Section Four: Chapter 23: The Female Reproductive System

The Female Reproductive System

The gonads of the female reproductive system are the ovaries and they function to produce gametes (**oocytes** or **egg cells**) in addition to the reproductive hormones, including estrogens and progesterone, as is the same concept for the male reproductive system. However, the female body has the additional role of supporting the developing embryo and fetus in the womb and delivering at birth a genetically unique baby into the world. There are many fundamental similarities in the male and female reproductive systems, and major differences too.

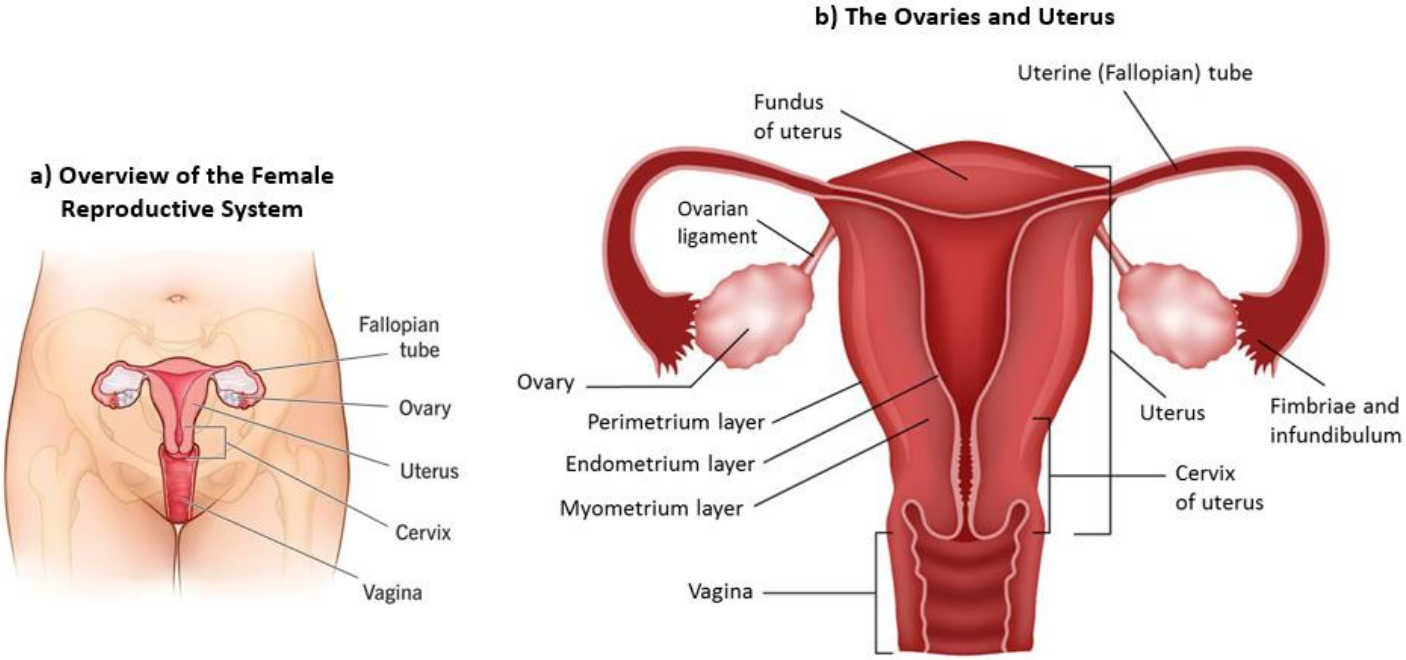


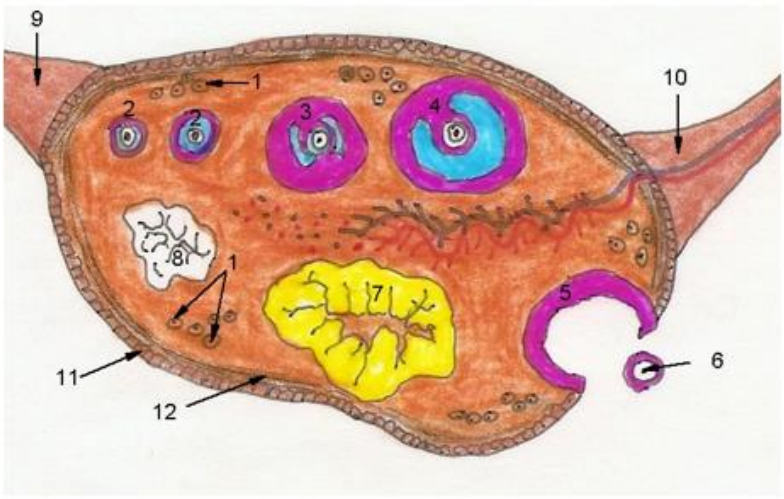
Figure 23.1 In **a)** is shown an overview of the position and arrangement of the female reproductive structures within the pelvic cavity. In **b)** is shown a more detailed representation of the ovaries and the uterus. The ovaries are the gonads and therefore where the egg cells are produced and released from. The oocytes flow onto the uterine tubes and travel to the uterus, where they will either continue out through the cervix and vaginal canal and exit the body, or if fertilized by a sperm cell to become a zygote, this will implant in the endometrial layer of uterus, usually in the fundus region. The thick myometrial layer of the uterus is made of smooth muscle and its contractions during labor push the baby out of the uterus into the vaginal canal during birth.

The Ovaries

The entire female reproductive system is snuggly nestled within the protection of the boney pelvic cavity, as seen in **Fig 23.1 a)** above. The **ovaries** are the primary reproductive structure of the female as these are the gonads that make the gametes and sex hormones. The paired oval-shaped ovaries can be seen in **Fig. 23.1 b)**, and within the body they are often remarkably small for all the things they do. The size can vary, but on average have the dimensions of 3.5 cm x 2 cm x 1 cm, in other words they are about the size and shape of a large **almond**. The size of a woman's ovary can have an impact, as women with larger ovaries have a greater egg reservoir which may mean they will have an easier time conceiving and also be able to conceive at older ages.

When examined closely, the ovary has many similarities to an elegant and meticulous cosmic clock! The processes that occur within the ovary have impeccable timing and are complexly cyclic in function. Like the gears and cogs of an intricate clock, the ovarian cycle depends on the cycles of the hypothalamus, and the uterine cycle depend of the cycles of the ovaries. Thus elements both upstream and downstream of the ovaries must be meticulously synchronized. As mentioned, the ovaries are contained within the pelvic cavity and they are tethered and supported in their position there by multiple ligaments, for example the ovarian, the suspensory and the broad ligaments. As will become clear, the ovaries are very closely associated with the uterus (seen in **Fig. 23.1 b**) both in proximity and in utility.

The drawing below (**Fig. 23.2**) is a representation of the histology of an ovary under microscopic examination. The figure is best read by going through the structures in order, from 1 to 12, flowing around the ovary in a clock-wise direction. This is how the clock-work elements of the ovary can be most appreciated. The central functional aspect of the ovary is to release a mature egg and then prepare the body for possible implantation of a zygote and pregnancy. If implantation does not occur, then the ovarian cycle moves on from ovulation to the end of the cycle, and repeats itself every other month. Since there are two ovaries, each takes a turn releasing a mature egg cell; one releases an egg one month, the other releases an egg the next month, and so on.



Structures of the Ovary

1. Primordial follicles (with oogonium)
2. Primary follicles
3. Secondary follicles with oocyte
4. Mature (Graafian) follicle with oocyte
5. Follicle at ovulation
6. Release of egg at ovulation
7. Corpus luteum
8. Corpus albicans
9. Suspensory ligaments
10. Ovarian ligament
11. Germinal epithelium
12. Tunica albuginea

Figure 23.2 This shows a drawing of the ovary indicating the cyclic nature of follicular and egg cell development. The important structures are highlighted with numbers and the numbered key to the right shows the usual progression of 'events' that occur.

As seen in **Figure 23.2** above, the ovary has a smooth outer covering of cuboidal epithelium called the **germinal epithelium**, it was so named because it was once (inaccurately) believed that the egg cells germinated from this layer of cells. Just deep to this is the **tunica albuginea**, which is a dense fibrous connective tissue that holds and protects the tissue organ.

Deep to the tunica albuginea is the **ovarian cortex** which is the large outer portion of the ovary, and is where all the action takes place! For instance, this is where the **oocytes** develop inside of **ovarian follicles**. Ovarian follicles are like a house that the egg cell (oocyte) matures in, becoming more developed as it cycles around the ovarian cortex in a very precise manner. In the deepest central region is the inner **ovarian medulla**, where blood and lymph vessels, the nerves supplying the ovary.

Once the mature cell is released from the mature ovarian follicle at **ovulation** (number 6 in **Fig. 23.2** above), the ovarian follicle become the **corpus luteum** (number 7 in **Figure 23.2** above) a name meaning 'yellow body'. This readies the body for pregnancy, should fertilization occur. If the egg is unfertilized, the corpus luteum becomes the **corpus albicans** (number 8 in **Fig. 23.2** above) a name meaning 'white body'. This structures is degraded by resident macrophages and the cycle begins again.

The Ovarian Cycle

Cycles are extremely meaningful and important in the body, and particularly in the reproductive system. The **ovarian cycle** is created by gonadotropic hormones form the anterior pituitary gland, and orchestrate the events that occur in the ovary. In healthy ovulating women these events are extremely predictable. During a woman's reproductive years, the ovarian cycle is usually 28 days. Yes, exactly like the cycles of the moon! To be clear, this is not the **uterine cycle** (what most know as the **menstrual cycle**), but the two are correlated because as we will see, it is the ovarian cycle that dictates the uterine cycle.

The ovarian cycle may be divided into three stages: **1)** the follicular phase, **2)** ovulation, and **3)** the luteal phase. Distilled into the simplest terms the sequence of events can be described as this:

- **Follicular Phase** – the follicles (with the oocyte inside) facilitate **oogenesis**, which is the growth and development of the primary ova into a mature ovum.

- **Ovulation** – triggers the release of the mature egg cell from the follicle and the ovary.

- **Luteal Phase** – the follicle becomes the corpus luteum, secreting estrogens and progesterone levels for potential implantation of a fertilized egg cell within the endometrium of the uterus.

Oogenesis

Now for some noteworthy details about how the primary egg cell (or ovum) becomes a mature ovum in the process called **oogenesis**.

This process actually begins with the ovarian stem cells called **oogonia**, this is basically a structure that is the prelude to the primordial follicle that can be seen under the microscope. The process of oogenesis is parallel to spermatogenesis in males. It requires **meiotic** cell divisions in order to reduce or half the number of chromosomes from 46 to 23, which then leads to the production of ova (eggs) in females.

However, unlike spermatogonia, the process of oogenesis is initiated very early in life, as in during the development of the fetal ovary. While the fetus is developing, the gametes begin as diploid (2n), then the oogonia cells divide by **mitosis** and differentiate to produce primary **oocytes** (still diploid with 46 chromosomes). The formation of cells around each of these primary oocytes combine and create an **ovarian follicle**. The primary oocytes that are housed inside a follicle commence **meiosis**, but only progresses to prophase I and are suspended in this stage until puberty and continuing until the woman is near menopause. The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately **400,000** at puberty, to zero by the end of menopause.

The Female Egg Cell

The female egg cell is small, but it may be bigger than you realize! This cell is the largest cell in the human body and can be seen without a microscope. Thus, comparatively, the egg cells are huge. They measure between about 100 to 200 µm (microns) in diameter. On the small side of the scale that size is similar to the width of a strand of hair, and larger eggs can be about the size of a single grain of reined granular sea salt.

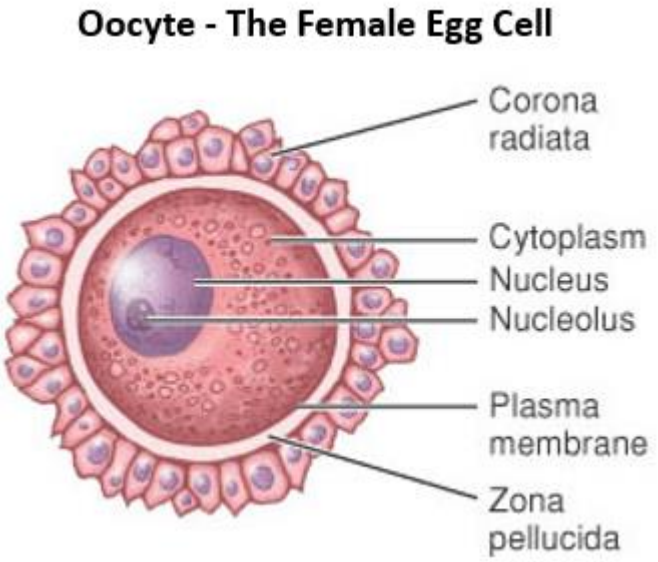


Figure 23.3 The oocyte is the immature or developing egg cell within the ovarian follicle. It contains a large nucleus with substantial cytoplasm. It is surrounded by a thick protective glycoprotein membrane called the zona pellucida (from Latin pellucerene, meaning to shine light through). The outer layer of follicular (granulosa) cells is called the corona radiate (from Latin meaning radiating crown) forming around the developing oocyte remaining present and in place at ovulation.

Why is the female egg cell so large? Like the male sperm cell, the female egg cell contains a large nucleus with haploid (half) the number of chromosomes as other body cells (see **Fig 23.3** above). Unlike a sperm cell, the egg contains a significant cytoplasm to ensure resources if it fertilized, which is why it is so big.

<u>The ovarian follicle have several stages of development</u>

1. **Primordial follicle**: An oocyte with a single layer of cells.

2. **Primary follicle**: Has two or more layers of encircling cells called **granulosa** cells.

3. **Secondary follicle**: Now contain the **antrum**, the fluid-filled central cavity.

