Chapter 27
Reproductive System

Slides by Karen Dunbar Kareiva and W. Rose.
figures from Marieb & Hoehn 10th ed.

Portions copyright Pearson Education
KAAP310-16S Test 11

9 am Mon May 23, 2016

Kirkbride 006
Part 3 – Female Reproductive Anatomy

• Reproductive role of female more complex because of pregnancy

• **Ovaries: female gonads**
  – Produce female gametes (ova)
  – Secrete female sex hormones, **estrogen** (estradiol, estrone, estriol), and **progesterone**

• **Internal genitalia**: located in pelvic cavity; include **ovaries** and **duct system** (uterine tubes, uterus, and vagina)

• **External genitalia**: external sex organs
Figure 27.13 Organs of the female reproductive system, midsagittal section.

- Peritoneum
- Perimetrium
- Uterosacral ligament
- Rectouterine pouch
- Posterior fornix
- Cervix
- Anterior fornix
- Vagina
- Anus
- Urogenital diaphragm
- Greater vestibular gland
- Mons pubis
- Clitoris
- Urethra
- Urogenital diaphragm
- External urethral orifice
- Hymen
- Labium minus
- Labium majus
- Peritoneum
- Rectum
- Infundibulum
- Uterine tube
- Ovary
- Fimbriae
- Uterus
- Round ligament
- Vesicouterine pouch
- Urinary bladder
- Pubic symphysis
- Mons pubis
- Urethra
- Clitoris
- External urethral orifice
- Hymen
- Labium minus
- Labium majus
27.8 Ovaries

- Each ovary is held in place by several ligaments
  - **Ovarian ligament**: anchors ovary medially to uterus
  - **Suspensory ligament**: anchors ovary laterally to pelvic wall
  - **Mesovarium**: suspends ovary
- Suspensory ligament and mesovarium are part of **broad ligament** that supports uterine tubes, uterus, and vagina
Figure 27.15a Internal female reproductive organs.
Figure 27.15b Internal female reproductive organs.

- Rectouterine pouch
- Right ovary
- Right uterine tube
- Right round ligament
- Uterus
- Vesicouterine pouch
- Urinary bladder
- Sigmoid colon
- Rectum
- Left ovary
- Left uterine tube
- Left round ligament
- Mesosalpinx
- Mesometrium of the broad ligament

(b) Superoanterior view
• Blood supply for ovaries: **ovarian arteries** and **ovarian branch of the uterine arteries**
  – Vessels travel through suspensory ligament and mesovaria
• Each ovary surrounded by fibrous **tunica albuginea**, which is then covered by germinal cuboidal epithelium outer layer
  – Germinal layer is continuation of peritoneum
27.8 Ovaries

- Two poorly defined regions
  - Outer *cortex*: houses forming gametes
  - Inner *medulla*: contains large blood vessels and nerves
27.8 Ovaries

- **Ovarian follicles**: tiny saclike structures embedded in cortex
  - Contain immature egg (**oocyte**) surrounded by:
    - **Follicle cells** (if only one cell layer is present)
    - **Granulosa cells** (if more than one layer present)
  - Follicles go through several stages of development
    - **Primordial follicle**: single layer of follicle cells plus oocyte
    - More mature follicles: several layers of granulosa cells plus oocyte
Follicular stages (cont.)

- **Vesicular (antral or tertiary) follicle**: fully mature follicle
  - Fluid-filled antrum forms; follicle bulges from ovary surface

**Ovulation**

- Ejection of oocyte from ripening follicle
- **Corpus luteum** develops from ruptured follicle after ovulation
Figure 27.14 Photomicrograph of a mammalian ovary showing follicles in different developmental phases.

- Germinal epithelium
- Tunica albuginea
- Cortex
- Medulla
- Primary follicles
- Secondary follicle
- Antrum of a vesicular (antral) follicle
27.9 Female Duct System

- Uterine tube system does not have direct contact with ovaries
  - Ovulated oocyte is cast into peritoneal cavity, where some oocytes never make it to tube system

- Tube system includes:
  - Uterine tubes
  - Uterus
  - Vagina
The Uterine Tubes

- **Uterine tubes**, also called **fallopian tubes** or **oviducts**, receive ovulated oocyte and are usual site of fertilization
- Each tube ~10 cm (4 in) long and extends from area of ovary to superolateral region of uterus
• Regions of uterine tube
  – **Isthmus**: constricted area where tube joins uterus
  – **Ampulla**: distal end of tube that curves around ovary
  – **Infundibulum**: distal expansion near ovary
    • Contains ciliated fimbriae that creates current to move oocyte into uterine tube
The Uterine Tubes (cont.)

• Oocyte is carried along toward uterus by smooth muscle peristalsis and ciliary action
• Nonciliated cells of tube function to nourish oocyte and sperm
• Externally, uterine tubes are:
  – Covered by peritoneum
  – Supported by a short mesentery called mesosalpinx
Figure 27.15a Internal female reproductive organs.

- **Broad ligament**
  - Mesosalpinx
  - Mesovarium
  - Mesometrium

- **Ovarian ligament**

- **Body of uterus**

- **Ureter**

- **Uterine blood vessels**

- **Isthmus**

- **Uterosacral ligament**

- **Cardinal (lateral cervical) ligament**

- **Lateral fornix**

- **Cervix**

- **Round ligament of uterus**

- **Suspensory ligament of ovary**

- **Ovarian blood vessels**

- **Uterine (fallopian) tube**
  - Ampulla
  - Isthmus
  - Infundibulum
  - Fimbriae

- **Fundus of uterus**

- **Lumen (cavity) of uterus**

- **Fundus of uterus**

- **Lateral fornix**

- **Cervix**

- **External os**

- **Cervical canal**

- **Internal os**

- **Vagina**

- **Uterine tube**
  - Ampulla
  - Isthmus
  - Infundibulum
  - Fimbriae

- **Round ligament of uterus**

- **Wall of uterus**
  - Endometrium
  - Myometrium
  - Perimetrium

- **Posterior view**
Clinical – Homeostatic Imbalance 27.4

- **Ectopic pregnancy**
  - Oocyte is fertilized in peritoneal cavity or distal uterine tube and begins developing there
    - Normally abort naturally with substantial bleeding

- **Pelvic inflammatory disease (PID)**
  - Spread of infection from reproductive tract to peritoneal cavity
    - May cause scar tissue and lead to infertility
The Uterus

• Hollow, thick-walled, muscular organ
• Function is to receive, retain, and nourish fertilized ovum
• Position of uterus
  – Anteverted: inclined forward (normal position)
  – Retroverted: inclined backward
The Uterus (cont.)

