens also produce influence the following secondary sex characteristics in females:

1. Skeletal System. Estrogens are potent stimulators of bone growth. Estrogens also cause early closure of the epiphyseal plates causing females to typically be shorter than males.
2. Protein Synthesis. Estrogens are potent stimulators of protein synthesis. Estrogens are usually associated with tissue growth.
3. Adipose Tissue Deposition. Estrogens result in adipose tissue (or fat) deposition under the skin at all areas of the body. This action of estrogens results in the feminine figure. On average, females have 25% more adipose tissue than do males due to estrogens.
4. Skin and Vascularity. Estrogens promote a softening of the skin and skin vascularity. Females are said to have warmer skin due to this subcutaneous vascularity.
5. Sodium Retention. Estrogens stimulate sodium and water reabsorption. This is the primary reason for water-weight build-up during the menstrual cycle in females. Estrogens cause sodium retention by two mechanisms:
    a. direct action on the kidney tubules to cause sodium retention
    b. stimulation of the zona glomerulosa to produce aldosterone resulting in sodium retention

Estrogens are metabolized in the liver. Initially it was believed that the metabolic pathway was relatively simple, i.e. the metabolic process was believed to be:

$$\text{estradiol 17-}\beta \rightleftharpoons \text{estrone} \longrightarrow \text{estriol}$$

Now it is believed that there may be 20 or more steps in the metabolic degradation of estradiol 17-β. The last step of this metabolic process of estrogens is similar to all of the other steroids in that it is a conjugation step. Estrogens are conjugated with glucuronic acid or sulfuric acid, making it more water soluble, therefore allowing passage and rapid elimination through the kidney.

Some of the tests that may be done to measure estrogens include:

1. Plasma estriol levels by immunoassay - this has its primary importance in pregnancy. A sudden decrease in plasma estriol levels indicates fetal distress.
2. Plasma estradiol and estrone levels by immunoassay.
3. Urinary estriol levels by immunoassay and fluorometric techniques - this also has significance in monitoring pregnancy.

It is important to remember when studying estrogen levels in females that these levels will vary due to the cyclic nature of the hypothalamus. Therefore, one single value is of no real significance. Estrogen levels usually must be monitored for a period of time before their clinical significance is determined.

Progesterones

Progesterones are 21-carbon steroids that are very similar structurally to corticosteroids and testosterone. The active hormone in this class is progesterone. Progesterone is a female sex hormone that works in conjunction with other hormones, primarily estrogen, to regulate various organs involved with the menstrual cycle.

Progesterone is secreted mainly by the corpus luteum in non-pregnant women. The corpus luteum is a glandular mass produced in the ovary by the ovarian follicle following the discharge of its ovum. During pregnancy, once there is the development of the placenta, this becomes a major source of progesterone. It is also produced to some extent by the testes and the adrenals. The production of progesterone is regulated by LH.

Ovarian progesterone is produced by a synthetic pathway that is similar to that seen in the adrenal cortex. Once released into the blood stream, progesterone is primarily transported by corticosteroid-binding globulin.

Progesterone produces the following changes in the post-puberty female during each monthly cycle in preparation for pregnancy:

1. The most important function of progesterone is to promote secretory changes in the endometrium of the uterus, preparing the uterus for the implantation of a fertilized ovum.
2. Progesterone functions to promote secretory changes in the mucosal lining of fallopian tubes. These secretions are important for the nutrition of the fertilized ovum as it moves through the fallopian tube on its way to the uterus for implantation

3. Progesterone promotes the development of the lobules and alveoli of the breasts. Progesterone causes alveolar cells to proliferate and become secretory in nature. Progesterone does not cause the actual secretion of milk, it just prepares for this secretion. The actual secretion is stimulated by prolactin (considered below).
4. Progesterone influences electrolyte balance within the body. Progesterone, in very large concentrations, can enhance sodium, chloride, and water reabsorption from the distal convoluted tubules in the kidney.
5. Progesterone exerts a catabolic effect on protein. Under normal circumstances, this is a mild catabolic effect and is probably not very significant. However, it appears to be significant during pregnancy when it is necessary that proteins be mobilized for use by the fetus.