4. **Mature follicle**: Also called a Graafian follicle (see **Fig. 23.4** below), the primary oocyte within it has completed meiosis I. Prior to its release at ovulation, the follicle will acquire these features:
   - **a)** The **zona pellucida** around the oocyte (a layer of transparent glycoprotein).
   - **b)** A ring of granulosa cells called the **corona radiata** encircle the zona pellucida.
   - **c)** The **cumulus oophorus**, the "egg-bearing little cloud" support cells.
   - **d)** Several layers of cells, called **theca cells**, surrounding the granulosa cells.

Mature (Graafian) Follicle

1. Oocyte
2. Zona pellucida
3. Corona radiate
4. Zona granulosa
5. Cumulus oophorus
6. Basement membrane
7. Theca interna
8. Antrum in follicular cavity

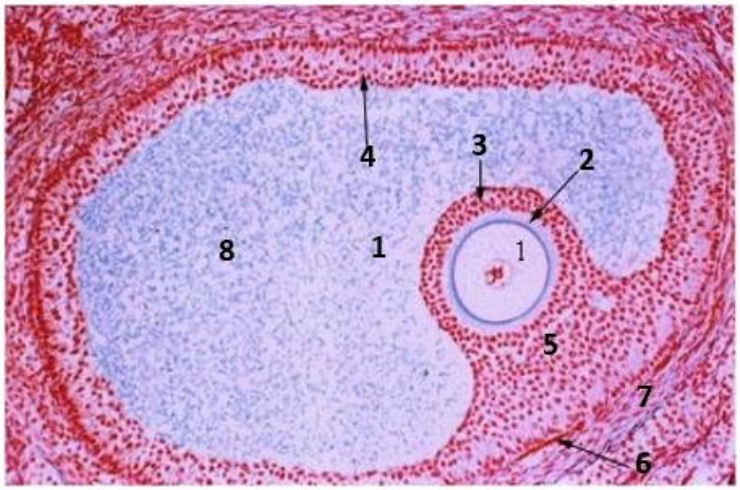


Figure 23.4 Shows the histology of the mature (Graafian) ovarian follicle with all of the structures listed to the left of the image to indicate the stage of development that precedes the release of oocyte at ovulation.

The Follicular Phase

Ovarian follicles grow and develop in a process called **folliculogenesis**, which just means 'follicle production', and this leads to ovulation of one follicle about every 28 days. It also involves the demise of other ovarian follicles, that process is called **atresia**. Put simply, the follicular phase is the time of the progression of follicular development from the tiny **primordial follicles**, which are actually present in newborn females and abundant in the adult ovary, to the fully **mature follicle** that is ready to release a mature egg cell. The primordial follicles residing within the ovary can remain in a dormant resting state in the ovary for many years, even decades, prior to being activated.

Once puberty starts, select primordial follicles respond to signals in the body to join a collection of growing **primary follicles** with their single layer of granulosa cells. These cell increase in size and proliferate to differentiate into **secondary follicles.** Becoming larger in diameter and adding **theca cells**, that together granulosa cells produce estrogens (see **Fig. 23.4** above).

At this stage the **primary oocyte** within the secondary follicle secretes a unique extracellular coat surrounding the maturing oocyte thin membrane called the **zona pellucida** which has an important role in fertilization. The zona pellucida prevents polyspermy (fertilization by more than one sperm) and enables the acrosome (at the tip of the sperm head) adhesion for penetration by the sperm cell into the egg.

The viscous follicular fluid fills the large space called the **antrum** (see **Fig. 23.4**) and when this is large and fully formed, it is then a **tertiary follicle** (antral follicles). Several tertiary follicles reach this stage at the same time, but most will undergo *atresia*. It is the one that does not die that will continue to grow and develop until ovulation. Throughout this entire process, about **99%** of the ovarian follicles undergo atresia.

At the very end of the follicular stage (just prior to ovulation), there is a surge of luteinizing hormone (LH) that triggers the resumption of meiosis in a primary oocyte. This initiates the transition from **primary to secondary oocyte**. This cell division does not result in two identical cells, but with an unequally divided cytoplasm. This larger daughter cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first **polar body**, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates, and again only one oocyte survives.

The Hormones Involved in the Ovarian Cycle

The **gonadotropic releasing hormones** (GnRH) from the hypothalamus signal the anterior pituitary to release the gonadotropins follicle stimulating hormone (**FSH)** and luteinizing hormone (**LH**) that bind to receptors on granulosa and theca cells of ovarian follicles.

As its name implies, follicle stimulating hormone (FSH) stimulates the growth and development of the ovarian follicles in females, including the development of the egg cell inside the follicle. It is the luteinizing hormone (LH) that binds to receptors on granulosa and theca cells of ovarian follicles to produce the sex steroid hormone estradiol, a type of estrogen, at ovulation. The LH also causes the release of progesterone by the corpus luteum after ovulation (see **Fig. 23.5** below).

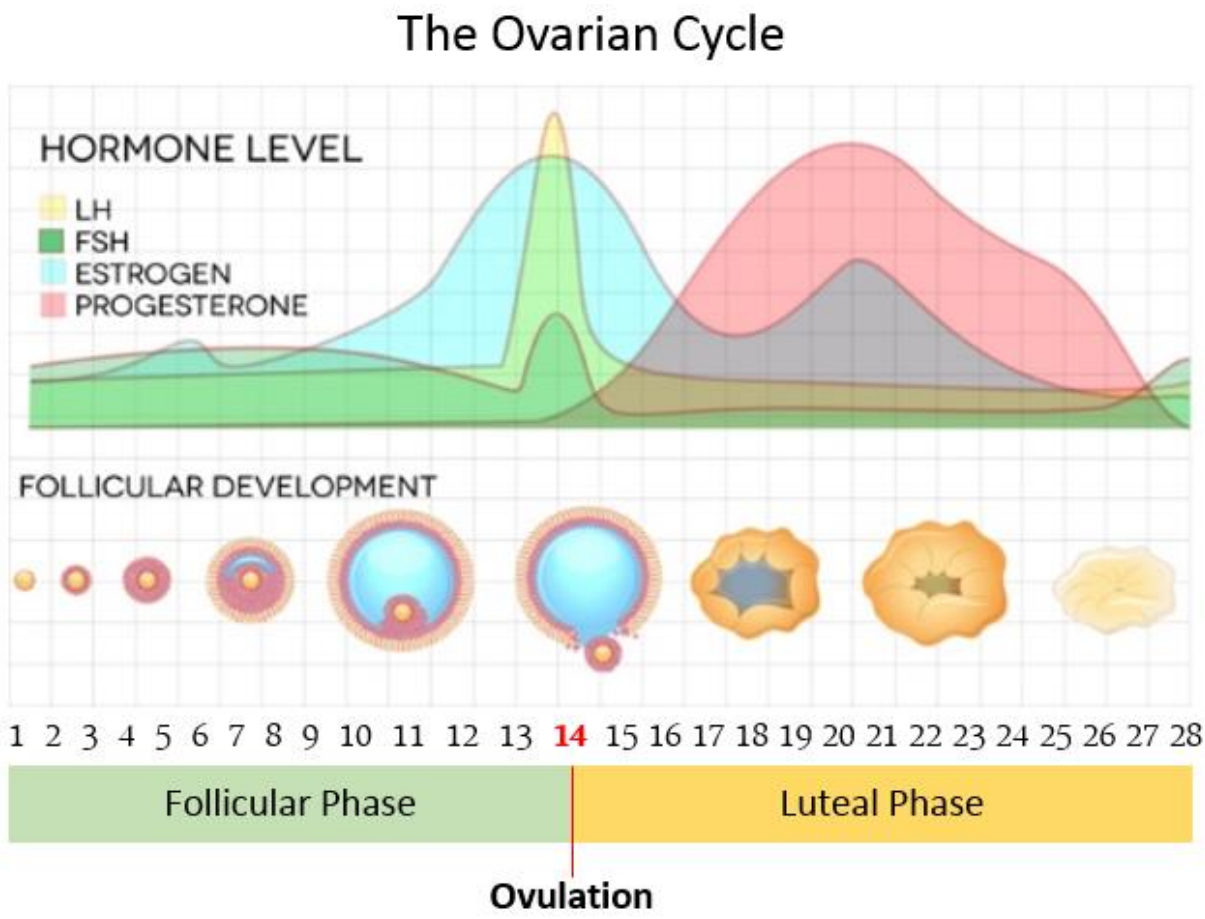


Figure 23.5 Shown above is a general graph of the changes in hormone levels during the 28 day ovarian cycle. There are three phases of this cycle, starting with the follicular phase when the follicle with the egg cell inside it develops. Then at ovulation, the mature egg cell is released at day 14. This triggers the last luteal phase in which the corpus luteum prepares for possible implantation of a fertilized egg cell (a zygote). LH stands for luteinizing hormone and FSH stands for follicle stimulating hormone.

As the ovarian follicle become larger and more developed, it produces more estrogen in response to LH, therefore as the follicular phase progresses, more and more estrogen is released, increasing systemic plasma estrogen concentrations (see **Fig. 23.5** above). The elevated estrogen levels stimulate a negative feedback loop in the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. This decrease in FSH causes most follicles to die, except the **dominant follicle**, which will be the one that releases an oocyte.

Ovulation

Ovulation occurs approximately once every 28 days. In the very last portion of follicular development, the cells of the follicle start to produce more **estrogen** than all the follicles previously, such massive amounts that raise plasma estrogen enough to trigger the anterior pituitary to secret more **LH** and **FSH**, and this makes more estrogen, a positive feedback loop ensues that releases more LH and FSH, etc. It is the large **surge in LH** leads to **ovulation of the dominant follicle**. It also induces the dominant follicle to resume meiosis of a primary oocyte to a secondary oocyte. This spike in LH triggers proteases that break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release of the egg cell at ovulation has the appearance of the structure in **Fig. 23.3**.

Interestingly, meiosis (the reduction division) of a released egg cell (oocyte) is only completed if a sperm cell penetrates its barriers. This action will trigger meiosis II to resume, producing a haploid (1n) genome and the cell is now called an **ovum**. It is not really necessary to be pedantic about the specific names of the egg cell, the best practice is to know that the mature egg cell is an oocyte that can become an ovum. Technically, the moment the haploid ovum is fertilized by a haploid sperm, it becomes the **fertilized egg cell** or a **zygote**. That union is the first diploid cell of the new offspring.

The cytoplasm of the female gamete is used to support the developing zygote in its journey to implantation into the endometrium of the uterus. As it turns out, the sperm cells provide their DNA at fertilization, not any cytoplasm because they do not really have any. They travel light. This is why all of the cytoplasmic organelles in the developing embryo are *from the mother*, because all of that extra material comes from the mother's egg cell. This includes **maternal mitochondria**, which has its own DNA.

The Luteal Phase

The surge of luteinizing hormone (LH) that triggers ovulation also converts the now empty follicle into the **corpus luteum** (yellow body) which is actually now acts as a secondary endocrine gland.

The granulosa and theca cells of the corpus luteum start to produce **progesterone** in very large amounts in preparation for the possibility of pregnancy. This occurs in order to support and maintain that condition, if it occurs. This high level of progesterone triggers a negative feedback of the hypothalamus and pituitary gland, which keeps GnRH, LH, and FSH release low in order to prevent any new dominant follicles to develop until the end of the luteal phase. This is sort of a failsafe mechanism so that no other egg cells are maturing in readiness for ovulation until the next cycle begins.

After ovulation, if pregnancy does not occur within about 10 to 12 days, the corpus luteum stops releasing progesterone and begins to transform into the **corpus albicans** (white body). This structure is then naturally degraded by resident ovarian macrophages. This change causes a reduction of progesterone, which then allows the release of FSH and LH to re-commence, and the ovary is now cycled back to the starting follicular phase, with a new bunch tertiary follicles start to develop and secrete estrogen.

The term *mittelschmerz* is a German word meaning "middle pain" and it is used to describe abdominal pain women have that is associated with ovulation, which of course occurs in the middle of both the ovarian and menstrual cycles. Some women can feel ovulation and this is accompanied by pelvic pain at about the 14 day of the typical 28 day cycle.

The Uterine Tubes

The **uterine tubes** (Fallopian tubes, or oviducts in other mammals) serve as a passageway for the oocyte as it departs the ovary and makes its way to the uterus. Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. Looking at **Fig. 23.6** below it shows the close physical proximity of the ovary and the fimbriae at the entrance of the uterine tube. The egg cell is released into the abdominopelvic cavity and it is the billowing fimbriae that guide the egg into the uterine tube. It is the inner mucosal lining of this tube that has ciliated cells which rhythmically beat and create a current that pulls the oocyte in the direction of the uterus.