• Regions of uterus
  – **Body**: major portion
  – **Fundus**: rounded superior region
  – **Isthmus**: narrowed inferior region
  – **Cervix**: narrow neck, or outlet; projects into vagina
  – **Cervical canal** communicates with:
    • Vagina via *external os*
    • Uterine body via *internal os*

• **Cervical glands** secrete mucus that blocks sperm entry except during midcycle

© 2016 Pearson Education, Inc.
Clinical – Homeostatic Imbalance 27.5

• Cervical cancer affects 450,000 women worldwide each year, killing half
  – Most common between ages 30 and 50
  – Risks: frequent cervical inflammation; STIs, including HPV; or multiple pregnancies
    • Gardasil: three-dose anti-HPV vaccine, recommended for girls 11-12 y.o.
  – Papanicolaou (Pap) smear for detection
    • Recommended every 3 years for ages 21–65
The Uterus (cont.)

- **Supports of the uterus**
  - **Mesometrium**: lateral support of broad ligament
  - **Cardinal (lateral cervical) ligaments**: from cervix and superior vagina to pelvic lateral walls
  - **Uterosacral ligaments**: secure uterus to sacrum
  - **Round ligaments**: bind uterus to anterior wall
Figure 27.15a Internal female reproductive organs.

- Ovarian blood vessels
- Broad ligament: • Mesosalpinx • Mesovarium • Mesometrium
- Ovarian ligament
- Body of uterus
- Ureter
- Uterine blood vessels
- Isthmus
- Uterosacral ligament
- Cardinal (lateral cervical) ligament
- Lateral fornix
- Cervix
- Uterine tube: • Ampulla • Isthmus • Infundibulum • Fimbriae
- Round ligament of uterus
- Wall of uterus: • Endometrium • Myometrium • Perimetrium
- Internal os
- Cervical canal
- External os
- Vagina

(a) Posterior view
Clinical – Homeostatic Imbalance 27.6

• **Prolapse of the uterus**: unsupported uterus may sink inferiorly, until tip of cervix protrudes through the external vaginal opening
• Caused by overstretching and sometimes tearing of muscles during childbirth
• Even though uterus has many anchoring ligaments, it is principally supported by muscles of pelvic floor, which are prone to damage
  – Chiefly urogenital and pelvic diaphragms
Figure 27.13 Organs of the female reproductive system, midsagittal section.

- Peritoneum
- Perimetrium
- Uterosacral ligament
- Rectouterine pouch
- Posterior fornix
- Cervix
- Anterior fornix
- Vagina
- Anus
- Urogenital diaphragm
- Greater vestibular gland
- Suspensory ligament of ovary
- Infundibulum
- Uterine tube
- Ovary
- Fimbriae
- Uterus
- Round ligament
- Vesicouterine pouch
- Urinary bladder
- Pubic symphysis
- Mons pubis
- Urethra
- Clitoris
- External urethral orifice
- Hymen
- Labium minus
- Labium majus
The Uterus (cont.)

• **Uterine wall**
  – Three layers of wall
    • **Perimetrium**: outermost serous layer (visceral peritoneum)
    • **Myometrium**: bulky middle layer consisting of interlacing layers of smooth muscle
      – Contracts rhythmically during childbirth
    • **Endometrium**: mucosal lining
      – Simple columnar epithelium on top of a thick lamina propria
      – Fertilized egg burrows into endometrium and resides there during development
The Uterus (cont.)

• Uterine wall (cont.)
  – Endometrium has two chief layers (*strata*)
    • Stratum functionalis (*functional layer*)
      – Changes in response to ovarian hormone cycles
      – Shed during menstruation
    • Stratum basalis (*basal layer*)
      – Forms new stratum functionalis after menstruation
      – Unresponsive to ovarian hormones
Figure 27.16a The endometrium and its blood supply.
The Uterus (cont.)

- **Uterine wall (cont.)**
  - Vascular supply plays key role in cyclic changes
    - **Uterine arteries** arise from *internal iliacs* and branch into:
    - **Arcuate arteries** in myometrium; branch into:
    - **Radial arteries** in endometrium; branch into:
      - Straight arteries in stratum basalis and
      - Spiral arteries in stratum functionalis
        » Degenerate and regenerate
        » Spasms cause shedding of functionalis layer during menstruation
Figure 27.16b The endometrium and its blood supply.

- Lumen of uterus
- Epithelium
- Capillaries
- Uterine glands
- Venous sinusoids
- Lamina propria (connective tissue)
- Spiral (coiled) artery
- Straight artery
- Endometrial vein
- Radial artery
- Smooth muscle fibers
- Arcuate artery
- Uterine artery
The Vagina

- Thin-walled tube 8–10 cm (3–4 inches) in length
- Functions as birth canal, passageway for menstrual flow, and organ of copulation
- Extends between bladder and rectum from cervix to exterior
- Urethra runs parallels to vagina anteriorly
The Vagina (cont.)

- Layers of wall
  - Fibroelastic *adventitia*
  - Smooth muscle *muscularis*
  - Stratified squamous *mucosa* with rugae
    - Dendritic cells in mucosa may provide route for HIV transmission
• Vaginal secretions are acidic in adult females, but alkaline in adolescents

• Mucosa near vaginal orifice forms incomplete partition called **hymen** that ruptures with intercourse

• **Vaginal fornix**: upper end of vagina surrounding cervix
Figure 27.13 Organs of the female reproductive system, midsagittal section.

