Clinical Notes: Contraception

The most commonly-used chemical contraceptive is a combination of estrogen and progesterone. Providing relatively low levels of these hormones causes an inhibition of GnRH, LH and FSH secretion. FSH levels are tonically maintained at such a low level that follicles never mature into antral (Graafian) follicles, so ovulation never occurs. Most combination chemical contraceptives come in packages of 28 pills, with 21 "active" pills (containing hormones) and 7 placebo pills. Taking the placebo pills allows a menstrual period to occur, as hormones are withdrawn. However, other contraceptive strategies are also used. For example, some women prefer an extended-cycle regimen, which entails taking 12 weeks of active pills followed by one week of inactive pills, to limit the number of menstrual periods per year.

In addition to delivering combined contraceptives orally, the hormones can be delivered through a patch on the skin or a flexible ring inserted into the vagina (NuvaRing®).

Progesterone provided alone can also serve as a chemical contraceptive. Progesterone-only contraceptives can be taken orally, through subdermal implants (e.g., Norplant®) or through an intrauterine system (e.g., Mirena®[see website for more information]). The later systems are prescribed for convenience, as they can last for many years. Progesterone-only contraceptives are not as effective in preventing ovulation as combined (estrogen + progesterone) contraceptives. The main efficacy of the progesterone-only contraceptives may be related to maintaining the cervical mucus in a state that is inhospitable for sperm. Over time, the progesterone-only contraceptives may also affect the uterine lining, such that implantation of a fertilized ovum is less likely. Progesterone-only pills do not carry the same risks as contraceptives that include estrogen (which include a small cardiovascular risk and a small risk of stimulating estrogen-sensitive cancers). However, since the half-life of progesterone is relatively short, and progesterone-only contraceptives rely on changes in cervical mucus, the effects rapidly diminish if a treatment is missed. Hence, progesterone-only pills must be taken within a 3-hour time window each day.

High doses of progesterone can also be used as a contraceptive. For example, Depo-Provera is a long-acting progesterone analog that is effective for three months. Depo-Provera is injected intramuscularly, and the dose of progesterone is high enough to prevent ovulation (by inhibiting GnRH, LH, and FSH secretion), to cause the cervical mucus to be inhospitable to sperm, and to make the endometrium un receptive for implantation of a blastocyst. Hence, Depo-Provera is a highly effective contraceptive. However, since the drug inhibits estradiol secretion, the benefits of estradiol are lost. For example, women who take Depo-Provera for an extended period may be at risk for osteoporosis. Depo-Provera also is effective in reducing GnRH, LH, and FSH secretion in men, and thus the drug lowers testosterone levels and renders the male sterile (chemical castration). Eight states and a number of countries have laws that require some male sex offenders to undergo chemical castration as a condition of their release from prison.

High doses of progesterone can also be used as an emergency contraceptive (e.g., “Plan B”). Although the mechanisms of emergency contraceptives are debated, they include an inhibition of ovulation and making the reproductive tract less hospitable for fertilization. If fertilization has already occurred, the treatment is ineffective (i.e., Plan B only works if fertilization has not yet occurred).
Transport of Gametes and Fertilization

At ovulation, the ovum that is released from the ovary is surrounded by a layer of specialized granulosa cells that are attached to the zona pellucida (the glycoprotein membrane surrounding the oocyte). These granulosa cells form the corona radiata, whose main function is to provide vital proteins to the oocyte.

The fimbriae of the fallopian tubes pick-up the ovum, and movements of the cilia and contractions of smooth muscle in the fallopian tubes propel the ovum towards the uterus.

Although an average fertile male deposits 150-600 million sperm into the uterus during ejaculation, only 50-100 of those sperm reach the ampulla of the fallopian tube. However, the sperm get there very quickly, within ~5 minutes of ejaculation. The swimming motion of the sperm alone cannot account for such rapid transport. Forceful contractions of the uterus, cervix, and fallopian tubes propel the sperm into the upper reproductive tract during female orgasm. Prostaglandins in the seminal plasma may induce further contractile activity.

