Teacher Background

Female and Male Reproductive System

Note: The Teacher Background Section is meant to provide information for the teacher about the topic and is tied very closely to the PowerPoint slide show. For greater understanding, the teacher may want to play the slide show as he/she reads the background section. For the students, the slide show can be used in its entirety or can be edited as necessary for a given class.

The female and male reproductive systems in mammals are designed to produce gametes – oocytes in the ovaries and sperm cells in the testes, respectively – and to place the oocytes and sperm in close proximity so a zygote (fertilized oocyte) will form and grow into the next generation of the species. The gametes are the result of meiosis and are haploid. The union of the oocyte and the sperm during fertilization results in a diploid cell. The number of chromosomes in the haploid gametes and in the diploid offspring is species specific.

How does the female reproductive system work?

In addition to producing the oocytes, the female reproductive system is designed to nurture the developing embryo in the womb until birth and by nursing providing milk through the mammary glands after birth. Both the female and male reproductive systems are regulated by circulating hormones produced in the brain and in the gonads (primary reproductive organs – the ovaries and testes). Hormones are chemical messengers that carry information from one cell to another via the bloodstream. Major types of hormones include small proteins (peptides) and the cholesterol-derivatives (steroids), such as insulin and estrogen, respectively.

In the human female reproductive system, the reproductive system is composed of the following: a) **ovaries**, the female gonads where the oocytes reside, b) the **fallopian tubes** (also known as oviducts) down which the oocyte travels once it leaves the ovary through ovulation and where fertilization usually takes place, c) the muscular **uterus** where the zygote will implant and grow if fertilization has occurred and where the unfertilized oocyte will pass if not, and d) the **vagina** which is often called the birth canal and leads to the outside of the body. Separating the vagina from the uterus is the **cervix** which is a narrow opening of the uterus. The vagina is also the site where the male would deposit the sperm which then swims through the cervix and uterus and up the fallopian tubes to possibly meet an ovulated oocyte. (1)

Before birth, the ovary of the human female contains all of the primordial follicles she will have during her life, approximately 400,000 of them. (1) An oocyte which is arrested at prophase I of meiosis resides in each follicle, which is the functional unit of the ovary. Clinically this stage is called **Germinal Vesicle (GV)**. The oocyte is surrounded by somatic (cells of the body as opposed to germ cells like oocytes) cells that produce hormones, such as estrogen. While a child, the ovaries grow and secrete small amounts of estrogen which inhibits release of gonadotropin-releasing hormone (GnRH) from the hypothalamus of the brain. As the child matures, beginning between ages 6 and 9 years, **adrenarche** (1, 2, 3) begins which is when the hypothalamus becomes less responsive to estrogen and begins to release GnRH in a pulse-like manner. This, in turn, stimulates the release of **follicle stimulating hormone (FSH)** and **luteinizing hormone (LH)** from the anterior pituitary located just beneath the hypothalamus in the brain. **Gonadarche** is the period following adrenarche in which these hormones continue to circulate in increasing amounts over about four years. Gonadarche ends with the attainment of reproductive competence with beginning of the first menstrual cycle, called **menarche** ('men' means month and 'arche' means first in Greek) usually between 8 and 14 years. A female is said to have reached puberty when she has the first menstrual period. At the same time, the levels of estrogen are increasing causing secondary sexual characteristics, such as axillary (underarm) and pubic hair to develop, breast development, and a growth spurt in height and weight around age 12. (2, 4)

In order to reach menarche, the **ovarian cycle** occurs in which an oocyte matures and is ovulated. There are two parts to this cycle – 1) the **follicular phase** in which the follicle containing the oocyte grows and 2) the **luteal phase** which occurs after the oocyte is ovulated (or released) and the remaining somatic follicular material forms the corpus luteum. This ovarian cycle will continue to occur once a month from puberty to menopause.

The uterine, or **menstrual cycle**, corresponds to the ovarian cycle, but reflects changes that occur in the uterus in response to ovarian hormones. The menstrual cycle has three parts – 1) the **proliferative phas**e during which the lining of the uterus, called the endometrium, grows; 2) the **secretory phase** where the glands in the endometrium begin to **secrete special proteins necessary for implantation of an embryo IF an embryo is present; and 3)** menstruation which occurs at the end of the uterine cycle when the endometrial lining is sloughed off if an embryo is not present. The menstrual cycle will occur once a month from puberty to menopause in correlation with the ovarian cycle.

Follicle growth: A **primordial follicle** containing an oocyte will mature. In response to FSH and LH, the squamous cells surrounding the primordial oocyte begin to become cuboidal and the oocyte grows; this stage is called the **primary follicle**. The primary follicle begins to add cuboidal cells in several layers around the oocyte; this stage is called the **secondary follicle**. These somatic cells of the secondary follicle surrounding the oocyte are called granulosa cells and they serve as nurse cells for the oocyte's maturation. Granulosa cells proliferate as the secondary follicle grows. The actual length of time it takes for a primordial follicle to grow to an antral follicle is not known, but believed to take 90 days or more.