- Peritoneum
- Perimetrium
- Uterosacral ligament
- Rectouterine pouch
- Posterior fornix
- Cervix
- Anterior fornix
- Vagina
- Anus
- Urogenital diaphragm
- Greater vestibular gland
- Suspensory ligament of ovary
- Infundibulum
- Uterine tube
- Ovary
- Fimbriae
- Uterus
- Round ligament
- Vesicouterine pouch
- Urinary bladder
- Pubic symphysis
- Mons pubis
- Urethra
- Clitoris
- External urethral orifice
- Hymen
- Labium minus
- Labium majus
Clinical – Homeostatic Imbalance 27.7

- Because uterus tilts away from vagina, attempts by untrained persons to induce an abortion by entering uterus with a surgical instrument may puncture posterior wall of vagina.
- Can cause hemorrhage and, if instrument is unsterile, peritonitis.
27.10 External Genitalia

- Female **external genitalia**, also called **vulva** or **pudendum**, include:
  - **Mons pubis**: fatty area overlying pubic symphysis
  - **Labia majora**: hair-covered, fatty skin folds
    - Counterpart of male scrotum
  - **Labia minora**: skin folds lying within labia majora
  - **Vestibule**: recess within labia minora
    - **Fourchette**: ridge formed by joining of posterior vestibule and labia minora
27.10 External Genitalia

- **Greater vestibular glands**
  - Flank vaginal opening
  - Homologous to bulbo-urethral glands
  - Release mucus into vestibule for lubrication

- **Clitoris**: anterior to vestibule
  - **Glans of the clitoris**: exposed portion
  - **Prepuce of the clitoris**: hoods glans
  - Counterpart of penis

- **Perineum**
  - Diamond-shaped region between pubic arch and coccyx
  - Bordered by ischial tuberosities laterally
Figure 27.17a The external genitalia (vulva) of the female.

- Mons pubis
- Prepuce of clitoris
- Clitoris (glans)
- Vestibule
- Anus
- Labia majora
- Labia minora
- External urethral orifice
- Hymen (ruptured)
- Vaginal orifice
- Opening of the duct of the greater vestibular gland
Figure 27.17b The external genitalia (vulva) of the female.

- Clitoris
- Labia minora
- Labia majora
- Anus
- Pubic symphysis
- Pubic symphysis
- Body of clitoris, containing corpora cavernosa
- Clitoris (glans)
- Crus of clitoris
- External urethral orifice
- Vaginal orifice
- Greater vestibular gland
- Bulb of vestibule
- Fourchette
Mammary glands are present in both male and female, but normally function only in female.

Main function is milk production to nourish newborn.
The Mammary Glands

• Modified sweat glands consisting of 15–25 lobes
• **Areola**: pigmented skin surrounding **nipple**
• **Suspensory ligaments**: attach breast to underlying muscle
The Mammary Glands (cont.)

- Lobules within lobes contain glandular alveoli that produce milk
  - Milk is passed into lactiferous ducts, then into lactiferous sinuses that open to outside at nipple
  - In non-nursing women, glandular structure is undeveloped

- Breast size is due to amount of fat deposits
Figure 27.18 Structure of lactating mammary glands.

- Skin (cut)
- Pectoralis major muscle
- Suspensory ligament
- Adipose tissue
- Lobe
- Areola
- Nipple
- Opening of lactiferous duct
- Lactiferous sinus
- Lactiferous duct
- Lobule containing alveoli
- Hypodermis (superficial fascia)
- Intercostal muscles
- First rib
Breast Cancer

• Invasive breast cancer is most common malignancy and second most common cause of cancer death in U.S. women
• 13% of women will develop condition
• Usually arises from epithelial cells of smallest ducts that eventually metastasize
• Risk factors
  – Early onset of menstruation and late menopause
  – No pregnancies or first pregnancy late in life
  – No or short periods of breast feeding
  – Family history of breast cancer

© 2016 Pearson Education, Inc.
Breast Cancer (cont.)

• 70% of women with breast cancer have no known risk factors
• 10% due to hereditary defects, including mutations to genes BRCA1 and BRCA2
  – 50% to 80% of women with these genes develop breast cancer
  – Greater risk of ovarian cancer as well
Breast Cancer (cont.)

• **Diagnosis**
  – Early detection via self-examination and **mammography**, a type of X-ray examination
    • American Cancer Society recommends screening every year for women age 40 and over
    • U.S. Prevention Services Task Force on Breast Cancer Screening recommends delaying mammography until age 50
    • Diagnostic MRIs recommended for high-risk women
Figure 27.19 Mammograms.

(a) Mammogram procedure

(b) Film of normal breast

(c) Film of breast with tumor
Breast Cancer (cont.)

• Treatment
  – Depends upon characteristics of lesion
    • Radiation, chemotherapy, or surgery often followed by radiation or chemotherapy to destroy stray cells
    • Drugs for estrogen-responsive cancers
      – Trastuzumab (Herceptin): for aggressive cancer cells
      – Tamoxifen: improves outcome for premenopausal women with early- or late-stage cancer
      – Letrozole (Femara): reduces recurrence
Breast Cancer (cont.)