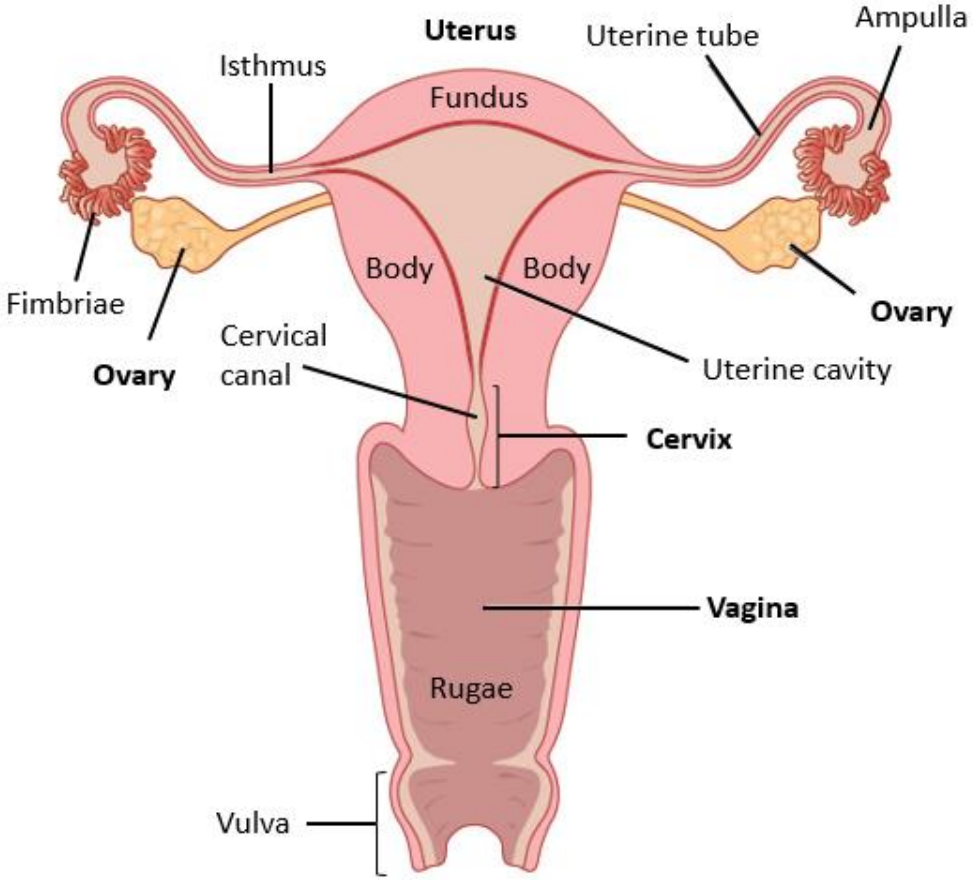


Figure 23.6 This diagram shows all of the internal reproductive structures of female as they are arranged in the pelvic region of the abdominopelvic cavity. Reading the figure from the ovaries first, flanking each side of the central uterus, the uterine tubes connect the ovaries to the fundus and body of the uterus. The lowest portion of the uterus is called the cervix which leads into the vagina and the vulva that becomes the external portion.

Hormonal Actions help Transport Gamete

The elevated **estrogen** levels around the time of ovulation cause the **smooth muscle** within the uterine tube to contract which helps the finger-like structures called fimbriae to sweep the egg into the fallopian tube. The egg travels through the fallopian tube, propelled in part by contractions in the **fallopian tube walls**. Here in the fallopian tube, the egg may be fertilized by a sperm. All of this contributes to the slow and steady movement of the oocyte toward the uterus, which typically takes about **3 days** if no fertilization occurs (see **Fig. 23.7** below). If fertilization occurs, the sperm usually makes contact with the egg while it is moving through the ampulla of the uterine tube. An **ectopic pregnancy** occurs when a fertilized egg grows outside of the uterus. It can occur if the egg cell travels into the abdominal cavity instead of the uterus. However, the vast majority of ectopic pregnancies (over 90%) occur in a fallopian tube.

The normal development of the blastula occurs in the uterine tube on the way to the uterus. There, it will implant in the nutrient laden inner endometrial layer and continue to develop and grow. If the egg is not fertilized, it will diminish in the uterine tube or in the uterus, and is usually shed during the following menstruation or menstrual period.

The Uterus

The **uterus**, also known as the **womb**, is the organ where the **embryo** becomes the **fetus** as it grows and develops. As we will see as we look more closely, the uterus is a very muscular organ, with about 90% of it being composed of smooth muscle. This component is an important structure that provides the very effective contractions during child birth. In females who are not pregnant, the uterus is surprisingly small, with an average size of 2 inches wide by 3 inches long (5 cm by 7 cm). The actual dimensions vary greatly, as all women are different, but this gives an idea of the relative size and how impressive it is that the uterus can dramatically change in order to accommodate a growing baby.

The superior portion that meets the uterine tubes of the uterus is called the **fundus** (a term which means 'opposite of the open end', like when a coin purse is tipped upside down, the top part in that position would be the fundus). The bulk of the uterus is the middle section called the **body of uterus** (or corpus). The lowest region is called the **cervix** (meaning neck) which contains the extremely narrow **cervical canal** that merges into the **vagina**. The cervix produces **mucus secretions** that become thin and stringy under the influence of high systemic plasma **estrogen** concentrations, and these secretions more effectively facilitate the movement of sperm through the female reproductive tract.

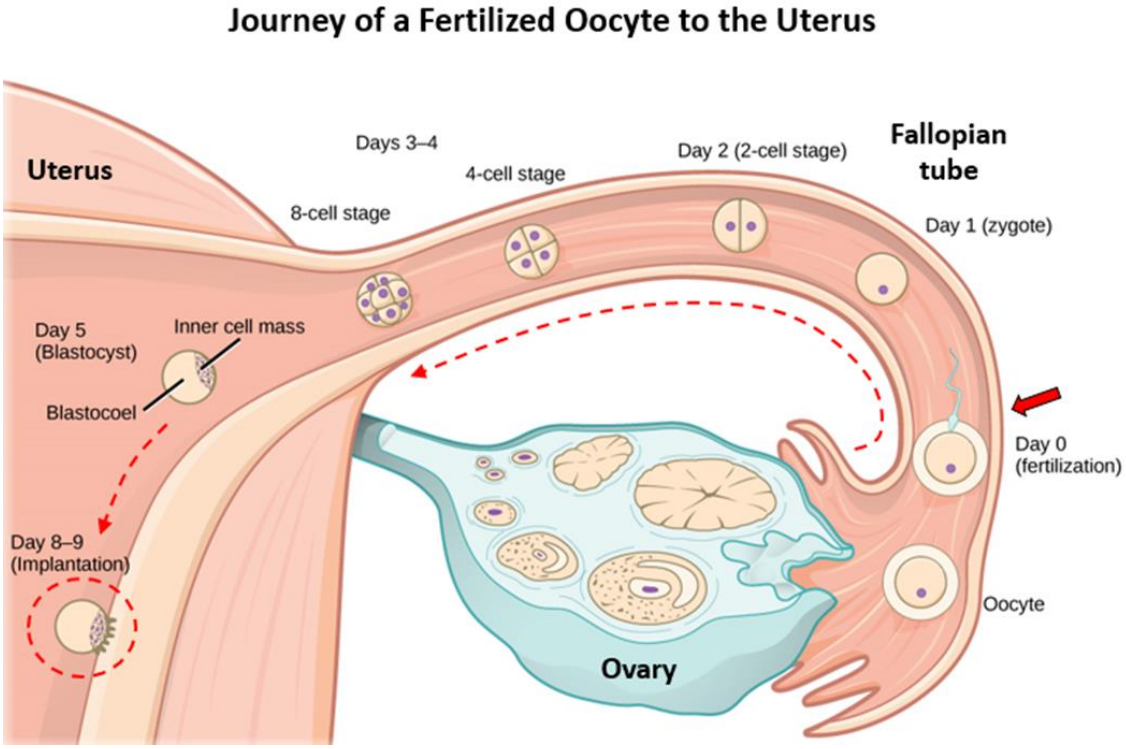


Figure 23.7 This image show the journey of a zygote (fertilized egg cell) if the oocyte that is released from the ovary at ovulation becomes fertilized by a sperm cell (red arrow). The process of fertilization must occur within 24 hours of ovulation and therefore occurs in the Fallopian (uterine) tube. The zygote starts to divide and multiply in the uterine tube on its way to the uterus, a journey that can take 3 to 4 days. Once in the uterus the blastocyst has formed, implantation of the embryo can occur into the endometrial layer of the uterus, about 8 or 9 days after fertilization occurs.

The Layers of the Uterine Wall

There are three layers of the uterine wall. From outermost to innermost they are the:
1) Perimetrium; 2) Myometrium; and **3) Endometrium.**

1) Perimetrium
The **perimetrium** is the most superficial exterior layer of the uterus that is in contact with the other organs and structures in the pelvic cavity. It is a slippery **serous membrane** that functions to protect the uterus and to reduce friction between it and the structures moving around.

2) Myometrium
The middle layer of the uterus is the **myometrium** and it is the thickest layer, making up about 90% of the uterine wall. It is composed of **smooth muscle** and this is the layer responsible for uterine contractions during childbirth.

The arrangement of the muscle fibers in the myometrial tissue is complicated and effective. The muscle fibers run horizontally, vertically, and diagonally, enabling for powerful and extremely effective contractions during child birth or labor. The myometrial layer of the uterus may also contract in a much more moderate way during menstruation or menstrual cycle. When prostaglandins are released they stimulate uterine contractions and this can cause discomfort and pain which are often experienced as cramps during the first two days of menses (menstruation) in order to facilitate menstrual blood flow from the endometrium.

In addition, myometrial contractions around the phase ovulation are thought to be a contributing factor in the transport of sperm cells from the cervix toward the uterine tubes of the female reproductive tract.

3) Endometrium
The innermost layer of the uterus is called the **endometrium**, this is the layer the fertilized egg cell would implant into. It consists of two layers: **a)** the **functional layer**, or stratum functionalis (the exposed surface), and **b)** the **basal layer**, or stratum basalis (on the bottom),

The thicker functional layer is the portion of the endometrial wall that is shed each month during **menses** (which means month in Greek), also called **menstruation**. The basal layer creates the lamina propria which connects to the myometrium below it. This bottom layer always remains and does not shed during menstruation or menses.

The condition of **endometriosis** can occur when tissue that is similar to the endometrial lining of the uterus grows outside the uterus, for example in the uterine tube or in the abdominal cavity. This tissue can thicken, break down, and bleed with each period, but is not able to be released the same way. It can lead to painful periods, heavy bleeding, pain during sexual intercourse or when having a bowel movement or urinating. Treatments can vary but the most fundamental issue is to determine the cause of this (or any) condition and address that directly, rather than suppress symptoms related to the issue.

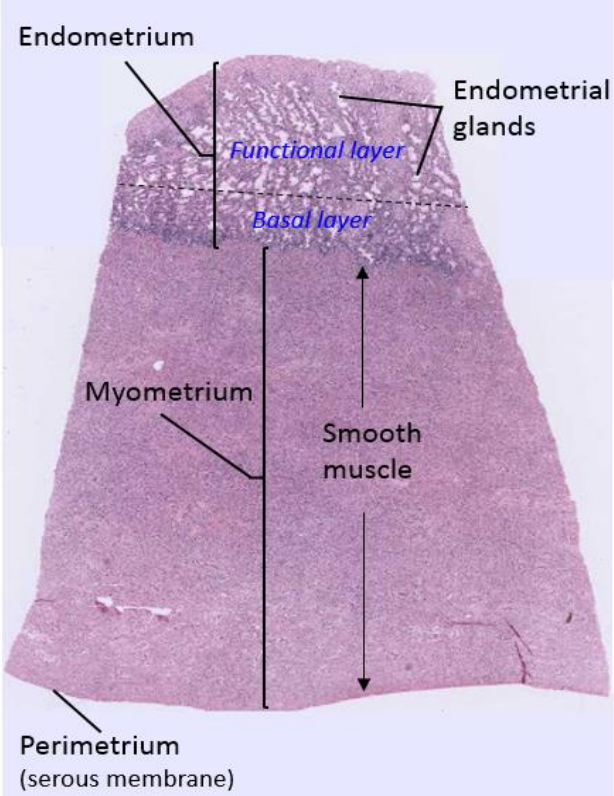


Figure 23.8 This is a histological section of the uterus showing the three layers of the uterine wall from top to bottom: The first is the innermost exposed endometrium (with two portions, the upper functional layer and lower basal layer); next is the deeper thick muscular myometrium in the middle; and lastly is the extremely thin serous membrane called the perimetrium on the outer surface of the uterus.

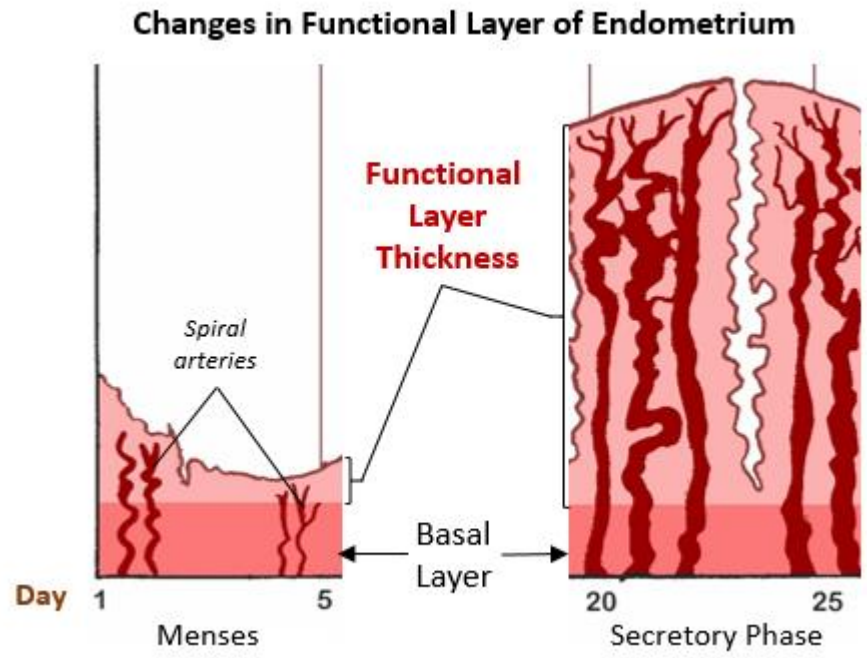
The Shedding of the Functional Layer

The most superficial exposed layer of the uterus is the stratum functionalis, or the functional layer. It is the ***functional layer*** that grows and thickens in response to increased levels of **estrogen** and **progesterone**. In the luteal phase of the ovarian cycle (and secretory phase of menstrual cycle) there are special branches coming off of the uterine artery called spiral arteries and these supply the thickened functional layer (**Fig 23.9** below). This inner functional layer provides the perfect site for implantation of a fertilized egg cell. Should fertilization *not* occur, it is then this functional layer *only* of the endometrium that sheds during menstruation. This layer is of course re-built every month.

The deeper stratum basalis or basal layer (meaning bottom layer) is the deepest tissue of the endometrium it sits atop muscular myometrium. It's the layer of endometrium that doesn't undergo any removal or structural changes during the uterine cycle and its purpose is to assist in the replacement of tissue that is loss during the menstruation.