Before a sperm can fertilize the oocyte, it must undergo capacitation. This process is not well understood, but requires exposure of the sperm to a variety of substances in the female reproductive tract. One of these proteins is fertilization promoting peptide, which is produced by the prostate gland. Sperm are first exposed to fertilization promoting peptide during ejaculation, but the concentration is too high in the seminal fluid to permit capacitation. Capacitation occurs only after the seminal fluid is diluted by the secretions in the female reproductive tract. In addition, secretion of sterol-binding albumin, lipoproteins, proteolytic and glycosidasic enzymes such as heparin by the uterus aids in the capacitation process. Capacitation involves the destabilization of the acrosomal sperm head membrane allowing greater binding between sperm and oocyte.

After ovulation, the egg in the fallopian tube is in an inactivated state. In the case of fertilization, the sperm normally comes into contact with the oocyte in the ampullary portion of the tube, usually several hours after ovulation. Fertilization activates the oocyte, initiating a series of morphological and biochemical events that lead to cell division and differentiation. Fertilization occurs in eight steps:
The sperm head weaves its way past the follicular cells and attaches to the zona pellucida that surrounds the oocyte. The zona pellucida is composed of three glycoproteins; ZP1 cross-links the filamentous ZP2 and ZP3 into a latticework. Receptors on the plasma membrane of the sperm cell bind to ZP3, thereby initiating a signal transduction cascade.

As a result of the sperm-ZP3 interaction, the sperm cell undergoes the **acrosomal reaction**, a prelude to the migration of the sperm cell through the zona pellucida. During the acrosomal reaction, an increase in intracellular Ca\(^{2+}\) triggers fusion of the outer acrosomal membrane with the sperm cell’s plasma membrane and results in the exocytosis of most of the acrosomal contents.

The spermatozoon penetrates the zona pellucida. One mechanism of this penetration is the action of the acrosomal enzymes. The sperm cell also penetrates the zona pellucida by mechanical action. The sperm head rapidly oscillates about a fulcrum that is situated in the neck region.

The cell membranes of the sperm and the oocyte fuse. Microvilli on the oocyte surface envelop the sperm cell, which probably binds to the oocyte membrane through specific proteins on the surfaces of the two cells. The sperm cell per se does not enter the oocyte. Rather, the cytoplasmic portions of the head and tail enter the oocyte and leaving the sperm cell plasma membrane behind.

The oocyte undergoes the **cortical reaction**. As the spermatozoon penetrates the oocyte’s plasma membrane, it causes Ca\(^{2+}\) release from internal stores. Small granules that lie just beneath the plasma membrane fuse with the oocyte’s plasma membrane. Exocytosis of these granules releases enzymes that act on glycoproteins in the zona pellucida and cause them to harden. This **cortical granule reaction** prevents polyspermy (introduction of more than one sperm into the oocyte).
Step 6: The rise in Ca$^{2+}$ inside the oocyte also causes the completion of the oocyte’s second meiotic division. One result is the formation of the second polar body, which contains a haploid number of unduplicated maternal chromosomes. The oocyte extrudes the chromosomes of the second polar body, together with a small amount of ooplasm, into a space immediately below the zona pellucida. As its chromosomes decondense, the nucleus of this mature ovum becomes the female pronucleus.

Step 7: The sperm nucleus decondenses and transforms into the male pronucleus, which, like the female pronucleus, contains a haploid number of unduplicated chromosomes. The cytoplasmic portion of the sperm’s tail degenerates.

Step 8: The male and female pronuclei fuse, to form a new cell, the zygote. The mingling of chromosomes (syngamy) can be considered as the end of fertilization and the beginning of embryonic development.

Summary: The rise in Ca$^{2+}$ inside the oocyte induces the completion of the oocyte’s second meiotic division and the formation of the second polar body, which usually lies next to the first polar body. The head of the sperm enlarges to become the male pronucleus. The male and female pronuclei fuse.
Movement of the Zygote to the Uterus
The ovum is usually fertilized in the ampullary portion of the fallopian tube several hours after ovulation. The conceptus remains in the fallopian tube for ~72 hours, during which time it develops to a solid mass of ~12 cells (called the **morula**), receiving nourishment from fallopian tube secretions. During these 3 days, smooth muscle contractions of the isthmus prevent advancement of the conceptus into the uterus while the endometrium is preparing for implantation. The mechanisms by which the ovum is later propelled through the isthmus of the fallopian tube to the uterus probably include beating of the cilia of the tubal epithelium and contraction of the fallopian tube.