- **Treatment (cont.)**
  - Until 1970s, standard treatment was **radical mastectomy** that removes breast, with all underlying muscles, fascia, and associated lymph nodes
  - **Lumpectomy**: less invasive and excises only cancerous lump
  - **Simple mastectomy**: removes only breast tissue, sometimes some axillary lymph nodes
  - Some women opt for breast reconstruction
• Always assumed that females’ total supply of eggs was determined at birth
• New evidence suggests stem cells can arise from epithelial cells at ovary surface
• May overturn previous assumption
27.12 Oogenesis

- **Oogenesis**: production of female gametes takes years to complete

- Begins in fetal period
  - **Oogonia** (2n ovarian stem cells) multiply by mitosis and store nutrients
  - **Primary oocytes** develop in primordial follicles that become surrounded by *follicle cells*
  - Primary oocytes begin meiosis but stall in prophase I
  - At birth, female presumed to have lifetime supply of primary oocytes
Oogenesis After Puberty

• Each month after puberty, a few primary oocytes are activated
• One from this group is “selected” each month to become dominant follicle that resumes meiosis I
• After division of meiosis I is completed, two haploid cells of different sizes are produced:
  – **Secondary oocyte**: large cell with almost all of mother cell cytoplasm and organelles
  – **First polar body**: small cell almost devoid of cytoplasm
Oogenesis After Puberty (cont.)

- Secondary oocyte arrests in metaphase II and becomes the ovulated ovum
- If not penetrated by sperm, it deteriorates
- If penetrated by sperm, second oocyte completes meiosis II, yielding:
  - **Ovum** (*functional gamete*)
  - Second polar body
Figure 27.20 Events of oogenesis.

<table>
<thead>
<tr>
<th>Meiotic events</th>
<th>Follicle development in ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before birth</strong></td>
<td></td>
</tr>
<tr>
<td>Mitosis</td>
<td>Oogonium (stem cell)</td>
</tr>
<tr>
<td>2n</td>
<td>Primary oocyte</td>
</tr>
<tr>
<td>2n</td>
<td>Primordial follicle</td>
</tr>
<tr>
<td><strong>Infancy and childhood</strong></td>
<td></td>
</tr>
<tr>
<td>Primary oocyte (arrested in prophase I; present at birth)</td>
<td>Follicle cells</td>
</tr>
<tr>
<td>Primordial follicle</td>
<td>Oocyte</td>
</tr>
<tr>
<td><strong>Each month from puberty to menopause</strong></td>
<td></td>
</tr>
<tr>
<td>Primary oocyte (still arrested in prophase I)</td>
<td>Meiosis I (completed by one primary oocyte each month in response to LH surge)</td>
</tr>
<tr>
<td>Primordial follicle</td>
<td>First polar body</td>
</tr>
<tr>
<td>Secondary follicle</td>
<td>Secondary oocyte (arrested in metaphase II)</td>
</tr>
<tr>
<td>Vesicular (antral) follicle</td>
<td>Ovulation</td>
</tr>
<tr>
<td>Spindle</td>
<td>Ovulation</td>
</tr>
<tr>
<td>Ovulated secondary oocyte</td>
<td>Ovulated secondary oocyte</td>
</tr>
<tr>
<td>Polar bodies (all polar bodies degenerate)</td>
<td>Meiosis II completed (only if sperm penetrates oocyte)</td>
</tr>
<tr>
<td>2n</td>
<td>Ruptured follicle</td>
</tr>
<tr>
<td>2n</td>
<td>Degenerating corpus luteum</td>
</tr>
</tbody>
</table>

2n → 2n → 2n → 2n → 2n → 2n → 2n → 2n → 2n

Meiosis II (completed only if sperm penetrates oocyte)
Comparison of Oogenesis and Spermatogenesis

• Number of functional gametes differ
  – Oogenesis produces one viable ovum with three polar bodies
    • Unequal divisions ensure oocyte has ample nutrients for 6- to 7-day journey to uterus
    • Polar bodies degenerate and die
  – Spermatogenesis produces four viable sperm

• Error rates differ
  – Spermatogenesis has an error rate of 3–4%
  – Oogenesis has an error rate of 20%
27.13 The Ovarian Cycle

- **Ovarian cycle**: monthly (~28 day) series of events associated with maturation of egg
  - Two consecutive phases, with **ovulation** occurring midcycle between phases
  - **Follicular phase**: period of vesicular follicle growth (days 1–14)
  - **Luteal phase**: period of corpus luteum activity (days 14–28)

- Only 10–15% women have 28-day cycle
  - Follicular phase varies, but luteal phase is always 14 days from ovulation to end of cycle
Stages of Follicle Development

- A primordial follicle becomes primary follicle
  1. Squamouslike cells surrounding primary oocyte become cuboidal, and oocyte enlarges
     • Process can take about one year
  2. Follicle is now called primary (1°) follicle
Figure 27.21 Schematic and microscopic views of the ovarian cycle: development and fate of ovarian follicles.

1. Primordial follicles

2. Primary follicle

3. Secondary follicle

4a. Early vesicular follicle

4b. Mature vesicular follicle carries out meiosis I; ready to be ovulated

5. Follicle ruptures; secondary oocyte ovulated

6. Corpus luteum (forms from ruptured follicle)

7. Secondary oocyte; forming antrum

Theca folliculi

Primary oocyte

Zona pellucida

Antrum

Secondary oocyte

Corona radiata

Zona pellucida

Antrum
• Primary follicle becomes secondary follicle

3. Follicular cells proliferate, forming stratified epithelium around oocyte
   • When more than one layer of cells are present:
     – Follicular cells now called *granulosa cells*
     – Primary follicle called **secondary follicle**
     – Granulosa cells and oocyte guide one another’s development via gap junction connections
Stages of Follicle Development (cont.)

• Secondary follicle becomes vesicular follicle
  – Connective tissue and granulosa cells condense to form theca folliculi
  – Zona pellucida: thick, glycoprotein-rich membrane secreted by oocyte, encapsulating it

4a. Early vesicular follicle formed when clear fluid begins to accumulate between granulosa cells

4b. Antrum: large cavity is formed when fluid coalesces

• Distinguishes vesicular follicle from previous follicles (pre-antral vs. antral)
Stages of Follicle Development (cont.)

