Ovarian Histology

1. The ovaries are covered by visceral peritoneum, which is called the ovarian epithelium.

2. The **tunica albuginea** is a connective tissue capsule that forms the outer part of the ovary.

3. Internally the ovary has two parts:
   A. The **cortex** is the outer part of the ovary containing oocytes (female sex cells) within ovarian follicles.
   
   B. The **medulla** is the inner part of the ovary containing blood vessels, lymphatic vessels, and nerves.

Oocyte Development and Fertilization

**Oocytes** are the female sex cells. **Oogenesis** is the production of secondary oocytes within the ovaries.

1. **Oogonia** are the cells within the ovary from which oocytes develop. The oogonia divide by **mitosis**, resulting in approximately 5 million oogonia in the ovaries at the fourth month of prenatal development.
   A. It has been thought that after the initial formation of oogonia that no more were formed. That leads to the amazing conclusion that a female has all the sex cells she will have before birth.
   
   B. Data in mice (2004) indicates that there are stem cells in the ovaries that can produce oocytes throughout life. The significance of this finding for humans is unclear.

2. **Primary oocytes** are oogonia that have started to divide by meiosis. The first meiotic division stops at prophase I. There are approximately 2 million primary oocytes at birth. The other oogonia degenerate.

3. At puberty there are approximately 300,000 to 400,000 primary oocytes, of which approximately 400 will complete development.

4. During follicle development (see below) the primary oocyte completes the first meiotic division to form a **secondary oocyte** and a **polar body**.

5. The secondary oocyte starts the second meiotic division, but stops at metaphase II. **Ovulation** is the release of the secondary oocyte from the ovary.
6. **Fertilization** is the fusion of a sperm cell with the secondary oocyte. If fertilization occurs, the secondary oocyte completes meiosis. Half of the secondary oocyte's genetic material goes into a polar body, and half combines with the genetic material of the sperm cell. The result is a polar body and a single cell, the **zygote**, which has received half of its genetic material from the mother and half from the father.

During meiosis, division of the cytoplasm between the oocytes and the polar bodies is unequal. The oocytes receive almost all of the cytoplasm. However, in spermatogenesis, each sperm cell receives an equal amount of cytoplasm. Explain this difference.

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**Follicle Development**

![FIGURE 28.14](image)

1. A **primordial follicle** consists of a primary oocyte surrounded by a single layer of flattened **granulosa cells**. At puberty there are approximately 300,000 to 400,000 primordial follicles within the two ovaries.

2. Approximately every 28 days, up to 25 of the primordial follicles become **primary follicles**.
   A. The granulosa cells become cuboidal and divide to form several layers of cells around the primary oocyte.
   B. The granulosa cells secrete a clear layer of fluid, the **zona pellucida**, around the primary oocyte.
      1) The zona pellucida forms an extracellular membrane around the oocyte. In order for fertilization to occur, a sperm cell must penetrate the zona pellucida.
      2) The zona pellucida contains species specific glycoproteins to which the heads of sperm cells can attach. This specificity is why different species cannot reproduce with each other.
      3) When the head of the sperm cell binds to the zona pellucida, it causes the release of digestive enzymes from the acrosome.
      4) When a sperm cell penetrates the zona pellucida, it binds to the surface of the oocyte and triggers reactions that prevent other sperm cells from entering the oocyte. This is why oocytes are usually fertilized by only one sperm cell. [}
3. The primary follicles become **secondary follicles**.
   A. The granulosa cells continue to divide.

   B. The granulosa cells produce secretions that accumulate within small spaces of the follicle. The secretions contain estrogen, some of which is released from the ovary.

   C. A two-layered capsule called the **theca** forms around the granulosa cells. The **theca interna** produces androgens, which are converted to estrogen by the granulosa cells. The **theca externa** is connective tissue with no secretory function.

4. The secondary follicle becomes a **mature, or graafian, follicle**.
   A. The granulosa cells continue to divide and form a mass of cells around the oocyte called the **cumulus mass**.

   B. The fluid-filled spaces combine to form the **antrum**.

   C. The granulosa cells increase the production of estrogen and begin to produce progesterone.

   D. Usually only one mature follicle develops and moves to the surface of the ovary. The other follicles degenerate.

**Ovulation**
1. **Ovulation** is the release of an oocyte from the ovary. Ovulation takes place on approximately day 14 of the ovarian cycle.