After the cell mass enters the uterine cavity, it floats freely in the lumen of the uterus and transforms into a **blastocyst**: a ball-like structure with a fluid-filled inner cavity. Blastocyst formation begins about 5 days after fertilization, when a fluid-filled cavity opens up in the morula. The morula's cells differentiate into two types: an inner cell mass growing on the interior of the **blastocoel** (the fluid-filled cavity) and **trophoblast** cells growing on the exterior. The trophoblast cells will develop into a variety of supporting structures, including the amnion, the yolk sac, and the fetal portion of the placenta. The inner cell mass will develop into the embryo.

Before the blastocyst implants in the endometrium, it must receive its nourishment from uterine secretions. Following conception, the endometrium is primarily controlled by progesterone, which initially comes from the corpus luteum. Implantation of the human blastocyst normally occurs 6 to 7 days following ovulation.

If the blastocyst is to survive, it must avoid rejection by the maternal cellular immune system. It does so by releasing immunosuppressive agents. The embryo also synthesizes and secretes macromolecules that promote implantation, the development of the placenta, and the maintenance of pregnancy.
Probably the most important chemical factor produced by the blastocyst is human chorionic gonadotropin (hCG), which is closely related to LH. The secretion of hCG is critically important in maintaining the corpus luteum, which secretes progesterone. Progesterone is necessary to maintain the uterine endometrium. Without the support of progesterone, the uterine lining degenerates and the pregnancy is terminated. Besides rescuing the corpus luteum, hCG is a growth factor that promotes trophoblast growth and placental development. hCG levels are high in the area where the trophoblast faces the endometrium. hCG may have a role in the adhesion of the trophoblast to the epithelia of the endometrium, and it also has protease activity.

Clinical Notes
Pregnancy tests detect hCG in the blood and urine. The levels are detectable 8-12 days following fertilization. If the test is done too early, a false negative result may be forthcoming. Since menstruation usually occurs ~14 days after ovulation, a pregnancy test is typically accurate if a menstrual period is delayed.

Progesterone is critically important in maintaining the uterine endometrium through the first weeks of pregnancy. Thus, a sudden drop in progesterone levels would result in a degeneration of the endometrium, and thus a miscarriage would occur.

Hence, progesterone receptor antagonists will cause a termination of pregnancy. The controversial drug Mifepristone (RU-486) is a progesterone receptor antagonist. RU-486 is approved by the FDA to terminate pregnancies of up to 49 days gestation. Typically, a second drug (misoprostol) is administered within 48 hours of giving RU-486. Misoprostol is a synthetic prostaglandin E1 (PGE1) analog, which induces uterine contractions. Misoprostol is also used to induce labor when natural delivery is delayed.

Implantation Entails Four Steps

The first stage of implantation of the zygote in the uterus is hatching, or degeneration of the zona pellucida. This occurs 6-7 days after ovulation. Lytic factors released by the endometrium play a key role in hatching. However, the blastocyst also plays a role, as hatching does not occur when an unfertilized ovum is placed in the uterus. Plasminogen release from the endometrium (which is converted to Plasmin through TPA produced by the blastocyst) may be key for hatching, since plasmin has been shown to lyse the zona pellucida in experimental studies.

The earliest contact between the blastocyst wall and the endometrial epithelium is a loose connection called apposition. Apposition occurs at a site where the zona pellucida is ruptured and where it is possible for the cell membranes of the trophoblast to make direct contact with the cell membranes of the endometrium. Since hatching is required before apposition occurs, it seems likely that apposition entails interactions between glycoproteins on the surface of trophoblast and endometrial cells.
After apposition, microvilli in the membranes of trophoblast cells form rigid attachments to the endometrial cells through ligand-receptor interactions. This process is called **adhesion**.

After adhesion occurs, the trophoblast cells rapidly proliferate and differentiate into two layers. Long protrusions from the outer layer extend among uterine epithelial cells. The protrusions secrete chemicals such as tumor necrosis factor that dissociate the endometrial cells (break cell-cell adhesions), so the protrusions can invade deep into the endometrium. Uterine stromal cells near the protrusions become transformed into **decidua** cells. The decidua cells initially provide nutrients to the blastocyst until the formation of the placenta.