• **Secondary follicle becomes vesicular follicle (cont.)**
  – Antrum continues to expand with fluid isolating oocyte
    • Isolated oocyte with its surrounding granulosa cells called **corona radiata**
    – Corona radiata sits on stalk on one side of follicle
    – When follicle is full size (2.5 cm or 1 inch), it bulges from external ovary surface
  – It is ready to be ovulated
Follicular Phase of the Ovarian Cycle

• During follicular phase, several vesicular (antral) follicles are stimulated to grow
  – Triggered by rising levels of FSH
• FSH levels drop around middle of follicular phase
  – Causes only one antral follicle, *dominant follicle*, to be selected to continue on
  – How dominant follicle is chosen is still uncertain
Follicular Phase of the Ovarian Cycle (cont.)

- Primary oocyte of dominant follicle completes meiosis I to form 2° oocyte and polar body
- Granulosa cells then send signal to oocyte, causing it to stop at metaphase II
Figure 27.20 Events of oogenesis.

**Meiotic events**

**Before birth**
- **Mitosis**
  - Oogonium (stem cell)
  - Primary oocyte

**Infancy and childhood**
- Ovary functionally inactive
  - Primary oocyte (arrested in prophase I; present at birth)

**Each month from puberty to menopause**
- Meiosis I (completed by one primary oocyte each month in response to LH surge)
  - First polar body
  - Secondary oocyte (arrested in metaphase II)

- Meiosis II of polar body (may or may not occur)
- Polar bodies (all polar bodies degenerate)
- Meiosis II completed (only if sperm penetrates oocyte)
  - Ovulated secondary oocyte
  - Ruptured follicle becomes a corpus luteum and ultimately degenerates.

**Follicle development in ovary**

- Follicle cells
- Oocyte
- Primordial follicle
- Primary follicle
- Secondary follicle
- Vesicular (antral) follicle
- Degenerating corpus luteum
Ovulation

- Rising levels of LH cause ovary wall to rupture, expelling secondary oocyte with its corona radiata to peritoneal cavity
- *Mittelschmerz*: twinge of pain sometimes felt at ovulation by some women
- 1–2% of ovulations release more than one secondary oocyte, which, if fertilized, result in fraternal twins
- Identical twins result from fertilization of one oocyte, then separation of daughter cells
Luteal Phase of the Ovarian Cycle

• After ovulation, ruptured follicle collapses, and antrum fills with clotted blood
  – Referred to as corpus hemorrhagicum; will eventually be absorbed
• Remaining granulosa cells and internal thecal cells enlarge to form corpus luteum
• Corpus luteum secretes progesterone and some estrogen
Luteal Phase of the Ovarian Cycle (cont.)

• If no pregnancy occurs, corpus luteum degenerates into **corpus albicans** (scar) in 10 days
  – *Luteolytic* or *ischemic phase*: last 2–3 days of luteal phase, when endometrium begins to erode

• If pregnancy occurs, corpus luteum produces hormones that sustain pregnancy until placenta takes over, at about 3 months
27.14 Regulation of Female Reproductive System

Hormonal Regulation of Ovarian Cycle

• Establishing the ovarian cycle
  – Before puberty, ovaries secrete small amounts of estrogen, inhibiting hypothalamic release of GnRH
  – As puberty nears, if leptin levels are adequate, hypothalamus becomes less estrogen-sensitive, so GnRH is released, stimulating FSH and LH release by pituitary that then acts on ovaries
  – Events continue until an adult cyclic pattern is achieved and menarche occurs

© 2016 Pearson Education, Inc.
Hormonal interaction during ovarian cycle

1. GnRH stimulates FSH and LH secretion
2. FSH and LH stimulate follicles to grow, mature, and secrete sex hormones
   - FSH stimulates granulosa cells to release estrogen, and LH prods thecal cells to produce androgens, which granulosa converts to estrogens
Figure 27.22 Regulation of the ovarian cycle.

1. Hypothalamus
2. GnRH
3. Travels via portal blood
4. Positive feedback exerted by large↑ in estrogen output by maturing follicle.
5. LH surge
6. Corpus luteum
7. Stimulation inhibits

Early and midfollicular phases

1. Slightly elevated estrogen and rising inhibin levels inhibit FSH secretion.
2. Convert androgens to estrogens
3. Estrogens

Late follicular and luteal phases

1. Ruptured follicle
2. Mature vesicular follicle
3. Ovulated secondary oocyte
4. Inhibin
5. Estrogens
6. Progesterone
7. Slightly elevated estrogen and rising inhibin levels inhibit FSH secretion.
3. **Negative feedback inhibits gonadotropin release**
   - Increasing levels of plasma estrogen levels exert negative feedback inhibition on FSH and LH release
   - *Inhibin* from granulosa cells also inhibits FSH release
   - Only dominant follicle can withstand this dip in FSH
     - Other developing follicles deteriorate
4. **Positive feedback stimulates gonadotropin release**
   
   • Estrogen levels continue to rise as a result of continued release by dominant follicle
   
   • When levels reach a critical high value, a brief positive feedback occurs on brain and anterior pituitary
   
   • Triggers LH surge
5. **LH surge triggers ovulation and formation of the corpus luteum**

   - High estrogen levels trigger release of stored LH, and some FSH, by anterior pituitary at midcycle
   - Surge triggers ovulation
     - LH surge triggers primary oocyte to complete meiosis I to become secondary oocyte
     - Secondary oocyte then enters meiosis II, continuing on to metaphase II
5. **LH surge triggers ovulation and formation of the corpus luteum (cont.)**

- LH also stimulates other events that lead to ovulation:
  - Increases local vascular permeability
  - Triggers inflammatory response that promotes release of metalloproteinase enzymes that weaken ovarian wall
    - Stops blood flow to protruding follicle wall, causing wall to thin, bulge, and rupture, forming a hole
    - Oocyte with corona radiata exits, accomplishing ovulation
5. LH surge triggers ovulation and formation of the corpus luteum (cont.)