Distal vessels are sloughed off, while the spiral arteries (named for their helical shape) retract into the stratum basalis and constrict to limit blood loss during menstruation

The uterine lining does not receive the progesterone, **causing the spiral arteries constrict and the endometrial tissue to become ischemic**. This causes cell death and the sloughing of the functional layer.



At the start of the ovarian cycle, estrogen release is stimulating ovarian follicles (in the follicular phase) and also during this phase the functional layer of the endometrium starts to rebuild from menses. It is the increase in progesterone after ovulation during the luteal phase which maintains the thick functional layer that steadily thickens in preparation for a potential implantation of a fertilized egg cell. If the corpus luteum in the ovary is still present and functioning, then the endometrial lining continues to prepare for implantation.

Figure 23.9 This shows the minimum and maximum thickness of the endometrial layer of the uterus from the start of the cycle at menses from days 1 to 5 (left), where the functional layer at its thinnest after being sloughed off, compared to the end of the secretory phase from days 20 to 25, where the functional layer has been restored to its maximum thickness in preparation for possible zygote implantation. Note the spiral arteries that retract down into the stratum basalis.

If no embryo implants into the endometrium, the corpus luteum will degrade and progesterone production will stop, ending the luteal phase of the ovarian cycle. In the uterus, the lack of progesterone, coupled with the impact of prostaglandins, causes the **spiral arteries** of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a consequence of this, the functional layer of the endometrium dies and blood along with endometrial tissue debris white blood cells are sloughed off and shed out via the vaginal canal during **menstruation,** which is also called the **menstrual period** or **menses**.

When an embryo does implant into the functional layer of the endometrium, a hormone called **human chorionic gonadotropin** (**hCG**) begins to be produced in the uterus. This hormone signals the corpus luteum to *continue* secreting progesterone in order to maintain the full state of the endometrium, and thus maintain the pregnancy. This is what prevents the uterine lining from being shed and this is why a woman does not have a period when she becomes pregnant. It is the levels of the hCG that a pregnancy test measures. Once hCG have reached high enough levels in the blood, which is usually 10 to 12 days after conception (after becoming pregnant), it can be detected in the urine with a pregnancy test.

The Uterine (Menstrual) Cycle

The ovarian cycle is determined by the hypothalamic and pituitary gonadotropic hormones, and the uterine cycle is dictated by the ovarian hormones. The **uterine** or **menstrual cycle** also has three phases:

1) Menses

2) Proliferative phase

3) Secretory phase

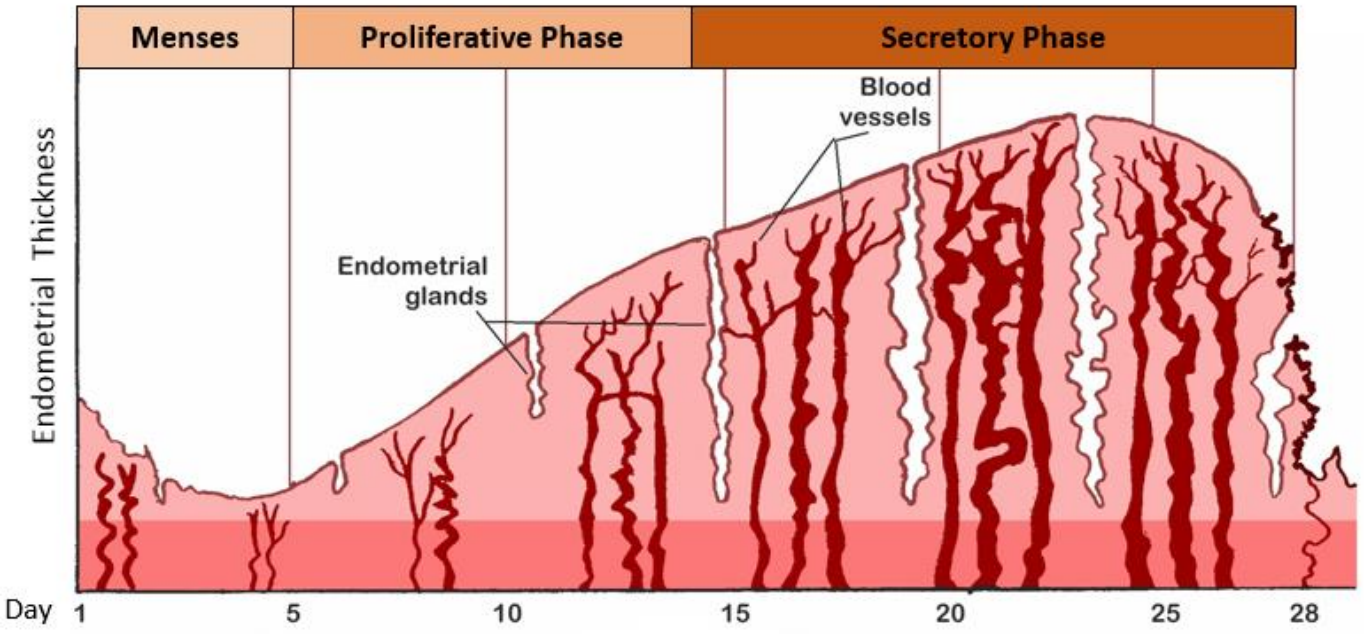


Figure 23.10 Shows the changes in the thickness of the endometrial layer of the uterus throughout the entire uterine cycle. At the end menses the functional layer is at its lowest thickness, having just been lost in menstruation (sloughing off during the menstrual period). This layer continues to build back steadily during the proliferative phase and reaches its maximum thickness right before the end of the secretory phase, where the cycle repeats.

Menses or Menstruation

As discussed earlier, **menses** means 'month' in Greek and it is the monthly shedding of the functional layer of the endometrium, which is also called the **menstrual period**, or **menstruation**. This phases typically goes from day 1 to day 5 of the 28 day cycle (see **Fig. 23.10** above), though it can be as short as 2 days or longer than 7. This time of menses coordinates with the early stages of the follicular phase of the ovarian cycle. The sloughing off of the functional layer occurs particularly significantly when progesterone (plus FSH and LH) hormone levels are low. It is important to note that menstrual flow is not composed of just blood but also contains remnants of the cellular debris from the functional layer of the endometrium. The first menses at the onset of puberty is called **menarche** and can occur before or after the first ovulation.

Proliferative Phase

Once menstrual flow ceases, the re-building of the endometrium commences making it the start of the **proliferative phase** of the uterine cycle. The increasing levels of estrogen from the granulosa and theca cells of the ovarian follicles stimulate the endometrial lining to increase and thicken. Ovulation on day 14 marks the end of the proliferative phase in the uterus (and the end of the follicular phase in the ovary).

Secretory Phase

The last phase on the uterine cycle starts with elevated **progesterone** that is produced by the corpus luteum, as the **secretory phase** centers on preparing the endometrial lining for possible implantation of a fertilized egg cell. The second peak of elevated estrogen levels is what facilitates the contractions of the uterine tube in order to conduct the oocyte to the uterus after ovulation. The corpus luteum within the ovary now pivots its activity into the luteal phase of the ovarian cycle which toward the end of it coincides with the start of the secretory phase of the uterine cycle.

During the secretory phase, the endometrial glands become long and twisted, and the secretion of a fluid rich in **glycogen** starts to occur. The uterine epithelial cells express the enzymes necessary to make and catabolize glycogen (glucose-6-phosphotase) that is necessary to liberate the glucose stored as glycogen. If an **embryo** does implant in the endometrium this nutrient rich fluid is perfect to nourish it. The **spiral arteries** develop in order to provide plenty of blood to the thickened functional layer. The estrogen levels during this phase also tend to lower the acidity of the vagina, making it more hospitable to sperm.

If no pregnancy occurs after about 10 to 12 days from the start of this phase, no signal will be sent for the corpus luteum to continue on, and thus it will degrade into the **corpus albicans**. The estrogen and progesterone levels fall (see **Fig. 23.5**) and the endometrium will not get any thinker but will start to thin. This is combined with **prostaglandins** being secreted which causes constriction of the spiral arteries, reducing oxygen supply which causes the endometrial tissue in the functional layer to die, signaling the onset of menses, which will be the first day of the next cycle.

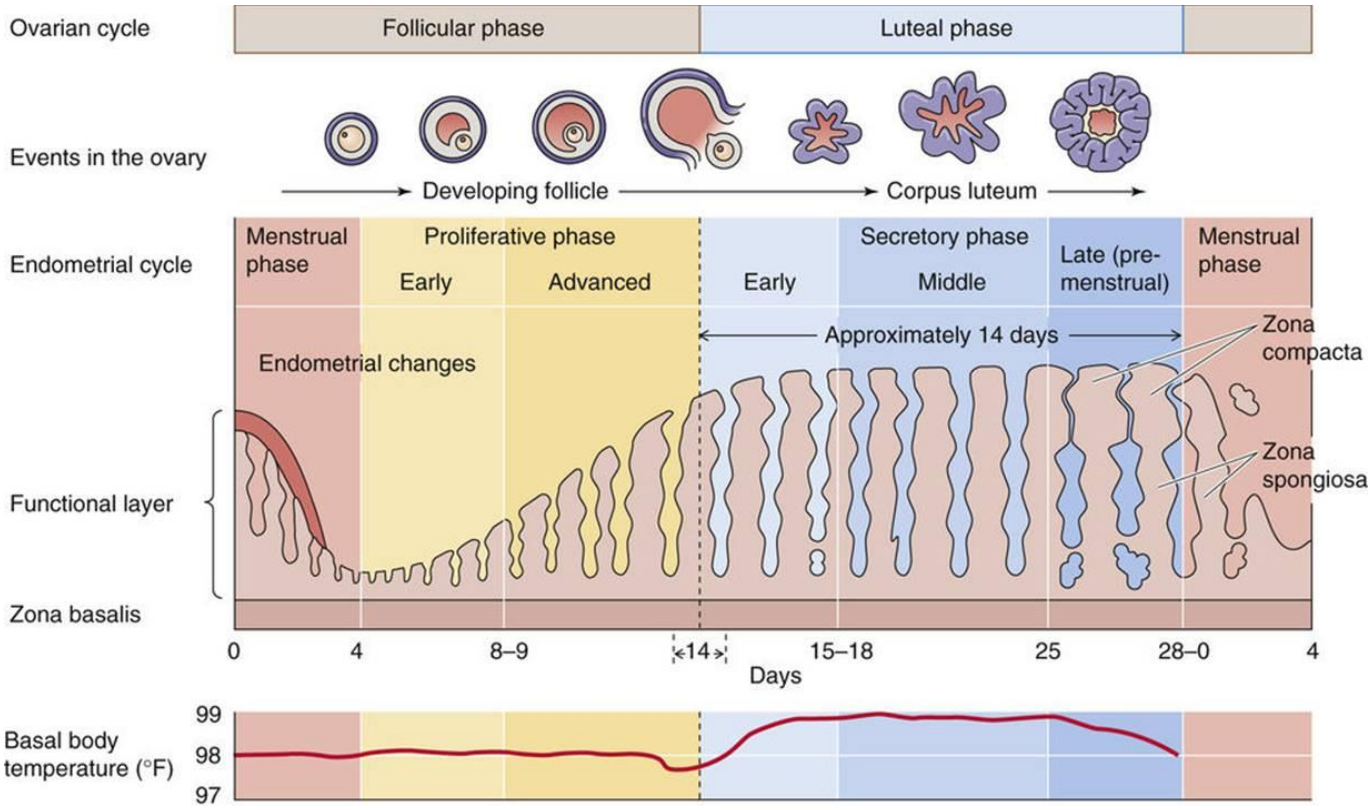


Figure 23.11 This images show the phases of the ovarian cycle (top panel), illustrating the developmental stages of the ovarian follicle, and the remnant of the follicle after ovulation, the corpus luteum. It also displays the specific stages of the endometrial or uterine cycle (middle panel), highlighting the physical changes in the inner lining of the uterus. Lastly, it shows the changes in body temperature of the female (lower panel) that occur immediately prior to ovulation, which is a small transient dip, followed by small (about 1° F) but lengthy elevation in body temperature until the start of the menstrual cycle.

Other Hormones in the Reproductive Cycle

Inhibin Hormones

The protein hormone **inhibin** is produced in the ovaries and the testes. There are actually two types of inhibin, **inhibin A** and **inhibin B**. They are secreted by **Sertoli cells** in the testis of men, and **granulosa cells**

in the ovaries of women. As the name implies, it **inhibits** the synthesis and secretion of follicle-stimulating hormone (**FSH**) and reduces the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Inhibin A is secreted mostly by the corpus luteum and **inhibits the secretion of FSH** secretion during the luteal to follicular phase. Inhibin B controls FSH secretion via a negative feedback mechanism associated with maturation of follicles in the ovaries.

Both inhibin A and B have several functions in the male and female body, with levels in women being linked to the menstrual cycle and playing a role in fetal development. As seen in the graph in **Fig. 23.12** below, in the female ovarian cycle inhibin A is low in the early **follicular phase** and rises at **ovulation** to maximum levels in the mid-luteal phase. And in almost an exact contrast, inhibin B levels increase early in the **follicular phase** to reach a peak with the onset of the mid-follicular phase decline in FSH levels. As with other endocrine hormones, the levels of these hormones can be influenced by other hormones. Fertility testing can include an assessment of levels of Inhibin (A and B) along with other hormones in the body to learn more about the reasons for infertility.