Progesterone is metabolized in the liver like most of the steroid hormones. Progesterone is primarily converted to the biologically inert metabolite, pregnanediol. This metabolite is then conjugated with glucuronide and excreted in the urine.

Progesterone levels may be measured either as plasma progesterone or as urinary pregnanediol. The evaluation of urinary pregnanediol serves as an index of endogenous progesterone.

The clinical significance of progesterone lies primarily with pregnancy. Almost throughout the entire pregnancy, progesterone (and therefore urinary pregnanediol) levels continue to increase up to immediately before delivery. A sharp fall in the production of progesterone (and therefore urinary pregnanediol) is usually associated with fetal death or abortion once the placenta degenerates and stops producing progesterone.

There is a great deal of variation in progesterone levels between individuals, and from day to day in the same individual. Therefore, with gynecological disorders or in abnormal pregnancies, several plasma progesterone measurements are necessary rather than just a single measurement in order for proper interpretation of the results.

Estradiol and progesterone are commonly known as a gonadal hormones. The female gonads are the ovaries, which actually serve a dual function:

1. They act as an exocrine gland, which has to do with the reproductive function of the ovaries (i.e. production of ova).
2. They act as an endocrine gland in that they secrete steroid hormones such as estradiol and progesterone.

Female Reproductive Cycles

There are two female reproductive cycles:

1. Menstrual (ovarian) cycle
2. Estrous (uterine) cycle

Menstrual (Ovarian) Cycle

The length of the menstrual cycle is defined as the period dating from the onset of one instance of menstrual bleeding (day 1) until the onset of the next. The cycle ranges from 20 to 50 days, with the

mean being 28 days. Therefore, a 28 day cycle is used in the explanation below. One should keep in mind however that 28 days is not normal for everyone.
The menstrual cycle occurs within the ovary itself. The uterine cycle will respond to this cycle. There are three phases of the menstrual cycle:

1. Menstrual phase - 5 days
2. Follicular phase - 9 days
3. Luteal phase - 14 days

To consider the hormone changes that occur during the menstrual cycle, we will begin at day 21 of the previous cycle. At day 21, FSH is relatively low. About two days before the end of the cycle there is a slight but important increase in FSH which acts on proliferative primordial cells. This increase in FSH is probably stimulated by the drop in estradiol levels that occurs at the end of the cycle. Recall that at birth there are approximately 750,000 primordial follicles. At this point, all of the primordial cells are in a non-proliferative state, but all throughout life, each month some of these non-proliferative follicles differentiate into proliferative follicles. The follicles that have differentiated into proliferative follicles are subject to FSH. Prior to puberty, there was insufficient FSH to support proliferative follicles.

When FSH acts on these proliferative primordial follicles, it results in mitosis of the granulosa cells, resulting in a space which is filled with follicular fluid. Besides the granulosa layer, there are two other layers of the follicle: the theca interna and the theca externa layers.

The primordial follicles are arranged so that the theca externa is the outside layer and is made up of dense connective tissue. Next comes the theca interna, whose major responsibility is for the secretion of estrogens. The major estrogen produced by these follicles is estradiol. Next comes the granulosa cells, then the cavity, and finally the ovum in the cavity.

FSH increases until about six to seven days into the cycle. The action of FSH on these follicles causes the follicle to product estradiol, which is low at the end of the cycle. With the increased development of the follicle, there is an increasing amount of estradiol. Through a negative feedback system, the increasing estradiol causes FSH levels to return to basal levels.

This follicular growth is also stimulated by estrogen production by the follicle itself. This type of situation is referred to as paracrine regulation. This is a type of positive feedback mechanism where the estradiol produced by the theca interna of the follicle stimulates the follicles own growth causing more estradiol to be produced.