**Clinical Notes**

**Ectopic pregnancies** are true medical emergencies and can cause death. Ectopic pregnancies occur when the zygote implants outside of the uterus. Most ectopic pregnancies occur in the Fallopian tube (so-called tubal pregnancies), but implantation can also occur in the cervix, ovaries, and abdomen. Due to the invasive nature of the blastocyst, an ectopic pregnancy can result in severe bleeding as the structure invades the wall of the structure it is attaching to. Since tissues other than the endometrium usually cannot provide necessary nutrients to the blastocyst, ectopic pregnancies are usually not viable, although in rare cases they can be.

Tubal pregnancies often occur because the fallopian tube becomes blocked, such that the zygote cannot migrate to the uterus. However, in many cases it is unclear why normal transfer of the zygote to the uterus has not occurred.

Women with ectopic pregnancies often seek treatment due to severe abdominal pain. Ectopic pregnancy is diagnosed by considering hCG levels and performing ultrasounds of the uterus as well as laparoscopy. If an ectopic pregnancy is discovered, it can be resolved surgically or by giving methotrexate. Methotrexate inhibits the metabolism of folic acid. Since folic acid is necessary for the production of new cells, for DNA synthesis, and for RNA synthesis, methotrexate inhibits the rapid growth of cells that is necessary for development of the zygote. The drug is also commonly used in cancer chemotherapy, and has many adverse effects such as decreased white blood cell count (as the drug inhibits differentiation of blood cells in the bone marrow).
Physiology of the Placenta

Within a few days, the blastocyst penetrates through the uterine wall. Fluid filled spaces develop in the trophoblast (lacuna), which become continuous with maternal blood vessels. Over time, the blood-filled cavities in the trophoblast merge to form intravillous spaces.

As the fetus matures, it develops blood vessels that form treelike structures called “villi” that protrude into the intravillous spaces (which are filled with maternal blood). This arrangement provides ample surface area for exchange of materials between the maternal and fetal plasma.

In addition to providing a conduit for nutrient exchange between fetus and mother, the placenta secretes a number of hormones that are critical for maintenance of the pregnancy, including hCG, inhibins, estrogens, and progesins. After ~8 weeks of gestation, the sex steroids are derived more from the placenta than from the corpus luteum. Note that the levels of estrogens and progesterone are much higher during pregnancy than at any point during the menstrual cycle. In addition, steroids that are not present during the menstrual cycle appear, including estriol and estrone. The presence of these hormones leads to an almost total suppression of GnRH, LH, and FSH secretion.

Functions of Hormonal Secretions During Pregnancy

hCG is secreted first by the blastocyst and then by the placenta during pregnancy. hCG plays a critical role in rescuing the corpus luteum, and preserving sex steroids during the first trimester. Under the influence of hCG, the corpus luteum grows to about twice its initial size by a month or so after pregnancy begins. Its continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium, which is necessary for the early development of the fetus. If the corpus luteum is removed before approximately the 7th week of pregnancy, spontaneous abortion almost always occurs, sometimes even up to the 12th week. After that time, the placenta secretes sufficient quantities of progesterone and estrogens to maintain pregnancy for the remainder of the gestation period. The corpus luteum involutes slowly after the 13th to 17th week of gestation.
Human chorionic gonadotropin also exerts an interstitial cell–stimulating effect on the testes of the male fetus, resulting in the production of testosterone in male fetuses until the time of birth. This small secretion of testosterone during gestation is what causes the fetus to grow male sex organs instead of female organs. Near the end of pregnancy, the testosterone secreted by the fetal testes also causes the testes to descend into the scrotum.

During pregnancy, the extreme quantities of estrogens cause:
1. Enlargement of the mother’s uterus.
2. Enlargement of the mother’s breasts and growth of the breast ductal structure.
3. Enlargement of the mother’s external genitalia.
4. Relaxation of the pelvic ligaments of the mother, so the sacroiliac joints become relatively limber and the symphysis pubis becomes elastic. These changes allow easier passage of the fetus through the birth canal.
5. Stimulating the rate of cell reproduction in the early embryo.
6. Increasing the number of oxytocin receptors on uterine smooth muscle cells
7. Eliciting a wide variety of physiological changes described below.

During pregnancy, the extreme quantities of progestins cause:
1. Changes in the uterus that are needed to sustain a pregnancy.
2. Reduced contractility of the uterus, reducing the risk of a spontaneous abortion.
3. Changes in the cellular development of the fetus.
4. Along with estrogens, changes in the breast to prepare for lactation.
5. Physiological changes described below.