Primordial follicles begin to grow throughout a woman's lifetime, and the fate of most of them is to die. Eventually the **antral follicle** (also called a vesicular or Graafian follicle) will form when clear fluid begins to accumulate between the granulosa cells and then combines to form a fluid-filled cavity, and the , and the granulosa cells now produce estrogen. The outer somatic cells surrounding the granulosa cells of the antral follicle are called theca cells and they produce androgen substrates for estrogen production in the granulosa cells. The follicular phase 'officially' begins when the antral follicles are present in the ovary. One antral follicle is selected to become the preovulatory follicle which is the one that will release the oocyte. The follicular phase lasts between 10 – 14 days and is the period of time during which an antral follicle grows to the preovulatory follicle.

Proliferative phase: As FSH and LH begin to increase, so do estrogen levels produced by the antral follicle leading to further growth of the follicle. In response to the increasing estrogen levels, the uterine lining (endometrium) begins to build. The endometrium is well vascularized, but not yet ready to accept an embryo for implantation.

LH surge: As the estrogen level increases, it causes a surge in FSH and an even larger surge in LH released from the anterior pituitary gland. At the surge of LH, the oocyte completes meiosis I (clinically **metaphase I (M1)**) and is arrested at metaphase II. Clinically, this stage is called **metaphase II (M2)** and is evident by the appearance of the first polar body next to the oocyte. The oocyte will not complete meiosis II unless it is fertilized by a sperm. Clinically called a **zygote**, it would have the first and second polar bodies next to the fertilized oocyte. (The first polar body does not divide so a third polar body does not form.) The first and second polar bodies eventually atrophy. The LH surge causes the antral follicle to release the secondary oocyte (metaphase II) in the process called ovulation. The LH surge stimulates special enzymes that break down the follicle wall allowing the oocyte and antral fluid are released into the peritoneal cavity of the abdomen directly adjacent to the fallopian tube. The oocyte is swept into the fallopian tube by the cilia on the finger-like fimbriae of the fallopian tube which loosely cover the ovary.

Luteal Phase: The luteal phase of the ovarian cycle begins after the oocyte is ovulated and the remaining somatic follicular tissue forms the corpus luteum. At ovulation, the high levels of LH cause the remaining follicular tissue to form a corpus luteum which begins to produce progesterone and estrogen, which are necessary for initiation and maintenance of pregnancy. These two hormones also provide negative feedback to the anterior pituitary, thus decreasing the levels of FSH and LH. In this way, development of a new follicle and ovulation are inhibited. The major role of the corpus luteum is to produce the hormone progesterone. The luteal phase typically lasts 14 days if there is no embryo present.

Secretory phase: In addition, high levels of estrogen and progesterone maintain the uterine lining and cause the glands to secrete proteins. If fertilization and implantation of the embryo occurs, the hormonal activity of the corpus luteum is maintained by a hormone similar to LH which is released by the developing embryo. If no fertilization occurs, the LH levels further decrease and the corpus luteum begins to atrophy. This, in turn, decreases the levels of estrogen and progesterone. The lining of the uterus is sloughed in menstruation and the cycle begins again.

The menstrual cycle is the recurring cycle of physiological changes that occur in reproductive age in humans and other primates that is hormonally regulated and results in in ovulation and preparation for the events of fertilization of the mature oocyte and implantation of an embryo. In other placental mammals, like the mouse, the related recurring female cycle is called an estrous cycle.

How does the male reproductive system work?

The male reproductive system is much less complicated than the female system. The male system consists of a tubular structure that is all connected. It begins with a) the **scrotum** which holds the **testes (plural)** (testis, singular), the male gonads where the sperm and testosterone are made. The scrotum is a sac-like structure made of skin and connective tissue into which the testes descend during the 9^{th} month of pregnancy or just after birth. (5) Viable sperm cannot be made at body temperature ($37^{o}C$) so the position of the testes in the scrotal sac lowers the temperature about $3^{o}C$ providing a cool enough place for sperm to be made. The testes are made of 250 to 300 compartments called lobules and each lobule contains one to four tightly coiled **seminiferous tubules** in which the sperm will develop. b) The **epididymis**, which receives the sperm, is a coiled tubule next to the testes where sperm mature as well as gain their motility and may be stored for a short time. c) From there, the **vas deferens (also called the ductus deferens)** transports the mature sperm from the epididymis to the penis. d) The **penis** is the male organ of copulation and, in mammals, of urinary excretion. The **urethra** is the terminal portion of the male tubular system; at different times, it carries urine from the bladder and mature sperm from the vas deferens through the penis to the outside of the body. e) The end of the vas deferens joins with the duct of the seminal vesicle to form a short **ejaculatory duct** which passes into a single prostate gland where it empties into the urethra. In the **seminal vesicles**, a yellowish viscous alkaline fluid containing fructose (nutrient), ascorbic acid, a coagulating enzyme (vesiculase), and prostaglandins are added. This makes up about 60% of the volume of the semen. The **prostate gland** secretion is a milky, slightly acidic fluid that contains citrate (nutrient), and several enzymes (fibrinolysin and acid phosphatase) and plays a role in activating the sperm. The prostate gland adds about 33% of the semen volume. f) The **bulbourethral glands** are just next to the prostate gland and just prior to ejaculation adds a thick, clear mucus that drains into the urethra to neutralize the acidic urine that might remain in that duct. (1)