- Shortly after ovulation:
  - Estrogen levels decline
  - LH transforms ruptured follicle into corpus luteum
  - LH stimulates corpus luteum to secrete progesterone and some estrogen almost immediately
    » Progesterone helps maintain stratum functionalis
    » Maintains pregnancy, if it occurs
6. **Negative feedback inhibits LH and FSH release**
   - Negative feedback from rising plasma progesterone and estrogen levels inhibits LH and FSH release
     - Inhibin, from corpus luteum and granulosa cells, enhances inhibitory effect
     - Declining LH ends luteal activity and inhibits follicle development
Hormonal Regulation of Ovarian Cycle (cont.)

– If no fertilization occurs:
  • Corpus luteum degenerates when LH levels start to fall
  • Causes a sharp decrease in estrogen and progesterone, which in turn ends blockage of FSH and LH secretion, causing cycle to start all over again

– Oocyte is actually activated 12 months prior to ovulation but matures 14 days before ovulation
The Uterine (Menstrual) Cycle

• **Uterine (menstrual) cycle**: cyclic series of changes in endometrium that occur in response to fluctuating ovarian hormone levels

• Three phases:
  1. **Days 1–5**: menstrual phase
  2. **Days 6–14**: proliferative (preovulatory) phase
  3. **Days 15–28**: secretory (postovulatory) phase
1. **Days 1–5: menstrual phase**
   - Ovarian hormones are at lowest levels
   - Gonadotropin levels are beginning to rise
   - Stratum functionalis detaches from uterine wall and is shed
     - Menstrual flow of blood and tissue lasts 3–5 days
   - By day 5, growing ovarian follicles start to produce more estrogen
2. **Days 6–14: proliferative (preovulatory) phase**

   - Rising estrogen levels prompt generation of new stratum functionalis layer
     - As layer thickens, glands enlarge, and spiral arteries increase in number
   - Estrogen also increases synthesis of progesterone receptors in endometrium
   - Thins out normally thick, sticky cervical mucus to facilitate sperm passage
   - Ovulation occurs at end of proliferative phase on day 14
3. **Days 15–28: secretory (postovulatory) phase**
   - Phase that is most consistent in duration
   - Endometrium prepares for embryo to implant
   - Rising progesterone levels from corpus luteum prompt:
     - Functional layer to become a secretory mucosa
     - Endometrial glands to enlarge and secrete nutrients into uterine cavity
     - Thickened mucus to form cervical mucus plug that blocks entry of more sperm, pathogens, or debris
3. **Days 15–28: secretory (postovulatory) phase (cont.)**

   • If fertilization does not occur:
     - Corpus luteum degenerates toward end of secretory phase; progesterone levels fall
     - Causes spiral arteries to kink and spasm
     - Endometrial cells die, and glands regress
     - Spiral arteries constrict again, then relax and open wide, causing a rush of blood into weakened capillary beds
     - Blood vessels fragment, and functional layer sloughs off

   • Uterine cycle starts all over again on first day of menstruation
(a) Fluctuation of gonadotropin levels: Fluctuating levels of pituitary gonadotropins (follicle-stimulating hormone and luteinizing hormone) in the blood regulate the events of the ovarian cycle.
(b) Ovarian cycle: Structural changes in vesicular ovarian follicles and the corpus luteum are correlated with changes in the endometrium of the uterus during the uterine cycle (d). Recall that only vesicular follicles (in their antral phase) are hormone dependent—primary and secondary follicles are not.
(c) Fluctuation of ovarian hormone levels: Fluctuating levels of ovarian hormones (estrogens and progesterone) cause the endometrial changes of the uterine cycle. The high estrogen levels are also responsible for the LH/FSH surge in (a).
(d) The three phases of the uterine cycle:
- Menstrual: The functional layer of the endometrium is shed.
- Proliferative: The functional layer of the endometrium is rebuilt.
- Secretory: Begins immediately after ovulation. Enrichment of the blood supply and glandular secretion of nutrients prepare the endometrium to receive an embryo.

Both the menstrual and proliferative phases occur before ovulation, and together they correspond to the follicular phase of the ovarian cycle. The secretory phase corresponds in time to the luteal phase of the ovarian cycle.
Figure 27.23 Correlation of anterior pituitary and ovarian hormones with structural changes of the ovary and uterus.

(a) Fluctuation of gonadotropin levels:
Fluctuating levels of pituitary gonadotropins (follicle-stimulating hormone and luteinizing hormone) in the blood regulate the events of the ovarian cycle.

(b) Ovarian cycle: Structural changes in vesicular ovarian follicles and the corpus luteum are correlated with changes in the endometrium of the uterus during the uterine cycle (d). Recall that only vesicular follicles (in their antral phase) are hormone dependent—primary and secondary follicles are not.

(c) Fluctuation of ovarian hormone levels:
Fluctuating levels of ovarian hormones (estrogens and progesterone) cause the endometrial changes of the uterine cycle. The high estrogen levels are also responsible for the LH/FSH surge in (a).

(d) The three phases of the uterine cycle:
- Menstrual: The functional layer of the endometrium is shed.
- Proliferative: The functional layer of the endometrium is rebuilt.
- Secretory: Begins immediately after ovulation. Enrichment of the blood supply and glandular secretion of nutrients prepare the endometrium to receive an embryo.

Both the menstrual and proliferative phases occur before ovulation, and together they correspond to the follicular phase of the ovarian cycle. The secretory phase corresponds in time to the luteal phase of the ovarian cycle.
Clinical – Homeostatic Imbalance 27.8

• Extremely strenuous physical activity can delay menarche in girls and disrupt normal menstrual cycle in adult women
  – Can cause amenorrhea, cessation of menstruation

Female Athletic Triad
  – Amenorrhea, disordered eating, osteoporosis
  – Figure skating, gymnastics, distance running, ballet…
  – Good site: [ACSM Female Athletic Triad](https://www.acsm.org/)
Clinical – Homeostatic Imbalance 27.8

- Female athletes have little body fat; adipose cells are needed to convert adrenal androgens to estrogens
  - Also, leptin plays role in female puberty
  - Leptin informs hypothalamus if energy stores are sufficient to support reproduction
  - If they are not, reproductive cycles are shut down
- Can also lead to osteoporosis
Effects of Estrogens and Progesterones

• Estrogens:
  – Promote oogenesis and follicle growth in ovary
  – Exert anabolic effect on female reproductive tract
  – Support rapid short-lived growth spurts at puberty
  – Induce secondary sex characteristics
    • Growth of breasts
    • Increased deposit of subcutaneous fat (hips and breasts)
    • Widening and lightening of pelvis
Effects of Estrogens and Progesterones (cont.)