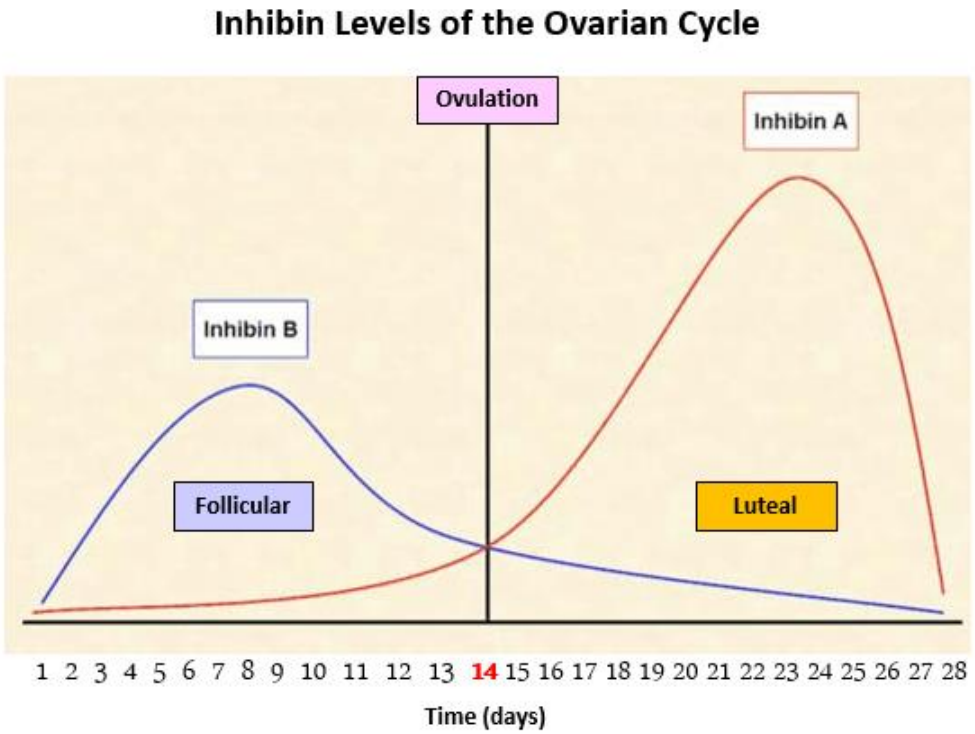


Figure 23.12 The levels of both inhibin A and inhibin B are shown during the ovarian cycle. In viewing the cycle in two parts, before and after ovulation, it is seen that inhibin A is very low for most of follicular phase, but after ovulation, it begins to rise steeply and peaks in the mid-luteal phase (which is toward the end of the entire cycle). In contrast, inhibin B levels are high early in the follicular phase reaching its peak at essentially mid-follicular phase, it then declines and remains low throughout the luteal phase.

Activin Hormone

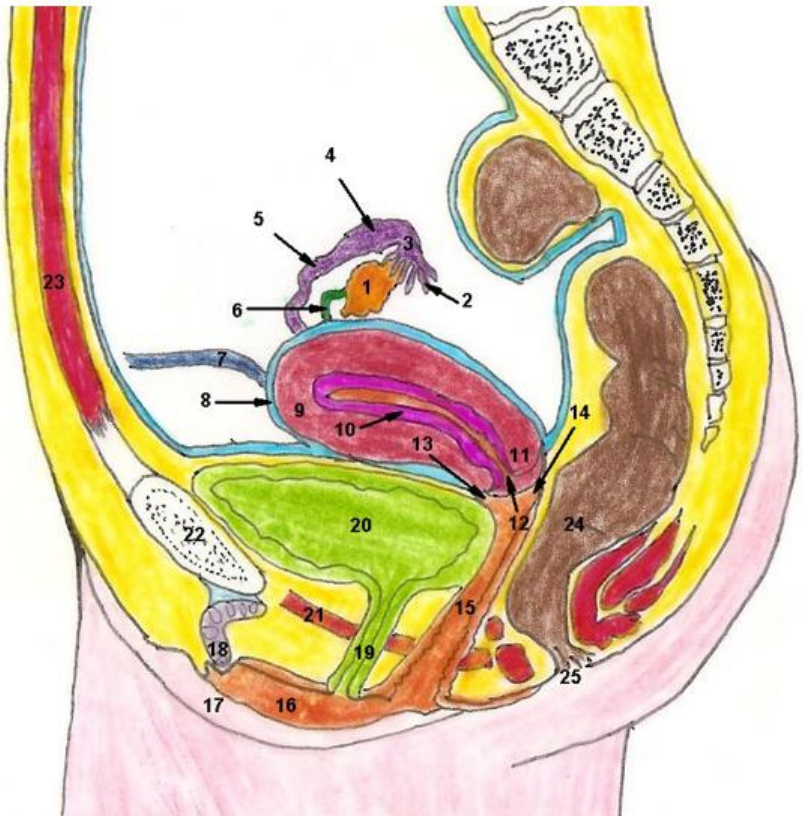
Another hormone, **activin**, has an action opposite to that of inhibin. This means that activin directly **stimulates FSH** synthesis and release from the anterior pituitary gland. The levels of inhibin and activin can fluctuate in both men and women in response to a number of cues, which can include changes in hormone levels that are triggered by natural biological processes, environmental pressures, and other factors. Activin is produced in the gonads, pituitary gland, placenta, and other organs.

In the ovarian follicle, activin **increases follicle stimulating hormone** (FSH) binding, and FSH-induced **aromatization**, this is an enzymatic process that promotes the conversion of an **androgen** into **estrogen**. It also participates in androgen synthesis enhancing **luteinizing hormone** (LH) action in the ovary and testis. In the male, activin enhances spermatogenesis.

External Female Genitals

The external female reproductive structures are referred to collectively as the **vulva**. The **mons pubis** is a pad of fat that is located at the anterior over the pubic bone. After puberty, it becomes covered in pubic hair. The **labia majora** (labia = "lips"; majora = "larger") are folds of hair-covered skin that begin just posterior to the mons pubis. The thinner and more pigmented **labia minora** (labia = "lips"; minora = "smaller") extend medially to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.

The superior anterior portions of the labia minora come together to encircle the **clitoris** (or glans clitoris), an organ that originates from the same tissue as the glans penis and has an abundance of nerves that make it important in sexual sensation and orgasm. The **hymen** is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of "virginity"; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra from the bladder and the anus. It is flanked by outlets to the **Bartholin's glands** (or greater vestibular glands).



The Female Reproductive Structures

1. Ovary
2. Fimbriae
3. Uterine (Fallopian) tube
4. Infundibulum
5. Ampulla
6. Ovarian ligament
7. Round ligament
8. Perimetrium layer (serous membrane)
9. Myometrium layer (of Fundus)
10. Endometrium layer
11. Cervix
12. External os (opening) of cervix
13. Anterior fornix
14. Posterior fornix
15. Vagina
16. Labia majora
17. Labia minora
18. Clitoris
19. Urethral orifice
20. Bladder
21. Urogenital diaphragm
22. Pubic symphysis
23. Rectus abdominis
24. Rectum
25. Anus

Figure 23.13 This is a mid-sagittal section of the female reproductive system. The structure key to the right starts at the ovary and follows the journey of the oocyte to the uterus and through the vagina. Also included are structures that provide a good frame of reference for the arrangements of internal structures.

The Secondary Characteristics of the Female Reproductive System

The Vagina

The **vaginal canal** or **vagina** is a muscular canal that invaginates from the external usually about 3 to 6 inches (6.5 to 15 cm) in length, see the mid-sagittal diagram in **Fig. 23.13** above. This passageway serves as the entrance to the female reproductive tract. It also serves as the exit from the uterus of blood and cellular debris during menses, and as the exit for the baby during childbirth. The vaginal canal leads directly into the most inferior portion of the uterus, the **cervix**.

The outer walls of the anterior and posterior vagina are formed into longitudinal columns or ridges, and the superior portion of the vagina creates a series of arches called the vaginal fornices (plural of fornix) where the canal meets the protruding uterine cervix. The tissue of the walls of the vagina are lined with an outer fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae**. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated **hymen** can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile-vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The Normal Flora and Conditions of the Vaginal Canal

The vagina is home to a normal population of microorganisms that help to protect this region against imbalances that cause infection and abnormal bacterial or yeast growth, as other organisms can enter the opening of vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus ***Lactobacillus***. This family is a highly beneficial bacterial flora which secretes lactic acid, and thus protects the vagina by maintaining an **acidic pH** (below **4.5**). Potential pathogens are less likely to survive in these acidic conditions.

Lactic acid, in combination with other **vaginal secretions**, makes the vagina a self-cleansing organ. In this way, the practice of douching or washing out the vagina with fluids and harsh synthetic chemicals can actually significantly disrupt the normal balance of healthy microorganisms within this region and tend to increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora as it normally does.

The Breasts and Mammary Glands

The breasts and mammary glands are considered accessory organs of the female reproductive system. The fully developed mammary glands have a distinct role in nourishment and bonding between the mother and the baby. They are located on the chest in very close proximity to the beating heart and also close to the mother's face. The function of the breasts is to supply nutrient rich milk to an infant in a process called **lactation**. The external features of the breast include a nipple surrounded by a pigmented **areola**, whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing and becoming sore. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast and Mammary Glands

1. Adipose tissue
2. Mammary lobes
3. Mammary lobules
4. Lactiferous duct
5. Lactiferous sinus
6. Nipple
7. Areola
8. Areolar glands
9. Suspensory ligaments of breast
10. Pectoralis major muscle
11. Pectoralis minor muscle
12. Intercostal muscle
13. Rib

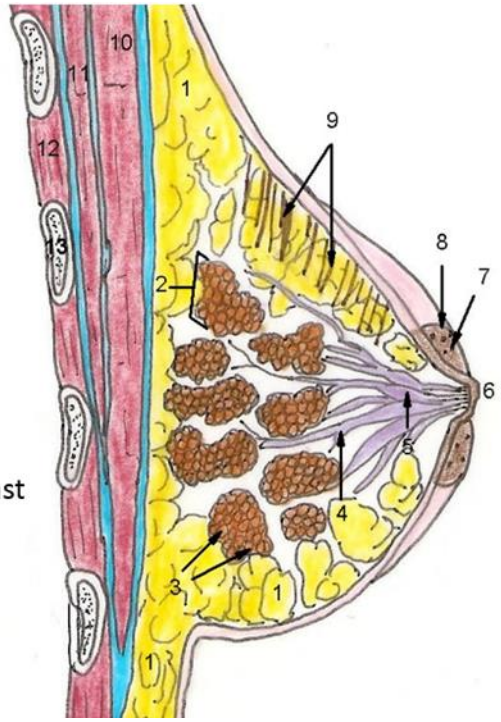


Figure 23.14 This is a mid-sagittal section of the female reproductive system. The structure key to the right starts at the ovary and follows the journey of the oocyte to the uterus and through the vagina. Also included are structures that provide a good frame of reference for the arrangements of internal structures.

In terms of navigating through the breast, the milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple, see **Fig. 23.14** above. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli**. The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called **suspensory ligaments** that connect the breast tissue to the dermis of the overlying skin.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

Breast Feeding and Breastmilk

During breastfeeding, the **letdown reflex** is a trigger that causes the release of breastmilk and allows it to flow. This reflex occurs when tactile stimulation of the nipple-areolar complex occurs when a baby begins to suckle. Nerves send afferent signals to the hypothalamus, triggering the release of **oxytocin**, which stimulates milk ejection or letdown reflex.

Breastmilk is produced by the **mammary glands**, which are modified sweat glands. This milk from a healthy mother is the best possible source of nutrients for a developing baby. Though there are numerous

scientific experiments that prove breast milk is far superior for babies than any formula, should we really need this 'proof'? Hopefully, as we understand more about the human body, issues like knowing breast milk is better for babies will become obvious and self-evident.

As the breast starts to empty, the fat globules begin to dislodge and move down the ducts (let-down facilitates this process). So the further into the feed, the higher the fat content of the milk, as more and more fat globules are forced out. The end result is that the milk gradually increases in fat as the feeding progresses, as described below in the difference between foremilk and hindmilk.

Breast milk is complex containing many subtle elements such as hormones and the perfect ratio of proteins, sugars (mostly from lactose), lipids (fats) and the vitamins and mineral needed to help your baby grow and develop. Breast also contains many other substances that protect your baby from many illnesses.

Figure 23.15 Shows the three types of breastmilk produced by mothers. Colostrum is extremely nutrient-rich and high in fats with production starting during pregnancy wherein it is the first breastmilk for the newborn baby up to 3 or 4 days after birth. After the colostrum is finished, foremilk is what the baby drinks at the beginning of a feeding and is mostly water with other nutrients. This is followed by hindmilk which is highly fatty and provides an abundance of nutrients for the baby.

Colostrum is a type of breastmilk that the breast begins to produce during pregnancy, and is the first breastmilk released by the mammary glands after birth. Its composition is very think and nutrient-rich to ensure the newborn baby has everything it needs, see **Fig 23.15** above for a compassion of the different stages of breastmilk. The colostrum changes to breastmilk within about two to four days after birth. There are then sort of two types of breastmilk, foremilk and hindmilk, but more accurately these terms describe the variations in the milk at the beginning and end of a breastfeeding session. **Foremilk** is what the baby drinks at the beginning of a feeding and is usually more watery, though it still contains many fatty nutrients and slightly higher in lactose (milk sugar) levels. This is followed by a gradual transition to **hindmilk**, which also has lactose but is much higher in fats and other growth promoting nutrients, including vitamins A and E. It is the hindmilk that satiates the baby's hunger.

Here are the main benefits of breastfeeding for both baby and mother:

- Breastmilk is the perfect nutrition for a baby.
- Creates the best digestion for baby
- Provides immense health protection for both baby and mother.
- Stimulates brain and nervous systems development.
- This food sources is almost always ready and portable.
- Numerous health and wellness benefits for mothers.
- This practice builds a special bond between mother and child.
- The advantages continue as the baby grows.

Succinctly, breastmilk is the best milk. The nutrients in breastmilk are unmatched by any other first food your baby can receive and the practice yields enormous benefits.

Further Sexual Development Occurs at Puberty

Ahhh puberty. Puberty is the stage of development at which individuals become **sexually mature**, ultimately what this means is that they are now able to reproduce. Regardless of the sex, either male or female, the general outcomes of puberty are similar in terms of the hormonal control of the process, in that the central issue is preparing the sex cells or gametes, the oocyte and the sperm. The onset of puberty may vary in terms of age, however the sequence of events and the changes that occur are very predictable for male and female adolescents.