By 7-8 weeks of development in the fetus, the male reproductive structures begin to develop as a result of secretions of male hormones due to the SRY (sex-determining region Y) gene (also known as TDF or testis-determining factor gene) on the Y chromosome. The protein produced by this gene attaches to specific regions of DNA and helps control the activity of particular genes in the process that causes the fetus to develop testes and the development of other female reproductive structures such as the uterus and fallopian tubes. (6) By 8-9 weeks in the development of the fetus, if the SRY gene isn't expressed, a female fetus will develop. Prenatal secretion of males hormones begin to be produced and the levels of testosterone and plasma gonadotropin are nearly equal to mid-pubertal levels at birth and for a few months after and then subside and remain low during childhood. As in girls, low levels of testosterone keep the levels of GnRH suppressed but as puberty nears, higher and higher levels are testosterone are required to suppress the increasing amounts of GnRH until the adult levels of hormones are achieved. Maturation of this brain-testicular hormonal cycle takes about 3 years to achieve and once done, it will be relatively stable throughout life, unlike the female who cycles monthly.

At puberty, GnRH in the hypothalamus stimulates the anterior pituitary to produce FSH stimulates spermatogenesis in the testes and to produce LH which binds to the interstitial cells called **Leydig cells** in the testis and stimulates production of testosterone. The testosterone continues to act as a negative feedback for production of GnRH. Inhibin which is a protein hormone produced by the **Sertoli cells** (elongated cells found in the seminiferous tubules of the testis where spermatids attach during spermatogenesis for nourishment) increases when the sperm count is high and inhibits GnRH and FSH release and when sperm count is low (below 20 million per millimeter), inhibin secretion sharply declines. (1) Thus, spermatogenesis begins at puberty in response to increased levels of testosterone and continues the entire lifetime of the male.

Unlike the female ovaries which contain all of the oocytes at birth, the male testes contain stem cells located along the outer most edge of the seminiferous tubules in the testes. Millions of sperm at made at a time. **Spermatogonia** (plural for spermatogium) are undifferentiated Type A (d) stem cells in the testes which divide by mitosis to produce Type A (p) cells and more Type A (d) cells. Type A (p) cells divide by mitosis to produce Type B cells which divide by mitosis to produce **primary spermatocytes**. The primary spermatocytes undergo meiosis I to form two equally sized secondary spermatocytes. The secondary spermatocytes each undergo meiosis II to form four equally sized haploid (monoploid) **spermatids**. The spermatids continue to develop through cell differentiation into four mature haploid sperm cells flagellated for motility. The **mature sperm cell (also called a spermatozoan)** is one of the smallest human cells. It consists of a round or cylindrical nucleated cell (head) which measures 0.005 mm by 0.003 mm, a short neck (midpiece) and a thin motile tail (flagellum). The entire mature sperm is 0.05 mm in length. The **acrosome** is an organelle covering the head of animal sperm and contains enzymes that digest the oocyte cell coating, thus permitting the sperm to enter the oocyte. The **midpiece** contains energy-producing mitochondria to power the movement of the tail. The **tail** allows the sperm to swim to the oocyte.

A sperm has the ability to swim the entire length of the female reproductive tract and can live in a female's cervical mucus and upper genital tract for about 72 hours (about 3 days). In a process called **sperm capacitation**, sperm acquire the ability to fertilize the oocyte inside the female reproductive tract *in vivo*. Involved is the destabilization of the sperm acrosomal head membrane through motility and a metabolic change in the sperm which removes steroids and glycoproteins from the acrosomal head, thus increasing permeability to Ca^{2+} so it will be able to penetrate the oocyte for fertilization. *In vitro*, capacitation occurs by incubating Sperm in a defined medium for several hours.

Testicular cancer, while rare, is the most common cancer in young men ages 15 – 35. The most common sign of testicular cancer is a painless solid mass in the testis. Self-examination is the best way to detect this cancer and if detected early, the survival rate is high. It is treated by surgical removal of the cancerous testis followed by radiation and chemotherapy.

When a female or male has radiation therapy and some chemotherapy treatments for cancer, all of the primordial oocytes in the ovaries and all of the stem cells in the testes can be destroyed. Oncofertility is a new discipline that makes connections between oncology (cancer therapy) and reproductive medicine, providing viable fertility preservation options for people with cancer and other fertility threatening diseases.

Bibliography

1. Human Anatomy and Physiology, Elaine N. Marieb and Katja Hoehn, 8th Ed, Pearson Education, Inc., 2010.
2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3410522/
3. http://www.merckmanuals.com/home/women-s-health-issues/biology-of-the-female-reproductive-system/puberty-in-girls
4. http://www.stanfordchildrens.org/en/topic/default?id=puberty-adolescent-female-90-P01635
5. http://www.embryology.ch/anglais/ugenital/diffmorpho04.html
6. http://ghr.nlm.nih.gov/gene/SRY