The placenta also generates additional hormones, including human chorionic somatomammotropin (HCS), which is also called human placental lactogen. HCS is a polypeptide that closely resembles growth hormone in structure. It modifies the metabolic state of the mother during pregnancy to facilitate the energy supply of the fetus. HCS does not enter the fetal circulation, and only affects the mother. Some of the particular actions of HCS include:

1. ↓ Maternal insulin sensitivity leading to an increase in maternal blood glucose levels.
2. ↓ Maternal glucose utilization, which helps ensure adequate fetal nutrition
3. ↑ Lipolysis with the release of free fatty acids. Hence, free fatty acids become available for the mother as fuel, so that relatively more glucose can be utilized by the fetus. Also, ketones formed from free fatty acids can cross the placenta and be used by the fetus.

Physiological Changes During Pregnancy
The hormonal changes discussed above as well as factors that are not well understood produce profound physiological changes in a pregnant mother.

Blood volume: Maternal blood volume may increase by as much as 45% near term in single pregnancies and up to 75% to 100% in twin or triplet pregnancies. The ultimate increase in blood volume results from an increase in the volume of both the plasma and erythrocytes. Renal perfusion increases as there is a dilation of the renal arteries. In addition, aldosterone secretion increases, which augments renal reabsorption of salt and water.

Cardiac output: Increases in preload resulting from an expanded blood volume result in an increase in cardiac output (~45% at term). However, blood pressure decreases because of decreased peripheral resistance. Vasodilation is prominent in the kidneys (~40% increase in blood flow), uterus (which receives 15% of cardiac output during pregnancy), skin, and breasts.

Ventilation: Very high progesterone levels are believed to play a key role in increasing alveolar ventila-
tion in pregnant women. The shape of the diaphragm changes, resulting in a decrease in residual volume. In addition, progesterone appears to stimulate the brainstem respiratory pattern generator, which is the primary reason alveolar ventilation increases. As a result, $P_{O_2}$ in arterioles decreases from 40 to 32 mmHg, resulting in a slight respiratory alkalosis, which is corrected by the kidney.

**Clinical Note: Preeclampsia and Eclampsia**

Preeclampsia is a serious and relatively common (5% of pregnancies) pregnancy complication characterized by high blood pressure and signs of damage to another organ system, often the kidneys. Preeclampsia usually begins after 20 weeks of pregnancy in a woman whose blood pressure had been normal. Even a slight rise in blood pressure may be a sign of preeclampsia. Preeclampsia is often characterized by excess salt and water retention by the mother's kidneys and by weight gain and development of edema in the mother. In addition, there is impaired function of the vascular endothelium and arterial spasm occurs in many parts of the mother's body, most significantly in the kidneys, brain, and liver. Both the renal blood flow and the glomerular filtration rate are decreased, which is exactly opposite to the changes that occur in the normal pregnant woman. The renal effects also include thickened glomerular tufts that contain a protein deposit in the basement membranes.

Although the exact cause of preeclampsia is unknown, the condition starts with a failure to provide adequate blood flow to the placenta. The placenta fails to implant normally into the uterine wall, such that normal pattern of placental blood flow is not established. Hypoxia of the placenta results in the release of a variety of chemical toxins such as tumor necrosis factor-α and interleukin-6, which may result in endothelial cell changes throughout the mother's circulatory system.

There is some evidence (which is not conclusive) that preeclampsia stems from an immunological intolerance of a woman's body to the genetic material provided by the father. In essence, the mother's body responds as though the developing fetus is foreign material, and the immunological response results in poor implantation with reduced placental blood flow. Following from this notion is the idea that repeated exposure of a woman to sperm from a particular male will result in immunological tolerance for the male, which reduces the risk of preeclampsia. There is some evidence that preeclampsia is more prevalent in first pregnancies with a particular father, if the father and mother did not have many instances of intercourse before conception of the fetus, or if the parents used barrier contraception prior to conception of the fetus. However, this notion is controversial.