– Estrogen also has metabolic effects:
  • Maintains low total blood cholesterol and high HDL levels
  • Facilitates calcium uptake
Effects of Estrogens and Progesterones (cont.)

• Progesterone works with estrogen to establish and regulate uterine cycle
  – Promotes changes in cervical mucus
  – Effects of placental progesterone during pregnancy
    • Inhibits uterine motility
    • Helps prepare breasts for lactation
<table>
<thead>
<tr>
<th>Source, Stimulus, Effects</th>
<th>Estrogens (Mostly Estradiol)</th>
<th>Progesterone</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus for release</td>
<td>FSH (and LH).</td>
<td>LH.</td>
<td>LH and declining levels of inhibin produced by the sustentocytes.</td>
</tr>
<tr>
<td>Feedback effects exerted</td>
<td>Both negative and positive feedback exerted on anterior pituitary release of gonadotropins.</td>
<td>Negative feedback exerted on anterior pituitary release of gonadotropins.</td>
<td>Negative feedback suppresses release of LH by the anterior pituitary and release of GnRH by the hypothalamus.</td>
</tr>
<tr>
<td>Effects on reproductive organs</td>
<td>Stimulate growth and maturation of reproductive organs and breasts at puberty and maintain their adult size and function. Promote the proliferative phase of the uterine cycle. Stimulate production of watery cervical mucus and activity of fimbriae and uterine tube cilia. Promote oogenesis and ovulation by stimulating formation of FSH and LH receptors on follicle cells. Stimulate capacitation of sperm in the female reproductive tract. During pregnancy stimulate growth of the uterus and enlargement of the external genitalia and mammary glands.</td>
<td>Cooperates with estrogens in stimulating growth of breasts. Promotes the secretory phase of the uterine cycle. Stimulates production of viscous cervical mucus. Progesterone surge after ovulation enhances beating of cilia in the uterine tube, promoting meeting of sperm and oocyte. During pregnancy, quiets the myometrium and acts with estrogen to cause mammary glands to achieve their mature milk-producing state.</td>
<td>Stimulates formation of male reproductive ducts, glands, and external genitalia. Promotes descent of the testes. Stimulates growth and maturation of the internal and external genitalia at puberty; maintains their adult size and function. Required for normal spermatogenesis via effects promoted by ABP, which keeps its concentration high near spermatogenic cells. Suppresses mammary gland development.</td>
</tr>
</tbody>
</table>
Table 27.1-2 Summary of Hormonal Effects of Gonadal Estrogens, Progesterone, and Testosterone (continued)

<table>
<thead>
<tr>
<th>SOURCE, STIMULUS, EFFECTS</th>
<th>ESTROGENS (MOSTLY ESTRADIOL)</th>
<th>PROGESTERONE</th>
<th>TESTOSTERONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion of secondary sex characteristics and somatic effects</td>
<td>Promote long bone growth and feminization of the skeleton (particularly the pelvis); inhibit bone reabsorption and then stimulate epiphyseal closure. Promote hydration of the skin and female pattern of fat deposit. During pregnancy act with relaxin (a placental hormone) to induce softening and relaxation of the pelvic ligaments and pubic symphysis.</td>
<td></td>
<td>Stimulates the growth spurt at puberty; promotes increased skeletal and muscle mass during adolescence. Promotes growth of the larynx and vocal cords and deepening of the voice. Enhances sebum secretion and hair growth, especially on the face, axillae, genital region, and chest.</td>
</tr>
<tr>
<td>Neural effects</td>
<td>Along with DHEA (an androgen produced by the adrenal cortex) are partially responsible for female libido (sex drive).</td>
<td></td>
<td>Responsible for libido in males; promotes aggressiveness.</td>
</tr>
</tbody>
</table>
27.15 Female Sexual Response

- Initiated by touch and psychological stimuli
- Clitoris, vaginal mucosa, bulbs of vestibule, and breasts engorge with blood; nipples become erect
- Vestibular gland secretions lubricate vestibule
- Orgasm is accompanied by muscle tension, increase in pulse rate and blood pressure, and rhythmic contractions of uterus
• Females have no refractory period after orgasm and can experience multiple orgasms in single sexual experience

• Orgasm is not essential for conception

• Female libido is prompted by dehydroepiandrosterone (DHEA), an androgen produced by adrenal cortex
Sildenafil ("Viagra")
- For erectile dysfunction. Does not directly affect desire.

Flibanserin ("Addyi", "female Viagra")
- For hypoactive sexual desire disorder (HSDD).
- Rejected due to hypotension, esp w/EtOH
- Drug enhances desire (originally studied as antidepressant)
- Use daily; 4 weeks before effect, peak 8 weeks
- 0.5-1 more SSE/month than placebo


*satisfying sexual events
STIs are also called sexually transmitted diseases (STDs) or venereal diseases (VDs)

U.S. has highest rates of infection among developed countries

Latex condoms help prevent spread

STIs are single most important cause of reproductive disorders
Gonorrhea

- Bacterial infection of mucosae of reproductive and urinary tracts
  - Caused by *Neisseria gonorrhoeae*
  - Commonly called “the clap”
- Spread by contact with genital, anal, and pharyngeal mucosae
- Treatment: antibiotics, but resistant strains are becoming prevalent
- Number of cases in U.S. declining because of availability of antibiotics
Gonorrhea (cont.)