There are several follicles that initially begin to grow with only one passing into full maturity. The generally accepted reason why there is only one follicle that makes it to full maturity is because at some point in the maturation process, one follicle will be larger than the others, and therefore it will produce more estrogen (or estradiol). When the negative feedback system of this increasing estrogen inhibits the production of FSH the larger follicle will be the only one that is able to produce enough estrogen to maintain its growth while the other follicles that were maturing undergo atresia due to two reasons:

1. not enough FSH (no longer being produced)
2. not enough estrogenic products to keep it alive

Therefore, follicle growth is under a dual regulation:

1. initially under the control of FSH
2. matures under the control of its own estrogen products

During the first five days of the menstrual cycle, follicular growth occurs. During the next nine days there is rapid follicular growth and a rapid increase in estrogen levels.

This leads to the luteal phase. There are two events that lead up to this phase. The first is that which brings about the transformation into the luteal phase and the second is that event which brings about ovulation.

At approximately two days before the mid-cycle (i.e. day 12) a spike or pulse of 2 gonadotropins occurs. These are FSH and LH, which are triggered by GnRH. These coincide with each other.

With a build-up of estrogens at mid-cycle, there is a switch from estrogens stimulating a negative feedback to estrogens stimulating a positive feedback. Therefore, GnRH is increased, leading to increased LH and FSH levels. This leads to a very large LH spike immediately prior to ovulation. The increase in LH acts on the ovarian follicular with the LH target being the granulosa cells of the follicle. These granulosa cells in-turn become "luteinized" and they primarily produce progesterone, as well as some estradiol as a secondary hormone.

The increased progesterone production causes two events within the ovarian follicle:

1. An increased proteolytic enzyme activity, specifically collagenase which acts to weaken the follicle wall.
2. An increased hyperemia of the follicle, i.e. there is an increased blood flow to the follicle. As a result, there is an increase fluid formation within the follicle, increased swelling, and increased pressure on the follicle wall.

As a result of these actions of progesterone, the follicle will rupture immediately proceeding ovulation. This rupture causes the ovum to pass into the ovaduct resulting in ovulation.

If there were no increase in LH, there would be no ovulation, i.e. the LH spike is very important for ovulation. Pharmacologically, the LH peak or spike can be shifted with the birth control pill. This will be discussed below.

This positive feedback that occurs during this process is good. However, the question is how to stop the positive feedback mechanism. Following ovulation, high levels of LH result in a rapid modification of the granulosa cells. This modification inactivates the theca interna cells, therefore estradiol levels decrease. As a result of these low, but above basal levels of estradiol, through the negative feedback system, LH and FSH also decrease.

At this point, there is a rapid transformation of the follicular cells which results in an increased production of more progesterone and some increase again in estradiol . The increased progesterone level is maintained throughout the luteal phase.

The period of this increased LH causes the hypothalamus to decrease the production of GnRH, and at the same time, decreases the production of PIF (prolactin inhibitory factor). Therefore, there is also an

increase in prolactin during the luteal phase (↑progesterone → ↓PIF, therefore ↑prolactin). Prolactin stimulates the production of more progesterone which is necessary to stimulate the endometrium of the uterus to prepare for implantation. Thus, the luteal phase of the menstrual cycle prepares the uterus for implantation in every cycle. If the level of progesterone were to decrease, there would be degeneration of the endometrium and the uterus would not be able to support a fertilized ovum.

By day 21, there is a fully functional corpus luteum which maintains a high progesterone level and a somewhat elevated estradiol level.

Toward the end of the luteal phase, the corpus luteum will regress into a corpus albicans. With this, progesterone and estradiol levels will decrease. The reason for this regression is there appears to be some type of genetic programming for the corpus luteum to last just a certain number of days before it becomes non-functional.

At the end of the menstrual cycle, estradiol and progesterone levels decrease due to the degeneration of the corpus luteum. This in-turn lifts the inhibition on FSH which then stimulates the development of another follicle.

Uterine (Estrous) Cycle

In the uterine wall there are three layers:

1. Serosa or epimetrium - thin layer of connective tissue - outermost layer
2. Myometrium - thick layer of smooth muscle
3. Endometrium - innermost layer

All of these layers respond to hormones with the endometrium having the greatest response. The whole system is designed for reproduction, i.e. it is designed for implantation of a fertilized ovum each month following ovulation.