2. Just before or during ovulation the primary oocyte completes the first meiotic division to become a secondary oocyte (see above).

3. The secondary oocyte enters a uterine tube where it may or may not be fertilized. The oocyte is surrounded by the zone pellucida and the **corona radiata**, which is the innermost cumulus mass cells around the oocyte.

**Fate of the Follicle**
1. After ovulation, the follicle becomes the **corpus luteum** (yellow body), which produces progesterone and estrogen that enters the blood.

2. If the oocyte is fertilized and implants in the uterus, human chorionic gonadotropin (HCG) secreted by the placenta stimulates the corpus luteum to function for several months and to continue secreting progesterone and estrogen.

3. If the oocyte is not fertilized, the corpus luteum degenerates into a white connective tissue scar call the **corpus albicans** (white body). This takes place on approximately day 26 - 28 of the ovarian cycle. Secretion of progesterone and estrogen by the ovary essentially stops.
PHYSIOLOGY OF FEMALE REPRODUCTION

Basic Endocrine System of the Female

- Hypothalamus
  - Gonadotropin releasing hormone (GnRH)
    - Anterior Pituitary
      - Follicle stimulating hormone (FSH)
      - Luteinizing hormone (LH)
        - Stimulates the primordial follicle to become the mature follicle
        - Stimulates estrogen secretion
        - Stimulates ovulation
          - Stimulates the formation of the corpus luteum
          - Stimulates the secretion of progesterone and estrogen

- Estrogen: Stimulates the secretion of progesterone
- Progesterone

Estrogen and progesterone have a negative-feedback effect on the hypothalamus and anterior pituitary. However, it is more complex than indicated in the above diagram.

Can you explain how birth control pills (daily doses of estrogen and/or progesterone prevent pregnancy?)

Structurally, which of the reproductive hormones produced by the female is human chorionic gonadotropin (HCG) probably most like?
**Puberty**
1. Before puberty, GnRH, LH, and FSH levels are low. At puberty, GnRH levels increase, causing an increase in LH and FSH, which cause an increase in estrogen and progesterone levels.

2. Primary sexual characteristics. Estrogen stimulates maturation of the vagina, uterus, and uterine tubes.

3. Secondary sexual characteristics.
   A. Breast development. See below.
   B. Estrogen effects.
      1) Skin becomes soft, smooth and vascular. A woman's skin may feel warmer and bleed more than a man's.
      2) Shorter height than men (earlier closure of the epiphyseal plate) and broader pelvis (better for delivery).
      3) Increased fat deposition, especially the breasts, mons pubis, buttocks, and thighs. Women have about 10% more fat per pound body weight than men.
   C. Testosterone (androgen) effects (produced by the theca interna).
      1) Production of axillary and pubic hair.
      2) Increased sebaceous gland activity that can contribute to the development of acne.

**Menstrual Cycle**
1. The **menstrual cycle** is a cyclic series of changes that occur in sexually mature, nonpregnant females. The typical length of time of the menstrual cycle is 28 days, but it can vary from 18 to 40 days.

2. The menstrual cycle can be divided into the ovarian cycle and the uterine cycle.

**Ovarian Cycle**

1. The **ovarian cycle** is the series of changes that take place in the ovaries of sexually mature, nonpregnant females approximately every 28 days.

2. During the **follicular phase**, the follicle develops under the influence of FSH produced during the FSH surge. This results in the production of estrogen and the formation of a secondary oocyte.

   How is it possible for the FSH surge to stimulate primordial follicles to become mature follicles?
3. **Ovulation** occurs on day 14 as a result of the LH surge. LH also promotes the formation of the corpus luteum.

4. During the **luteal phase**, the corpus luteum forms and produces progesterone and additional estrogen.

### The Uterine Cycle

1. The fluctuation of estrogen and progesterone produced during the ovarian cycle prepares the female to accept a developing embryo and start the production of a new individual.

2. One of the most important aspects of the changes induced by these hormones are modifications of the uterus, called the **uterine cycle**.