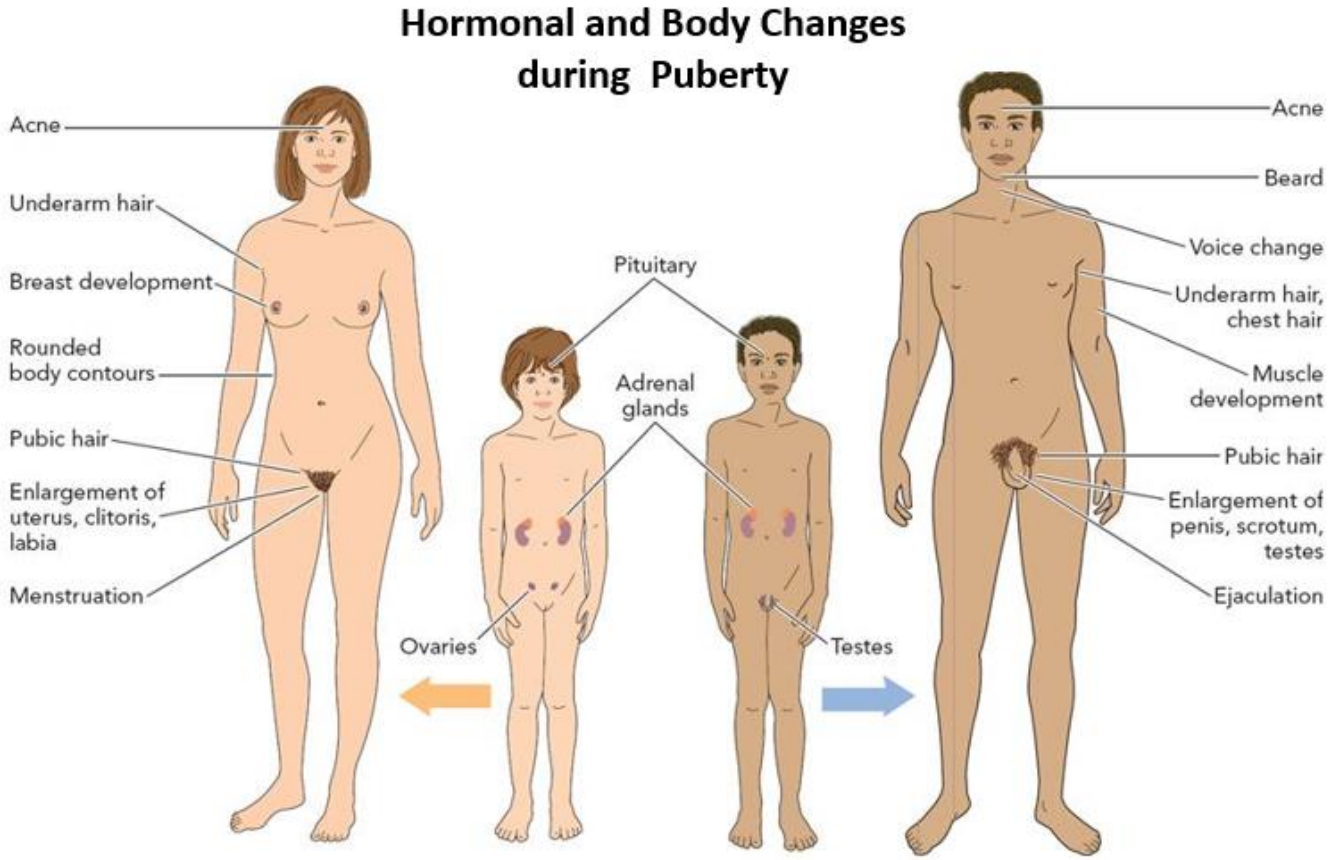


Figure 23.16 During puberty many bodily changes begin to occur. Female genitals and uterus enlarge, breasts develop and enlarge with characteristic fat deposits for women on hips and thighs and menstruation (periods) begins. In males, the penis, testes and scrotum get larger. Males also experience enlarged larynx (Adam's apple) producing voice changes (deeper), broad shoulder 'triangle' body shape, body hair distribution, and facial hair.

It is quite a symphony of hormones that facilitates this stage of development. The concerted release of hormones from the hypothalamus **gonadotropic releasing hormone** (**GnRH**), the anterior pituitary **luteinizing hormone** (**LH**) and **follicular stimulating hormone** (**FSH**), and the gonads (either testosterone or estrogen) are responsible for the maturation of the reproductive systems and the development of **secondary sexual characteristics**, which are the often visible physical changes that occur which serve auxiliary roles in reproduction.

The first changes begin sooner than some may realize. At around the age of eight or nine the production of LH becomes detectable (see **Fig. 23.16**). The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low

concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

Two important changes in sensitivity occur as an individual approaches puberty. First, there is a decrease of sensitivity in the hypothalamus and the anterior pituitary to the usual negative feedback mechanism, such that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change is an increased sensitivity of the gonads to the FSH and LH signals, meaning the **gonads of adults are more responsive to gonadotropins than are the gonads of children**. Due to these two changes, the levels of **LH** and **FSH** steadily, slowly increase and lead to the **enlargement and maturation of the gonads**, which in turn leads to secretion of higher levels of **sex hormones** and the initiation of **spermatogenesis** (development of sperm) and **folliculogenesis** (development of eggs).

Males

The physical changes of puberty for a boy usually start with enlargement of the testicles and sprouting of pubic hair, followed by a growth spurt between ages 10 and 16, this is typically 1 to 2 years later than when girls start puberty. A male's arms, legs, hands, and feet also grow faster than the rest of his body (see **Fig. 23.16** above as a reference). The first real physical sign of the beginning of puberty for boys is the growth of the testes, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the **larynx** (Adam's apple) and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the **end** of puberty, at approximately age 11 to 13, and a boy's height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

Females

Girls usually begin puberty between the ages of 8 and 13 years old. Typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can increase 3 inches a year. The next step in puberty is menarche, the start of menstruation. There are continued changes including vaginal discharge and expansion and further development of the pelvis, creating wider hips for child bearing, and also the female fat distribution patterns, especially on the hips, thighs (see **Fig. 23.16** above as a reference).

Factors Effecting the Onset of Puberty

Multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche (the first period for girls). This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

Secondary Sexual Characteristics

Men and women are physically different and that is a great thing because it is accurate and can be seen, and one of the most obvious systems that exemplify how very different men and women are is the reproductive system. The key to the physical differences that exist and can be defined and measured between men and women are the **sex hormone concentrations differences** between the sexes. An important aspect of these hormone differences is that they contribute to the development and function of **secondary sexual characteristics**. This can be seen in **Figure 23.16** above and in **Table 23.1** below.

Table 23.1 Comparison of Male and Female Secondary Sexual Characteristics.

Development of the Secondary Sexual Characteristics	
Male	**Female**
Increased larynx size (Adam's apple) and deepening of the voice.	Deposition of fat, predominantly in breasts, hips and thighs.
Broader Shoulder to Hip ratio (Triangle)	Broader Hip to Shoulder to ratio (Pare)
Increased muscular development.	Breast development.
Growth of facial, axillary, and pubic hair, and increased growth of body hair.	Broadening of the pelvis and growth of axillary and pubic hair.

The Q angle, also known as quadriceps angle, is defined as **the angle formed between the quadriceps muscles and the patella tendon**. The Q angle has become accepted as an important factor in assessing knee joint function and determining knee health in individuals suffering from an anterior knee pain

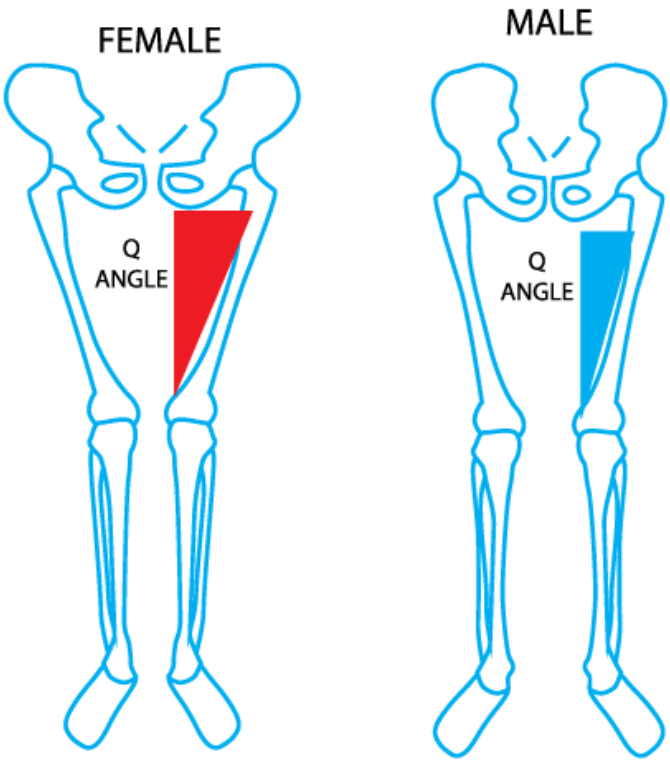


Figure 23.17 Shows the differences in female and male quadriceps or Q angle, which is formed between the quadriceps muscles and the patella tendon. The female Q angle is much larger than in males.

Refer to the **Figure 23.17** to the left:

* The female pelvis is larger and broader than the male pelvis, which is taller (owing to a higher iliac crest), narrower, and more compact.
* The distance between the ischium bones is small in males. This causes the sides of the male pelvis to converge from the inlet to the outlet, whereas the sides of the female pelvis are wider apart.
* This results in the female inlet being large and oval in shape, while the male inlet is more heart shaped.
* The angle between the inferior pubic rami is acute (70 degrees) in men, but obtuse (90–100 degrees) in women. Accordingly, the angle is called the subpubic angle in men and pubic arch in women.
* The greater sciatic notch is wider in females.
* The ischial spines and tuberosities are heavier and project farther into the pelvic cavity in males.
* The male sacrum is long, narrow, straighter, and has a pronounced sacral promontory.
* The female sacrum is shorter, wider, more curved posteriorly, and has a less pronounced promontory.
* The acetabula are wider apart and face more medially in females than in males. This change in the angle of the femoral head gives the female gait its characteristic swinging of hips.

Birth Control

Birth control is how to prevent pregnancy before it begins. There are several different methods and it is extremely important for anyone considering these to know all of the consequences involved, as many options can irreparably harm the health of the person using it.

The most obvious and fail-proof method of birth control is abstinence from sexual intercourse. In terms of birth control methods that involve sexual intercourse, these can be broadly classified into three different methods. Firstly is the **barrier methods**, this prevents the sperm cells from reaching the egg. Condoms and diaphragms are examples of barrier birth control methods. Secondly are methods that **prevent ovulation** such as the birth control pill, because it prevents ovulation from occurring. Thirdly are methods that allow fertilization of the egg but **prevent implantation of zygote** (the fertilized egg) inside the uterus (womb). An example of this is the intrauterine device (IUD). No method of birth control is 100% effective in preventing pregnancy, nor do they have any real impact on sexually transmitted diseases (STDs). A woman should carefully weigh the short and long term risks and side effects with the benefits.

How Birth Control Pills Work

Birth control pills prevent pregnancy through several mechanisms, primarily by **stopping ovulation**. If no egg is released, there is nothing to be fertilized by the sperm and the woman cannot get pregnant. Most birth control pills contain **synthetic forms of estrogen and progestin**. These synthetic hormones are more potent and harsh, thus not really like the natural female hormones, and they alter a woman's normal hormone levels and prevent estrogen from peaking mid-cycle. Without the estrogen bump, the pituitary gland does not release the other hormones that normally cause the ovaries to release mature eggs.

Synthetic estrogen in the pill works to:

- Stop the pituitary gland from producing follicle stimulating hormone (FSH) and luteinizing hormone (LH) in order to prevent ovulation
- Support the uterine lining (endometrium) to prevent breakthrough bleeding mid-cycle

Synthetic progestin works to:

- Stop the pituitary gland from producing LH in order to prevent egg release
- Make the uterine lining inhospitable to a fertilized egg
- Partially limit the sperm's ability to fertilize the egg
- Thicken the cervical mucus to hinder sperm movement

Menopause

As women approach their mid-40s to mid-50s, the ovaries begin to lose their sensitivity to follicle stimulating hormone (**FSH)** and luteinizing hormone (**LH)** to an extent that the menstrual periods become less frequent and ultimately finally cease. This process is known as menopause. Interestingly, there are still eggs and potential follicles within the ovaries, however, without the stimulation of FSH and LH, they will not be able to produce a viable egg to be released. The signals the end of the potential for child bearing.

There are various symptoms associated with menopause, including hot flashes, heavy sweating, headaches, muscle pain, vaginal dryness, insomnia, depression, changes in weight (usually gain), and initial mood swings. Estrogen is involved in calcium metabolism and, without it, blood levels of calcium decrease. To replenish the blood, calcium is lost from bone, which may decrease the bone density and lead to osteoporosis.

Natural Sources of Estrogen for Menopause

During menopause women's estrogen levels decline, which can lead to the symptoms described. The most widely cited natural remedy is **soy** because it is very high in **phytoestrogens**, however there are many significant drawbacks from eating unfermented soy. Unfermented soy in and of itself, organically grown or not, contains a number of problematic components that can wreak havoc with your health, including:

Too much **phytoestrogen**, can disturb endocrine function. Thyroid **goitrogens** are in all unfermented soy and interfere with thyroid function. **Phytates** in soy bind to metal ions, preventing the absorption of minerals, including: calcium, magnesium, iron, and zinc - all of which are co-factors for optimal biochemistry in your body. **Hemagglutinin**, this is a clot-promoting substance causing clumping of red blood cell. This can disrupt blood flow and can prevent the distribution of oxygen to your tissues. **Trypsin Inhibitors** in soy such as saponins, soyatoxin, ***protease inhibitors***, and oxalates will interfere with enzymes needed to digest protein. While small occasional amounts are not likely cause problems, daily supplements may not be advisable for all.