There are three phases of the uterine cycle:

1. Menstrual phase - 5 days
2. Proliferative phase - 11 days
3. Secretory phase - 12 days

In the menstrual cycle, the first 5 days are characterized by estradiol production and follicular development. As estradiol levels continue to increase, there is an increased growth of the endometrium (during the proliferative phase), and two characteristic changes occur:

1. There is an increased thickening of the endometrium due to mitosis and cell growth.
2. There is an increase in the glandular development and vascular development in the endometrium.

Therefore, the uterine wall is preparing itself for implantation of a fertilized ovum during the proliferative phase.

During the secretory phase, the predominate hormones that are present are estradiol and progesterone. Due to the presence of these hormones, the glands that were developed in the proliferative stage becomes productive, producing endometrial fluids. At this point the endometrium is prepared for the implantation of the fertilized ovum.

At the end of the proliferative phase, 16 days have elapsed. Recall that ovulation occurs at 14 days. If the ovum is fertilized it usually does not implant in the uterus until two to five days after fertilization. This allows time for the uterus to become fully functional.

Increased levels of estradiol and progesterone are necessary for the maintenance of the endometrium. Regression of the corpus luteum results in a decrease in estrogens and progesterone. The withdrawal of these hormones initiates several events within the endometrium. Arteriolar vasomotor changes result in rhythmic vasoconstriction and vasodilation in endometrial tissue. Each successive vasoconstrictive spasm is more severe, ultimately leading to tissue necrosis and interstitial hemorrhages due to capillary breakdown. As ischemia and tissue weakness progresses, bleeding into the endometrial cavity occurs and menstruation begins. This is the menstrual phase of the uterine cycle.

During pregnancy, once there is the implantation of the fertilized ovum, there will be no sloughing of the uterine lining. In addition, the corpus luteum will not undergo degeneration and the corpus luteum will continue to produce estradiol and progesterone. This all occurs following implantation due to the release of a signal hormone. This signal hormone is human chorionic gonadotropin (HCG). HCG signals the corpus luteum to continue functioning and producing progesterone and estradiol. Thus, HCG is how the ovaries know the uterus is pregnant.

By the end of the second trimester of pregnancy, the corpus luteum is no longer required to maintain adequate progesterone and estradiol levels. By this time, the placenta is also a potent producer of these two hormones.

Birth Control Pills

Enovid is an example of a birth control pill that is a steroid. It was first available on the market on March 15, 1960. A 10 mg tablet of Enovid is made up of approximately 9.75 mg of a progesterone-like material and 0.25 mg of an estrogen-like material. This ratio of progesterone to estrogen is used because it closely mimics that found in the female under normal conditions.

This is taken days 5 through 26 (based on a 28 day cycle). Typically, dosage begins five days after the menstrual flow begins and it is taken for 21 days. Then there is seven days of either taking no pill, an inert pill, or an iron supplement. As a result of these increased circulating levels of progesterone and estrogen, there is a suppression of GnRH. Decreased GnRH results in decreased FSH, no follicular development, and no ovum to fertilize.

Some people have the misconception that a woman who takes birth control pills for ten years will put off menopause by ten years. This is not true because the primary action of most contraceptives do is depress FSH production. Non-proliferative primordial follicles are still converted to proliferative primordial follicles, but there is no FSH action on these follicles. Therefore, these follicles undergo atresia.

Hormones in the Birth Process

As we begin to consider hormones associated with the birth process, we need to consider some characteristics of oxytocin. Oxytocin, and the related hormone ADH, are both hormones from the neurohypophysis (posterior pituitary). These both have nine amino acids and they differ only in thespecific amino acids at position three and eight in this sequence. The table below summarizes the differences in the actions of these two hormones. The numbers given in the table are in terms of activity units.

	Uterine Stimulation	Milk Ejection	Pressor Action	ADH Activity
Oxytocin	500	500	7	3
ADH	30	100	600	600

Comments regarding this table:

- Uterine stimulation is the ability to stimulate the myometrium to contract.
- Considering milk ejection, recall the mammary gland contains both alveoli (which produce milk) and ducts (which carry fluid out). There are specialized myoepithelial cells found in both areas giving both areas the ability to contract. Note that oxytocin only affects milk ejection and not formation.
- Pressor activity is the ability to stimulate smooth muscle of the vascular system to contract (i.e. vasoconstriction). From the chart one can see that oxytocin has a great affinity for stimulating the smooth muscle of the uterus and little effect on vascular smooth muscle; the opposite is true for ADH.