3. Structure of the uterus.

   ![FIGURE 28.11](image)

   A. The **serous coat** (visceral peritoneum) forms the outer layer.

   B. The **myometrium** forms the thick middle layer. It consists of smooth muscle and elastic connective tissue.

   C. The **endometrium** is a mucous membrane that forms the inner layer of the uterus. It has two parts.

   ![FIGURE 28.20](image)

   1) The **functional layer** is the portion that changes the most during the uterine cycle. It is also sloughed off (shed) during each uterine cycle.

   2) The **basal layer** is the permanent part of the endometrium. It replaces the lost functional layer.

4. The uterine cycle is usually divided into three phases. Actually it is a continuous process and the phases overlap each other. The three phases are menses, the proliferative phase, and the secretory phase.

   ![FIGURES 28.18 and 28.20](image)

5. **Menses**.
   A. The first day of menstrual bleeding is considered day 1. **Menses** or **menstruation** is a period of mild bleeding during which the functional layer of the uterus is sloughed and expelled from the uterus.
B. Menses occurs during days 1 to 5 of the uterine cycle.
   1) There is a breakdown of the endometrium, which had thickened and become very vascular during the previous uterine cycle.
   2) Normally there is a loss of 25 to 65 ml of menstrual fluid (i.e., disintegrated endometrium, blood, secretions).

C. Before menses has completely ceased, repair of the endometrium begins.

6. **Proliferative phase.**
   A. The proliferative phase occurs during days 6 to 14 of the uterine cycle.
   
   B. FSH stimulates the production of estrogen by the developing follicles, causing the endometrium to become thicker and more vascular (e.g., increased cell division, gland formation, and blood vessels grow into the newly formed tissue).
   
   C. LH stimulates ovulation on day 14 and the formation of the corpus luteum following ovulation.

7. **Secretory phase.**
   A. The secretory phase occurs during days 15 to 28 of the uterine cycle.
   
   B. As a result of a drop in estrogen after ovulation, the thickening of the endometrium may stop temporarily and there may be intermenstrual bleeding.
   
   C. As the corpus luteum develops, there is a large increase in progesterone secretion and a slight increase in estrogen secretion.
   
   D. Effects of estrogen and progesterone on the endometrium.
      1) Estrogen stimulates the development of many spiral tubular glands and increased vascularization with many spiral arteries. The endometrium doubles in thickness (now 4-5 mm).
      
      2) Progesterone stimulates the spiral tubular glands to produce a secretion rich in glycogen.
   
   E. Effects of estrogen and progesterone on smooth muscle contraction of the myometrium.
      1) Estrogen stimulates smooth muscle contraction.
      
      2) Progesterone inhibits smooth muscle contraction. The high levels of progesterone overcome the stimulatory effects of estrogen.

8. The whole purpose of these endometrial changes is to produce a vascular endometrium containing stored nutrients (e.g., glycogen) that can provide nourishment for the developing blastocyst (see next page of notes).
   A. If a developing blastocyst implants on the endometrium, it will digest the endometrium and eventually link up to the blood supply of the mother.
   
   B. If there is no implantation, the cycle begins again with menses.

9. Menses again.
   A. During the last two days of the ovarian cycle there is a drop in progesterone and estrogen production from the corpus luteum.
B. Vasospasms of the spiral arteries cut off blood supply to the endometrium. The functional layer dies and is shed.

C. Dead tissue, blood, and secretions are expelled by uterine contractions (i.e., contractions of the myometrium)

Why does the smooth muscle in the myometrium contract at this time?

Female Sexual Behavior and the Female Sex Act
1. Sex drive. The hormonal role of sex drive is less clear in women than in men. The usual statement made is: "Sex drive in women is a combination of sex hormones (testosterone and ?) and psychological experiences."

2. As in males, sacral reflexes, moderated by input from the brain, stimulate vasodilation of blood vessels and increase secretions in the genitals.

3. Orgasm is not necessary for fertilization to occur.

Female Fertility and Pregnancy
1. The oocyte is capable of being fertilized for up to 1 day after ovulation. Sperm cells can survive for 6 days within the female's reproductive tract.

If fertilization is to occur, when must intercourse take place?
2. The sperm cells and the oocyte move toward each other by three methods.  
   A. Swimming of the sperm cells.  
   B. Movement of the cilia lining the uterine tube.  
   C. Contractions of the uterus and uterus tubes. The contractions are stimulated by hormones.  
      1) Oxytocin released from the posterior pituitary of the female during intercourse.  
      2) Prostaglandins in semen.  
3. While in the uterus and the uterine tubes the sperm cells undergo capacitation, which enables the sperm cells to release enzymes from the acrosome.  
4. Fertilization normally occurs in the ampulla of the uterine tube.  