Great sources of **estrogen** building foods are: Unfermented soy products like miso, tempeh and natto beans, flax seeds, sesame seeds, red clover, hummus, garlic and dried fruit.

Fertilization, Pregnancy and Parturition (Birth)

The female carries the developing embryo and fetus in the womb (uterus) for approximately 40 weeks after the zygote (fertilized egg cell) is created. Many have the impression that the duration of a pregnancy is 9 months, but it's actually about 10 months (40 weeks). As seen in **Fig. 23.18** below, there are three stages of prenatal development, they are: **1)** Germinal (red dashed line); **2)** Embryonic (green dashed line); and **3)** Fetal (solid red line). Prenatal development is also organized into three equal trimesters, which do not correspond with the three stages.

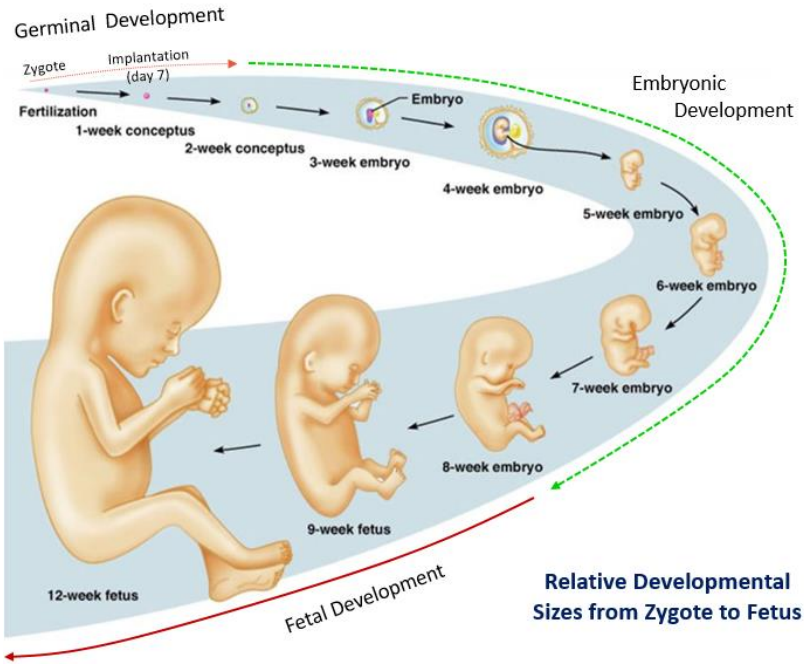


Figure 23.18 Shows the zygote which became fertilized in the uterine tube. As it continues to travels toward the uterus, the process of cell multiplication starts and continues, forming the blastula of dividing cells, then the embryo, which implants in the endometrial layer of the wall of the uterus for embryonic development from week 2 until week 8. At the ninth week post-conception, fetal development period begins, with continued rapid growth and development, culminating with partition (giving birth) after about week 40.

From the earlier details in this chapter regarding the female ovarian and uterine cycles, we know that if fertilization does occur soon after ovulation (release of that oocyte), this will trigger the release of **human chorionic gonadotropin** (hCG) from the developing embryo, and the corpus luteum in the ovary will be maintained in order to oversee the pregnancy proceedings, allowing the corpus luteum to produce the levels of **progesterone** required to sustain the pregnancy.

Also as previously briefly mentioned, most over the counter pregnancy tests are detecting **hCG** as an indicator of implantation of a zygote. The levels of hCH are very low initially and may take a few weeks to be high enough for detection by the test of hCH in the blood. The subsequent speedy rise in hCG levels in the urine can then be tested, even prior to the missed period, which of course is a big indicator of pregnancy, but is not fool proof.

Fertilization and Pregnancy

The secondary oocyte is directed into the lumen of the uterine tube by the fringe-like fimbriae of the fallopian tube. Fertilization normally occurs in the **ampulla** of the uterine tube. Capacitated sperm contact the surrounding corona radiata cells of the oocyte. The acrosome reaction then occurs, causing proteolytic enzymes to be released from the head of the sperm. This allows the sperm to penetrate the oocyte (corona radiata and zona pellucida).

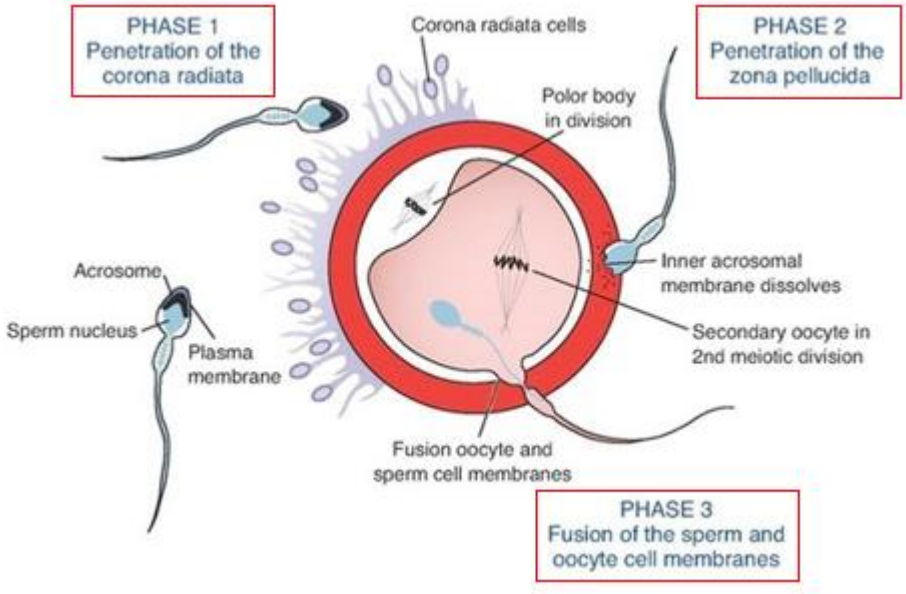


Figure 23.19 There are three phases for the sperm cell during fertilization. Phase 1 is when a sperm penetrates the corona radiate cells on the outermost layer of the egg cell. Phase 2 is when a sperm comes in contact with the zona pellucida layer of the ovum and induces changes in the membrane that block the entry of additional sperms. Thus, it ensures that only one sperm can fertilize an ovum. Phase 3 is the fusion of that sperm cell and egg cell membrane.

As seen in **Fig 23.19** above, there are three phases of activity for the sperm cell during fertilization. This can be further detailed by six stages. They are: **1)** The acrosome reaction occurs as the sperm approaches the oocyte. **2)** The corona radiata of the oocyte plays a role in chemotaxis of sperm and induction of the acrosome reaction. The sperm penetrates the epithelium of the corona radiata within a few seconds with powerful tail movements, then adheres to the zona pellucida for several minutes. **3)** The zona pellucida is penetrated after a few minutes. Sperm pass through this layer at an angle and meet the cell membrane of the oocyte tangentially. **4)** Contact of the sperm with the oocyte cell membrane releases cortical

granules that induce an excitatory potential that is responsible for initiating the zona pellucida reaction (blocking polyspermy), removing the block on metaphase II, and activating oocyte metabolism. Embryonic development is almost ready to begin. This proceeds in three steps: **a)** The sperm head dips into the microvilli on the surface of the oocyte membrane; **b)** Incorporation of sperm into the membrane; **c)** Sperm head, neck, and tail sink into the yolk sac. **5)** Fertilization causes completion of the second meiotic division, and the second polar body is expelled. **6)** The chromosomes of the sperm and oocyte (haploid sets) decondense and form the female and male pronuclei. The flagellum disintegrates in the oocyte.

Stages of Fertilization and Implantation

The first stage is when fertilization activates the oocyte, wherein the haploid egg nucleus and the haploid sperm nucleus are transformed into female and male pro-nuclei. Both pronuclei go through a phase of DNA synthesis, and their replicated chromosomes are arranged on a common spindle. The second stage is when the oocyte travels along the uterine tube toward the uterus as its cells divide within the zona pellucida. The third stage is when the **blastocyst** forms consisting of an inner cell mass (embryoblast) and an outer cell mass (trophoblast). The blastocyst hatches out of the zona pellucida, allowing it to attach to the uterine endothelium which is implantation in the uterine wall.

Fusion of Parental DNA

The very first sperm cell that comes in contact with the oocyte's plasma membrane will activate the oocyte to respond. The activation causes chemical and physiological changes in the oocyte which prevents the egg cell from being fertilized by more than one sperm cell. The cell membranes of the oocyte and sperm fuse, with the much smaller sperm cell being engulfed into the significantly larger oocyte. It is at this point when the male and female DNA of the parents fuse within the oocyte to complete the fertilization process.

Mitosis of the one cell zygote into a morula preembryo (16 cells) occurs within the oviduct. At the late morula stage (32 cells), the preembryo reaches the uterine lumen, where blastocyst development occurs. A blastocyst consists of an outer layer of trophoectoderm (trophoblast), which will become the fetal placenta, an inner cell mass (embryoblast), which will become the fetus, and a blastocele (fluid-filled cavity).

Implantation

The **blastocyst** must hatch out of the **zona pellucida** before implantation into the endometrium can occur. Trophoblast cells in the attachment zone differentiate into cytotrophoblast cells. These cells fuse together to form the syncytiotrophoblast, which is able to penetrate into the endometrium. Implantation is complete by the second week of pregnancy, marking the end of the preembryonic stage.

Stromal cells in the endometrium surround the endometrial spiral arteries and cuff them to stop the flow. This protects maternal tissues from the invading trophoblast and helps protect the fetoplacental unit from rejection by the maternal immune system.

Ectopic Pregnancy – Wrong Implantation Location

An ectopic pregnancy is when the fertilized egg cell implants in the wrong place, and that is anyplace outside the uterine cavity, usually in the fallopian tubes. If implantation occurs in the uterine tubes, it is called a '**tubal pregnancy**', and they are not viable. This is a rare condition, but it is more likely to occur in **salpingitis**, which is an inflammation of the uterine tubes. It may also occur after a tubal infection, from tubal damage due to previous ectopic pregnancies or endometriosis, or from taking what can be toxic fertility drugs in an attempt to stimulate ovulation. Other signs of ectopic pregnancy are abdominal pain,

vaginal bleeding, cramping, and faintness. There may also be an odd and seemingly disconnected pain in the tip of the shoulder. This can occur because the presence of blood in peritoneum (which is abnormal) irritates the phrenic nerve of the diaphragm passing near the shoulder area.

Treatment of ectopic pregnancy depends on what stage the ectopic pregnancy is detected. If detected early, methotrexate may be given to arrest the development of the fertilized ovum, which is then resorbed by the body. Laparoscopy may be needed to stop any bleeding into the peritoneum.

Stages of Pregnancy: The 3 Trimesters
A pregnancy is divided into trimesters:

1. The first trimester is from week 1 to the end of week 12.
2. The second trimester is from week 13 to the end of week 26.
3. The third trimester is from week 27 to the end of the pregnancy.

Figure 23.20 shows the three phases of pregnancy which are the first, second and third trimesters.

In the first trimester, the baby will grow from a fertilized egg into a moving fetus with eyes, ears, and working organs. In the second trimester, the baby's features develop and you may be able to feel your baby move. In the third trimester, the baby will grow rapidly to get ready for birth. Easy as that!

First Trimester
With the formation of the primary germ layers (ectoderm, mesoderm, and endoderm) and extraembryonic membranes (amnion, yolk sac, allantois, and chorion), the **embryonic stage** begins, which is represented as occurring from **week 3 to week 8** of development.

During the first trimester, the placenta becomes firmly established, and embryonic/fetal organ development occurs. For this and other reasons it is often considered that the first trimester is the typically the most critical with regard to the baby's development. At the early stage the mother may not be showing much outwardly, but internally the baby's major body organs and systems are commencing their genius formation. At all stages of pregnancy, and this stage especially, it is crucial to eat very good highly nutritious food with as few toxins as possible. Also equally important is to avoid unnecessary stress!

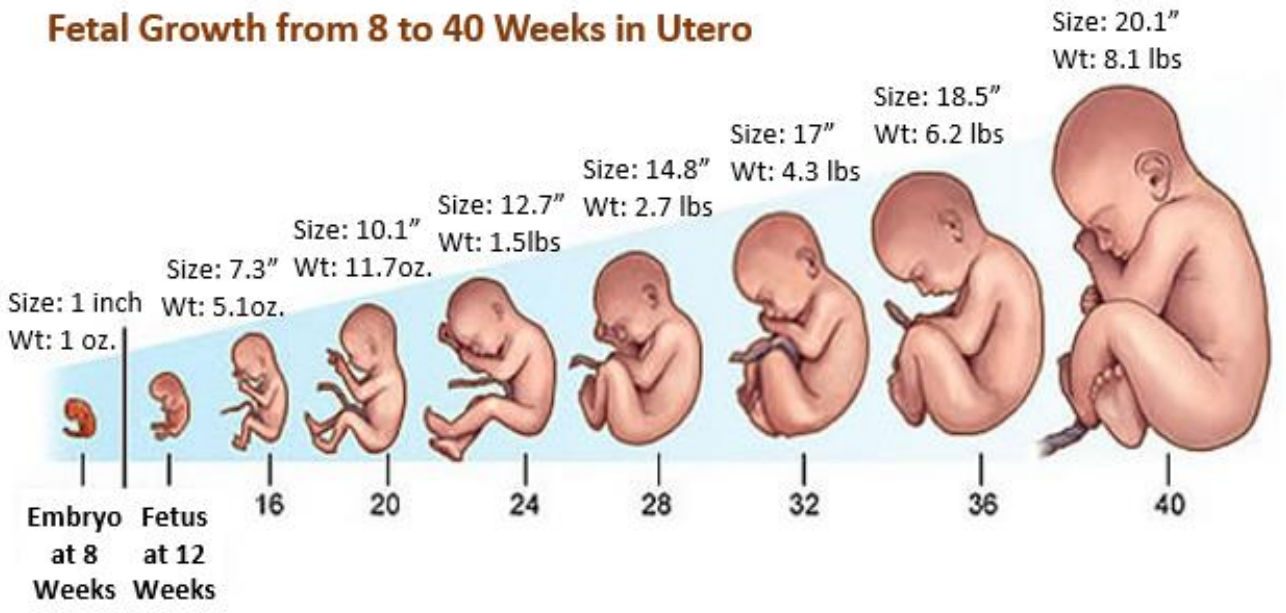


Figure 23.21 Shown here are the estimated head-to-bottom height measurements in inches (") up to 13 weeks, then head-to-toe height in inches measured at week 14 and beyond. The weight (Wt) measurements are in ounces (oz.) and pounds (lbs.) as development continues. The size and weight of a boy fetus is statistically larger than for a girl fetus, as such the values displayed are taken from an average of boy and girl measurements. It is totally normal for values of a fetus to be lower and higher than the numbers reported here.