There are three main functions of oxytocin in the female:

1. fertilization
2. parturition
3. lactation

Fertilization

During copulation when sperm passes into the reproductive tract it stimulates the cervix. The cervix, in response, sends an impulse to the brain to release oxytocin. Oxytocin then stimulates uterine smooth muscle (i.e. increases uterine motility) creating currents which sweep sperm to the ovaduct. Therefore, sperm transport is a function of oxytocin.

Oxytocin also increases ovaduct smooth muscle activity which adds to sperm transport.

Parturition

Parturition is the birth process itself. There are three factors involved in the birth process:

1. mechanical factor
2. oxytocin
3. changes in hormone profile

The mechanical factor results from stretching of the smooth muscle of the myometrium. With this stretch, there is increased irritability of the myometrium. Therefore, the myometrium is more responsive to stimuli such as fetal rotation prior to birth. With fetal rotation, the head presses on the cervix stimulating uterine contraction.

The second factor in parturition is oxytocin. The head pressing on the cervix also stimulates a neuronal pathway leading to oxytocin production. This stimulates further contraction of the myometrium.

The last factor in parturition is changes in hormonal profile. Estrogens are known to increase the irritability of the myometrium. Progesterone, on the other hand, decreases myometrium irritability. Throughout pregnancy, there is more progesterone than estrogen. Therefore, there is a tranquilizing effect on the myometrium. Immediately prior to birth, progesterone levels drop and the estrogen to progesterone ratio increases, increasing myometrium irritability. This triggers parturition.

Lactation

During pregnancy, there is excessive development of the mammary gland due to the high levels of estrogens and progesterone. Also, development is dependent upon prolactin, which is absolutely necessary. Prolactin affects the secretory apparatus in the alveoli cells by stimulating growth. Also, after parturition, prolactin will stimulate milk secretion. Consider the following levels of prolactin:

Normal prolactin level in a non-pregnant female:	9 ng/mL
Prolactin at the end of the first trimester:	50-60 ng/mL
Prolactin at the end of the second trimester:	120 ng/mL
Prolactin right before birth:	250 ng/mL

To consider why prolactin increases during pregnancy, one should note that there are two regulatory hormones for prolactin secretion:

1. PIF - prolactin inhibitory factor - This regulates prolactin in non-pregnant females.
2. PRF - prolactin releasing factor - This regulatory hormone is only associated with lactating females.

$$\text{Pregnancy} \longrightarrow \uparrow \text{estrogens} \longrightarrow \downarrow \text{PIF} \longrightarrow \uparrow \text{prolactin}$$

The increased prolactin stimulates milk production, but, the increase in estrogens blocks the actual secretion of milk and causes milk to build-up. Immediately after birth, estrogen levels decrease and this then allows secretion of milk; the first milk secreted is known as colostrum.

At parturition, estrogen and progesterone levels drop.

$$\downarrow \text{Estrogen} \longrightarrow \uparrow \text{PIF} \longrightarrow \downarrow \text{prolactin}$$

Therefore, no lactation occurs. This is where PRF (prolactin releasing factor) comes into play. After parturition in normal lactating mothers, the mechanical stimulus of the infant sucking on the breast sends a signal to the hypothalamus to release PRF, resulting in an increase in prolactin.

Prolactin takes approximately four hours to stimulate milk production. Therefore, at one feeding there is the stimulus for milk formation for the next feeding. Also, stimulation of the breast by the infant stimulates oxytocin release which stimulates immediate milk ejection at the time of feeding.

Supposedly, a nursing mother cannot get pregnant. Sucking stimulates the release of PRF which is antagonistic to FSH and LH. Therefore, chances are of ovulating and conceiving are slim. Note, however, there are documented cases where nursing mothers have become pregnant.