   FIGURE 28.21  
5. After fertilization, cell division begins and a hollow ball of cells, the blastocyst, is formed. The outer layer of the blastocyst is the trophoblast. The trophoblast digest its way into the endometrium and implantation occurs. This usually occurs at 7 to 8 days after ovulation (day 21 or 22 of the menstrual cycle).  

   FIGURE 29.3  
6. Menses normally occurs 14 days after ovulation, and the functional layer of the endometrium is sloughed from the uterine wall. If this should happen after an embryo has implanted, pregnancy would be terminated (spontaneous abortion).  
7. The endometrium is maintained as a result of the actions of human chorionic gonadotropin (HCG) secreted by the chorion. The chorion is a layer of tissue derived from the trophoblast. The chorion along with the uterine wall forms the placenta.  

   FIGURE 28.22  

A. HCG is structurally similar to LH and stimulates the corpus luteum to persist (i.e., not become a corpus albicans) and produce progesterone and estrogen.  
   1) Progesterone acts to maintain the endometrium and decrease the contractibility of the uterus. It also is involved in changes in the breast in preparation for lactation.  
   2) Estrogen acts to maintain the endometrium and prepare the breast for lactation.  
B. HCG stimulates interstitial cells to produce testosterone (if the individual is genetically a male). Testosterone promotes the development of the male reproductive system.  
C. HCG can be detected shortly after implantation (as little as 8 days after ovulation). This is used as a test for pregnancy (test the urine).
D. The rate of secretion of HCG peaks at about 2 months and then declines.
   1) Without HCG the corpus luteum becomes the corpus albicans and production of progesterone and estrogen by the ovary drops.

   2) Normally by the time the placental production of HCG decreases, the placenta starts producing progesterone and estrogen. This replaces the estrogen and progesterone that had been produced by the corpus luteum.

   The third month of pregnancy can be a critical time. What could go wrong at this time? Explain.

**Parturition (see 1104-1106 in text)**

1. **Parturition** or labor is the process of childbirth. The exact mechanism that causes the initiation of labor is unclear. Several factors have been identified.

2. At the end of pregnancy estrogen levels increase and progesterone levels level off.
   A. Estrogen stimulates uterine contractions, whereas progesterone inhibits uterine contractions. The effects of estrogen can overcome the inhibitory effect of progesterone on uterine contractions.

   B. The fetus can affect the levels of estrogen and progesterone.

   FIGURE 29.20

   1) Stress on the fetus at the end of pregnancy stimulates secretion of corticotropin-releasing hormone (CRH) from the fetal hypothalamus.

   2) CRH travels through the hypothalamohypophyseal portal system to the fetal anterior pituitary gland, which secretes adrenocorticotropic hormone (ACTH).

   3) ACTH stimulates the fetal adrenal glands to secrete glucocorticoids (adrenal cortical steroids).

   4) The glucocorticoids increase estrogen secretion by the placenta, which increases uterine smooth muscle contraction.

   5) The glucocorticoids decrease progesterone by the placenta, which decreases the inhibitory effect on the uterine smooth muscle, i.e., makes it easier to have contractions.

3. Oxytocin and prostaglandins stimulate the uterus to contract.
   A. Stretch of the uterus sends action potentials to the mother’s hypothalamus. Action potentials from the hypothalamus stimulate the release of oxytocin from the mother’s posterior pituitary gland.
B. Oxytocin stimulates contractions of the uterus.

C. Oxytocin stimulates production of prostaglandins by the placenta. The prostaglandins also cause uterine contractions.

D. Both oxytocin and prostaglandin seem to be necessary for successful delivery.

Mammary Glands (see pages 1056-1058 in the text)

1. The mammary glands are the organs of milk production. They are located in the mammae or breasts.

2. The breasts attach to the fascia of the pectoralis major muscle by suspensory ligaments called mammary ligaments.

3. Each mammary gland is divided into 15 to 20 lobes which are in turn divided into lobules. 
   A. In the nonlactating gland, each lobule has a system of ducts. In the lactating gland, the ends of the ducts expand to form alveoli (secretory sacs) that are the site of milk production.