The **corpus luteum** is the major source of progesterone (and estrogen) during the first 6 to 8 weeks of gestation. The function of the corpus luteum is stimulated by the release **human chorionic gonadotropin** hCG (from the syncytiotrophoblast). Human chorionic gonadotropin (hCG), secreted by the placenta during pregnancy, is the predominant hormone during the first trimester. It stimulates the synthesis of dehydroepiandrosterone sulfate (DHEA-S) from the fetal adrenal cortex, suppresses follicle maturation in the maternal ovaries, and maintains the production of estrogen and progesterone in the corpus luteum.

Maternal concentrations of **human placental lactogen** (hPL), **corticotropin-releasing hormone** (CRH), and **estrogen** rise sharply during the third trimester. The hPL stimulates **lactogenesis**, the production of milk by the mammary glands, after parturition. CRH concentration plays a role in the timing of parturition by increasing adrenocorticotropic hormone (ACTH) production by the fetal pituitary, which increases cortisol. It also stimulates fetal lung development.

In addition, estrogen plays a critical role in parturition by mitigating the pregnancy-sustaining effects of progesterone, and it also helps propagate uterine contractions. At about the eighth week of gestation, the trophoblast takes over the secretion of the hormones progesterone and estrogen, making the **placenta** the main source of progesterone during the remainder of the pregnancy.

Placental Abruption

Placental abruption is the separation of the placenta from the uterus. The consequences of this depend on the extent of the placental separation and the amount of blood loss. In severe abruptions, the fetus may not receive an adequate supply of oxygen, causing neurologic defects or death. The mother's life may also be at risk from shock or disseminated intravascular coagulation (DIC). DIC is a pathological activation of clotting that ultimately consumes the body's supply of clotting factors and platelets, causing bleeding from the skin, mucous membranes, and viscera. Signs of placental abruption include shock that is out of

keeping with visible vaginal blood loss, backache (if the abruption is posterior), abdominal pain, uterine tenderness, fetal distress, lack of fetal heartbeat, and DIC. Treatment also depends on the extent of the abruption. If it is a small abruption, then the mother is monitored frequently, but the pregnancy is allowed to progress. If severe, urgent delivery of the baby is necessary.

Placenta Previa

The condition of **placenta previa** when the placenta is situated low in the uterus, partially or completely covering the cervix. As the cervix begins to dilate later in pregnancy, the placenta stretches and tears, leading to painless vaginal blood loss. Shock may occur if the blood loss is severe. In contrast to placental abruption, there are usually no coagulation problems or uterine tenderness. Fetal distress is also less common, as the frank vaginal bleeding alerts the mother and health care providers to the problem before the fetus becomes distressed. Placenta previa is more common in women who have uterine damage, most common from previous cesarean sections, births, or fibroids, or if the placenta is larger than usual, for example with twins. Treatment depends on the severity, in minor cases bed rest for the mother for the remainder of the pregnancy, whereas more severe cases may warrant early delivery of the baby.

Second and Third Trimesters

In **Figure 23.21**, a clear progression of fetal growth during the second and third trimesters can be clearly seen. In the start of the second trimesters, now that the placenta has taken over progesterone synthesis, the **corpus luteum** in the ovary degenerates. Interestingly, the placenta cannot convert progesterone to estrogens because of a deficiency of the enzyme 17α-hydroxylase, therefore it need to rely on the conversion of dehydroepiandrosterone sulfate (**DHEA-S**) from the adrenal glands of both the fetus and the mother to synthesize estriol, estradiol, and estrone.

As already seen, **human placental lactogen** (**hPL**) is produced by the placenta, with its peak blood concentrations occurring in the third trimester. The hPL is very similar in structure and function to growth hormone and prolactin, and its secretion causes an increase in **lipid metabolism**, enhanced carbohydrate stimulated insulin secretion, and **increased insulin resistance** in some maternal tissues. Collectively, these alterations in maternal metabolism enhance maternal free fatty acid utilization while sparing glucose for use by the growing fetus. This is one aspect of the susceptibility of mothers acquiring **gestational diabetes** at this stage, due to the shifting of metabolism in order to ensure that any additional glucose goes to the developing baby. The hPL may also play an important role in mammary gland development.

Hormonal Synthesis in the Placenta, Mother, and Fetus

The **placenta** produces **human chorionic gonadotropin** (**hCG**) hormone, which stimulates the synthesis of steroids such as DHEA and DHEA-S, by the **fetal adrenal cortex**. The hCG also maintains the production of estrogen and progesterone in the corpus luteum until the placenta is able to produce sufficient quantities of these hormones.

In addition, the placenta must receive **cholesterol** or **androgens** from either the maternal or fetal adrenal cortex, respectively, before it can synthesize progesterone and estrogen. Progesterone is then transported to the fetal adrenal cortex, where it is converted to DHEA and DHEA-S. DHEA and DHEA-S pass to the placenta, where they are used for estrogen synthesis. **Progesterone** is converted to **testosterone** in the **testes** of the **male fetus**.

Maternal Changes during Pregnancy

The process of pregnancy is not without radical and dramatic changes in the female, both anatomically and physiologically. In other words it's not all fun, and can be very taxing on the body. Most of the changes are definable and ultimately all normal changes are tolerable.

Some of the more significant changes include **preeclampsia**, this is a type of hypertension, **proteinuria**, an excess protein filtered by the kidneys which leads to protein in the urine, and systemic **edema**, which is tissue swelling form retaining fluid in the body during pregnancy. These more radical changes can usually be seen after 20 weeks gestation. Preeclampsia can cause fetal distress, low birth weight, and pre-term birth due to lack of blood flow to the placenta. It also increases the occurrence of placental abruption.

Parturition (Birth)

During a normal pregnancy, which consists of 270 pre-determined days, the secretion of **progesterone** prevents uterine contractions by elevating the threshold for myometrial contractility. This is referred to as the **progesterone block**.

Just prior to the occurrence of child birth, or parturition, placental estrogen production is increased relative to progesterone, thereby increasing the estrogen-to-progesterone ratio. This removes the progesterone block and allows estrogen to increase the synthesis of receptors for estrogen, prostaglandins, and oxytocin on myometrial cells. This upregulation of receptors is necessary for the **increase in myometrial contractility** at parturition.

Myometrial stretching and pressure exerted on the cervix by the fetus cause a reflexive release of oxytocin from the posterior pituitary. **Oxytocin** binds to **myometrial receptors**, where it stimulates the production of uterine and placental prostaglandins, which, in turn, increase intracellular Ca^{2+} and promote myometrial contractility.

Estrogen also affects the cervix by increasing its responsiveness to **relaxin**, which is secreted by the corpus luteum and the placenta. The prostaglandins are secreted by the uterus and placenta. These hormones cause the cervix to become more vascular and change its structure. This results in **cervical dilation** and **effacement**, which is when the cervix becomes softer and shorter during labor.

The Stages of Child Birth

Stage 1. This is the period from the onset of regular contractions until the cervix is fully dilated. Contractions originate in the fundus and progress toward the cervix, forcing the head of the fetus against the cervix. The cervix starts to dilate from the effects of estrogen and **relaxin** and the mechanical force from fetal pressure. During this time the cervix becomes softer and shorter (effaces). Changes in the cervix result from physical breakdown of connective tissue of the cervix with increased water content, vascularization, and mass. The fetal membranes rupture, so the contents of the amniotic sac are lost. This enhances the effects of contraction for applying fetal pressure on the cervix.

Stage 2. This is the period from full dilation of the cervix until parturition. Uterine muscle contractions are of high frequency and high amplitude. This stage typically lasts < 1 hour but can be longer.

Stage 3. The placenta separates and is delivered. This occurs within about 10 minutes after birth and is associated with weak muscle contractions.

Lactation

During pregnancy, estrogen, growth hormone, human placental lactogen (hPL), and cortisol continue to stimulate the development of the mammary glands, which started at puberty. Progesterone converts duct epithelium to a secretory epithelium. **1)** Relaxation of the cervix: the cervix remains tightly closed during pregnancy but is stimulated to relax around the time of parturition by **relaxin**, secreted by the corpus luteum and placenta. **2)** Onset of labor: locally, prostaglandins cause contractions of the uterine muscles. Systemically, oxytocin, from the posterior pituitary gland, is released in response to cervical irritation caused by pressure from the fetal head. Oxytocin causes further prostaglandin secretion.

During the latter stages of pregnancy, estrogen acts on the anterior pituitary, causing levels of prolactin to rise. This is accompanied by a fall in prolactin-inhibiting hormone (PIH). Prolactin is the hormone after delivery that initiates **lactogenesis**, or **milk production**. Lactation does not occur during pregnancy because placental estrogen and progesterone prevent prolactin from acting on the mammary glands. However, when estrogen and progesterone are withdrawn at birth, lactation is able to occur. Suckling is a mechanical stimulus for the continuation of lactation, as it stimulates increased levels of prolactin (by inhibiting PIH) and oxytocin.

Breast Feeding (Nursing) and Pregnancy

When a mother breastfeed or naturally nurses an infant, this can be effective in preventing another pregnancy because the prolactin inhibits ovarian function in the following ways: **1)** it inhibits the hypothalamic release of gonadotropic releasing hormone (**GnRH)**; **2)** from the decreased GnRH, there is an inhibition in the release FSH and LH from the anterior pituitary; and finally, **3)** the decreased levels of FSH and LH have **inhibitory effects on ovulation**, thus reducing the releasing of viable eggs from the ovaries.

The Letdown Reflex for Breastfeeding

As discussed earlier in the chapter in the section regarding breastmilk, the letdown reflex starts the breastfeeding process. The mechanical sensory input to the spinal cord from the stimulation of the breast nipple when the baby begins to suckle ascends to the hypothalamus and posterior pituitary, causing the release of oxytocin from the posterior pituitary. **Oxytocin** stimulates smooth muscle contractions. This helps shrink the uterus to pre-pregnancy size and creates high pressure in the milk ducts, which can squirt milk into the infant's mouth. This can also contribute to leakage of milk. Mechanical stimulation of the cervix can also release oxytocin.

Infertility

The inability of a couple to conceive a baby is the basic definition of **infertility**. More formally, it is the failure to conceive after repeated attempts to become pregnant over the course of a year. It affects approximately one in five couples in the United States. More than half of couples who have not conceived after 1 year will eventually conceive. In about one-third of cases of infertility, there are problems with sperm; in about one-third, there are problems with the fallopian tubes; and in about one-sixth, there are ovulation problems. Rarely are there problems with cervical mucus. The cause of infertility is unidentified in the remainder of cases.

Many causes of infertility can be reversed with natural therapeutic remedies. The most significant practices would be to decrease the stress levels in everyday life. Also vitally important is to avoid toxins and poisons (including situations or thoughts), maintain a whole food fat-rich diet and create a healthy happy positive attitude.

Review Questions for Chapter 23: Female Reproductive System

1. What usually occurs between days 13 and 15 of the menstrual or uterine cycle?
- **a)** The lining of the uterus builds up
- **b)** Ovulation
- **c)** The lining of the uterus remains in place in preparation for the possible arrival of an embryo
- **d)** Shedding of the lining of the uterus

2. This occurs on days 1 to 5 of the menstrual cycle.
- **a)** The lining of the uterus remains in place in preparation for the possible arrival of an early embryo.
- **b)** An egg is released from the ovaries
- **c)** Shedding of the lining of the uterus
- **d)** The lining of the uterus builds up

3. The entrance to the womb is also known as theentrance.png
- **a)** cervix
- **b)** ovary
- **c)** fallopian tube
- **d)** vagina
- **e)** fimbriae

4. Which hormone is responsible for ovulation in females?
- **a)** GH
- **b)** TSH
- **c)** PRL
- **d)** ACTH
- **e)** LH

5. In a typical menstrual cycle of 28 days, what is the most likely fertile period?
- **a)** Days 5 to 10
- **b)** Days 11 to 14
- **c)** Days 14 and 15
- **d)** Days 1 to 5
- **e)** Days 26 t0 28

6. This carries the egg to the uterus.
- **a)** Wave of mucus in the fundus
- **b)** The Fallopian tube
- **c)** The vagina
- **d)** The ovaries
- **e)** The cervix

7. Fertilization takes place in what region of the female reproductive tract? The:

a) fallopian tube
b) vagina
c) cervix
d) uterus
e) endometrium

8. During the menstrual cycle, which events happens if a released egg does not become fertilized?

a) The lining of the womb wall stays built up.
b) Another egg is immediately released.
c) The lining of the womb wall builds up again.
d) The lining of the womb wall breaks down and sloughs off.

9. Comparing secondary sexual characteristics of males and females, in general females have:

a) a higher basal metabolic rate
b) lower levels of androgens than males
c) greater muscle mass
d) lower levels of estrogen than males
e) lower pitched voices than males

10. The female gonads make gametes called _____ and sex the hormones _____.

a) follicles: progesterone
b) egg cells: androgens
c) sperm: estrogen
d) egg cells: estrogen
e) egg cells: estrogen and progesterone

Answers in Appendix B