The only definitive treatment for preeclampsia is removal of the fetus and placenta from the mother. Depending on the age of the fetus and the severity of the condition, the mother may be treated with antihypertensive drugs until the fetus is viable, at which time delivery occurs through induced labor or Caesarian section. Preeclampsia may evolve into even more serious conditions, including:

- **Eclampsia:** a condition where severe hypertension eventually causes the breakdown of the blood-brain barrier, vascular dilation, and leakage of considerable fluid into the brain (cerebral edema). As a result, severe headache and convulsions can occur. Similar pathology can occur in the retina, leading to visual problems and potential blindness. Untreated eclampsia will often result in death.
- **HELLP (hemolysis-elevated liver [enzymes]-low platelets) Syndrome:** this syndrome includes rupture of red blood cells (hemolysis), liver damage resulting in high liver enzymes in the blood, and low platelets in the blood. The syndrome is believed to result from aberrant and chronic triggering of the coagulation cascade, following endothelial cell damage. For unknown reasons, this seems to occur most often in arteries perfusing the liver. The crosslinking of fibrin in small blood vessels causes the rupture of erythrocytes as they are forced through the mesh (like a strainer). The recruitment of a large number of platelets in the aberrant clotting process results in a drop in blood
platelet levels. Furthermore, blockage of small arteries perfusing the liver can result in liver necrosis and the release of large amounts of liver enzymes into the blood as liver cells lyse.

Preeclampsia and its complications are the main causes of maternal death during pregnancy. Sometimes the conditions can become much worse during and just following parturition, such that the mother dies after the child is born.

**Parturition**

Parturition (childbirth) is likely initiated by signals from the placenta or fetus. Progesterone levels remain constant near the end of gestation, whereas estrogen levels continue to increase. It has been argued that the estrogen-progesterone ratio in the blood contributes to initiating labor. The fetus releases increasing amounts of a variety of hormones including oxytocin, cortisol, and prostaglandins near the time of labor, which also may serve as triggers.

The factors that generate and maintain uterine contractions during labor have been well established. They include the following:

- **Prostaglandins.** The uterus, the placenta, and the fetal membranes synthesize and release prostaglandins. Prostaglandins from the uterine decidual cells, particularly prostaglandins F2 and E2 (PGF2α and PGE2), act by a paracrine mechanism on uterine smooth muscle cells. Oxytocin stimulates uterine decidual cells to increase their PGF2α synthesis. Arachidonic acid, the precursor of prostaglandins, is present in very high concentrations in the fetal membranes near term.

Prostaglandins have three major effects. First, prostaglandins strongly stimulate the contraction of uterine smooth muscle cells. Second, PGF2α potentiates the contractions induced by oxytocin by promoting formation of gap junctions between uterine smooth muscle cells; estradiol also increases the number of gap junctions. These gap junctions permit synchronous contraction of the uterine smooth muscle cells, reminiscent of the contraction of the ventricles of the heart. Third, prostaglandins cause softening, dilatation, and thinning (effacement) of the cervix, which occurs early during labor.

Prostaglandins may physiologically initiate labor. Both PGF2α and PGE2 evoke myometrial contractions at any stage of gestation, regardless of the route of administration. Arachidonic acid instilled into the amniotic cavity causes the uterus to contract and to expel its contents. Aspirin, which inhibits the enzyme cyclooxygenase, reduces the formation of PGF2α and PGE2, thus inhibiting labor and prolonging gestation.

- **Oxytocin.** As noted above, rising estrogen levels during pregnancy cause an expression of oxytocin receptors on the surface of uterine smooth muscle cells. Once labor is initiated, maternal oxytocin is released in bursts, and the frequency of these bursts increases as labor progresses. The primary stimulus for the release of maternal oxytocin appears to be distention of the cervix; this effect is known as the **Ferguson reflex**. Oxytocin is an important stimulator of uterine smooth muscle contraction late in labor. Oxytocin may also indirectly induce uterine contractions by virtue of its ability to stimulate prostaglandin release.

- **Positive Feedback.** Once labor is initiated, several positive feedback loops involving prostaglandins and oxytocin help to sustain it. First, uterine contractions stimulate prostaglandin release, which itself increases the intensity of uterine contractions. Second, uterine activity stretches the cervix, thus stimulating oxytocin release through the Ferguson reflex. Because oxytocin stimulates further uterine contractions, these contractions become self-perpetuating.
**Clinical Note: Artificial Induction of Labor**

Medical intervention is required to initiate labor during some pregnancies, including those extending past 41 weeks, when the mother is experiencing preeclampsia, or when the fetus dies in the uterus. Labor can be induced by the administration of oxytocin, prostaglandins, or both in combination. Oxytocin is provided as an IV drip, with the dose increasing over time.