   B. Ducts from the lobe converge to empty into lactiferous ducts
      1) There is a lactiferous duct from each lobe of the mammary gland.

      2) The lactiferous sinus is an enlargement of the lactiferous duct that can store milk.

   C. The lactiferous ducts open onto the nipple.

4. The areola is the area of pigmented skin about the nipple. The areola has small bumps that are made by rudimentary mammary glands called areolar glands. Secretions from these glands provide protection against chafing during nursing.

5. The development of the breasts of males and females is controlled by hormones. Rarely, the breast in a male can enlarge and this is called gynecomastia.
Lactation (see pages 1110-1111 in the text)

1. **Lactation** is the production of milk. In young men (before age 20) hormones can induce some milk production.

2. Estrogen effects.
   A. During puberty, estrogen initiates growth of the breasts, causing fat deposition and development of the breasts’ duct system.
   
   B. During pregnancy, estrogen causes breast enlargement (fat deposition) and further duct system development.

3. Progesterone stimulates development of the alveoli of the mammary glands during pregnancy. Prior to pregnancy there are no alveoli. After lactation ceases, almost all the alveoli disappear.

4. Prolactin effects.
   A. Prolactin stimulates milk production. At first, **colostrum** is produced instead of milk. Colostrum is high in protein, but contains less lactose than true milk, and has almost no fat content. About the fourth day after delivery true milk is produced.

   B. Regulation of prolactin secretion.
      1) Hormones from the hypothalamus regulate prolactin release from the anterior pituitary.
         a. **Prolactin releasing factor (PRF)** stimulates prolactin release.
         b. **Prolactin inhibiting factor (PIF)** inhibits prolactin release.

      2) Regulation of PRF and PIF.
         a. Suckling by the infant sends action potentials from the mother's nipple to her hypothalamus.
         b. PIF is inhibited and PRF release is stimulated. The result is prolactin production by the anterior pituitary and milk production by the mammary glands. The milk produced is used in the next nursing event.
         c. As long as suckling continues there will be a surge of prolactin and the mammary glands will produce milk. Milk production can continue for several years.
         d. If suckling stops, prolactin levels fall to pre-pregnancy levels, and milk production stops.
5. Oxytocin effects.
   A. Suckling sends action potentials to the hypothalamus. Action potentials from the hypothalamus go to the posterior pituitary and oxytocin is released.

   B. Oxytocin causes contraction of specialized cells in the alveoli and milk is released from the alveoli into the duct system of the breast. The milk can be removed by the sucking action of the infant.

   C. The release of milk is called **milk letdown** or **milk ejection**.

   What effect would suckling of one breast have on milk letdown in the other breast? Explain.

   While nursing her baby, a woman noticed that she developed "stomach cramps." Explain what was happening.
Lactation often inhibits FSH and LH production by the anterior pituitary for several months. What effect might this have on the ability of the woman to become pregnant? Explain.

Give the name of the hormone that has each of the following effects on the breasts.

1. Fat deposition and duct development.
2. Development of the alveoli.
3. Production of milk.
4. Milk letdown.

**Menopause**

1. Between 40 to 50 years of age the ovarian cycle becomes irregular and eventually stops. This is called the female climacteric. The complete cessation of the menstrual cycle is called menopause.

2. The exact cause is unknown. There are still some follicles left in the ovary. However they become less responsive to FSH and LH.

What effect will the less responsive follicles have on hormone levels in the female? Explain.

3. Symptoms of menopause include hot flashes, irritability, fatigue, difficulty in breathing, anxiety, and possibly psychotic states.

4. Sometimes hormone replacement therapy (HRT) is used to relieve the symptoms
   A. If estrogen use is discontinued, symptoms reappear. Therefore the estrogen is taken for the rest of the woman's life.

   B. The estrogen dosage can be gradually reduced. This approach reduces the severity of the symptoms but also prolongs them.

   C. The Woman's Health Initiative, started in 1991, examined over 16,000 women to see the effect of estrogen taken with progesterone on women's health. The study was stopped in 2002 because it was found to be causing more harm than good. This particular HRT increased the risk of breast cancer, uterine cancer, heart attacks, strokes, and blood clots, but decreased the risk of hip fractures and colorectal cancer.