**Lactation**

The fundamental secretory unit of the breast is the alveolus, which is surrounded by contractile myoepithelial cells and adipose cells. These alveoli are organized into lobules, each of which drains into a ductule. Groups of 15 to 20 ductules drain into a duct, which widens at the ampulla—a small reservoir. The lactiferous duct carries the secretions to the outside.

Breast development at puberty depends on several hormones, but primarily on the estrogens and progesterone. During pregnancy, gradual increases in levels of prolactin and human chorionic somatomammotropin, as well as very high levels of estrogens and progesterone, lead to full development of the breasts.

Milk is an emulsion of fats in an aqueous solution containing sugar (lactose), proteins (lactalbumin and casein), and several cations (K⁺, Ca²⁺, and Na⁺) and anions (Cl⁻ and phosphate). The composition of human milk differs from that of human colostrum (the thin, yellowish, milk-like substance secreted during the first several days after parturition) and cow’s milk. Cow’s milk has nearly three times more protein than human milk, almost exclusively a result of its much higher casein concentration. It also has a higher electrolyte content. The difference in composition between human milk and cow’s milk is important because a newborn, with their delicate gastrointestinal tract, may not tolerate the more concentrated cow’s milk.
Several hormones contribute to lactation. The actions of **prolactin** on the mammary glands include the promotion of mammary growth, the initiation of milk secretion, and the maintenance of milk production once it has been established. Although the initiation of lactation requires the coordinated action of several hormones, prolactin is the classic lactogenic hormone. Initiating milk production also necessitates the abrupt fall in estrogens and progesterone that accompanies parturition.

Suckling is the most powerful physiological stimulus for prolactin release. Nipple stimulation triggers prolactin secretion through an afferent neural pathway through the spinal cord, thereby inhibiting dopaminergic neurons in the median eminence of the hypothalamus. Because dopamine normally inhibits prolactin release it is called a prolactin-inhibitory factor. Thus, because suckling decreases dopamine delivery through the portal vessels, it relieves the inhibition on the prolactin-secreting cells in the anterior pituitary and stimulates bursts of prolactin release. Treating women with dopamine-receptor agonists rapidly inhibits prolactin secretion and milk production.

During the first 3 weeks after childbirth, maternal prolactin levels remain elevated. Thereafter, prolactin levels decrease to a baseline level higher than that observed in women who are not pregnant. If the mother does not nurse her young, prolactin levels generally fall to nonpregnant levels after 1 to 2 weeks. If the mother does breast-feed, increased prolactin secretion is maintained for as long as suckling continues. Suckling causes episodic increases in prolactin secretion with each feeding. After the infant completes a session of nursing, prolactin levels return to their elevated baseline and remain there until the infant nurses again.

**Oxytocin**, which promotes uterine contraction, also enhances milk ejection by stimulating the contraction of the network of contractile cells surrounding the alveoli and ducts of the breast. During nursing, suckling stimulates nerve endings in the nipple and triggers rapid bursts of oxytocin release. This neurogenic reflex is transmitted through the spinal cord, the midbrain, and the hypothalamus, where it stimulates neurons in the paraventricular and supraoptic nuclei that release oxytocin from their nerve endings in the posterior pituitary. The result is to promote the release of pre-existing milk after 40 to 60 seconds, a process known as the **let-down reflex**.
In addition to the suckling stimulus, many different psychic stimuli also promote oxytocin release. For example, the site or sound of an infant may trigger milk let-down. Thus, the posterior pituitary releases oxytocin even in anticipation of suckling. This psychogenic reflex is suppressed when fear, anger, or other stresses are encountered, and the results are inhibition of oxytocin release and suppression of milk outflow.

Lactation generally inhibits ovulatory function. Suckling likely reduces the release of GnRH by neurons in the arcuate nucleus and the preoptic area of the hypothalamus. Thus, the decreased GnRH release induced by suckling reduces the secretion of FSH and LH and has a negative effect on ovarian function. As a result, breast-feeding delays ovulation and normal menstrual cycles. However, if the mother continues to nurse her infant for a prolonged period, ovulatory cycles will eventually resume. Suckling intensity and frequency, which decrease with the introduction of supplementary foods to the infant, determine the duration of anovulation and amenorrhea. If the mother does not nurse her child after delivery, ovulatory cycles resume, on average, 8 to 10 weeks after delivery, with a range of up to 18 weeks.