• Signs and symptoms
  – Males
    • Urethritis, painful urination, discharge of pus
  – Females
    • Majority of females display no signs or symptoms
    • Abdominal discomfort, vaginal discharge, or abnormal uterine bleeding
    • Can result in pelvic inflammatory disease and sterility
Syphilis

• Bacterial infection transmitted sexually or congenitally
  – Caused by *Treponema pallidum*
  – Infected fetuses can be stillborn or die shortly after birth
• Bacteria invades mucosae or even broken skin
• Infection is asymptomatic for 2–3 weeks and then painless *chancre* appears at site of infection
  – Disappears within a few weeks
Syphilis (cont.)

- If untreated, secondary signs appear several weeks later
  - Pink skin rash, fever, and joint pain can develop
  - Appear for 3–12 weeks, then disappear
- Disease can enter *latent period*, which may or may not progress to *tertiary syphilis*
- Tertiary syphilis is characterized by *gummas*, lesions that develop in CNS, blood vessels, bones, and skin
- Treatment: penicillin
- Number of cases is increasing
Chlamydia

- Most common bacterial STI in United States
  - Caused by *Chlamydia trachomatis*
  - Can be contracted from birth canal by newborns
- Responsible for 25–50% of all diagnosed cases of pelvic inflammatory disease
- Symptoms: urethritis; penile and vaginal discharges; abdominal, rectal, or testicular pain; painful intercourse; irregular menses
  - 80% of women have no symptoms
  - Left untreated, can lead to sterility

© 2016 Pearson Education, Inc.
Chlamydia (cont.)

• Can also cause arthritis and urinary tract infections in men
• Newborns picking bacteria up from birth canal can develop:
  – Trachoma, a painful eye infection that can lead to corneal scarring
  – Respiratory tract inflammations, including pneumonia
• Treatment: tetracycline
Trichomononiasis

• Most common curable STI in active young women in U.S.
  – 7.4 million new cases each year
• Protozoan infection; easily, inexpensively treated
• Symptoms: yellow-green vaginal discharge with strong odor; however, some patients can be symptomless
Genital Warts

• Caused by human papillomavirus (HPV)
• Second most common STI in United States
  – About 6.2 million new cases each year
• 80% of cases of invasive cervical cancer are linked to some strains of HPV
  – Most strains do not cause cancer
• Treatment: difficult and controversial; some physicians prefer to leave warts alone, and some prefer to remove with cryosurgery, laser, or alpha-interferon treatments
Genital Herpes

• Caused by herpes simplex virus 2
  – Possibly one-fourth to one-half of American adults carry this virus
  – Only 15% display signs of infection
• Characterized by latent periods and flare-ups with vesicle formation
• Can be passed on to fetus
  – Congenital herpes can cause malformations
• Treatment: acyclovir and other antiviral drugs
Embryological and Fetal Events

• Determination of genetic sex
  – Of 46 chromosomes in fertilized egg, two are sex chromosomes (other 44 are autosomes)
    • X chromosome (large)
    • Y chromosome (quite small)
  – Females are XX: each ovum always has an X chromosome
  – Males are XY: so ~50% of sperm contain X chromosome, and ~50% contain Y chromosome
Determination of genetic sex (cont.)

- If fertilizing sperm delivers an X chromosome, fertilized egg will contain XX, and embryo will develop ovaries
  - X egg + X sperm $\rightarrow$ XX (female offspring)

- If fertilizing sperm delivers a Y chromosome, fertilized egg will contain XY, and embryo will develop testes
  - X egg + Y sperm $\rightarrow$ XY (male offspring)

- \textit{SRY} gene is master switch on Y chromosome that initiates testes development and maleness
  - So, father determines sex of child
• **Nondisjunction**: abnormal distribution of sex chromosomes to gametes that can cause abnormalities in sexual and reproductive system development

• *Turner’s syndrome*: females with only a single X chromosome (XO) never develop ovaries
• Females with four or more X chromosomes: intellectually disabled; have underdeveloped ovaries with limited fertility

• *Klinefelter’s syndrome*: males with single Y chromosome and two or more X chromosomes; are sterile and are normal or only slightly below normal intellectually
Developmental Aspects of Reproductive System

• Sexual differentiation of reproductive system
  – Sexually indifferent stage: embryo could develop into male or female
    • Paramesonephric (Müllerian) ducts (future female ducts) form lateral to mesonephric (Wolffian) ducts (future male ducts)
  – Gonads begin development in week 5 as gonadal ridges
Developmental Aspects of Reproductive System

• Sexual differentiation of reproductive system (cont.)
  – Primordial germ cells migrate to gonadal ridges to provide germ cells destined to become spermatogonia or oogonia
  – Testes formation begins in week 7 for males; female ovaries start to develop in week 8
Figure 27.24-1 Development of the internal reproductive organs.

- **Mesonephros**
- **Gonadal ridge**
- **Metanephros (kidney)**
- **Mesonephric (Wolffian) duct**
- **Paramesonephric (Müllerian) duct**
- **Cloaca**

5- to 6-week embryo: sexually indifferent stage

© 2016 Pearson Education, Inc.
Figure 27.24-2 Development of the internal reproductive organs.

- Testes
- Efferent ductules
- Epididymis
- Paramesonephric duct (degenerating)
- Mesonephric duct forming the ductus deferens
- Urinary bladder
- Seminal gland
- Urogenital sinus forming the urethra

7- to 8-week male
Figure 27.24-3 Development of the internal reproductive organs.

- **Ovaries**
- **Paramesonephric duct forming the uterine tube**
- **Mesonephric duct (degenerating)**
- **Fused paramesonephric ducts forming the uterus**
- **Urinary bladder (moved aside)**
- **Urogenital sinus forming the urethra and lower vagina**

8- to 9-week female
Figure 27.24-4 Development of the internal reproductive organs.

At birth: male development

- Urinary bladder
- Seminal gland
- Prostate
- Bulbo-urethral gland
- Ductus deferens
- Urethra
- Efferent ductules
- Epididymis
- Testis
- Penis

© 2016 Pearson Education, Inc.
Figure 27.24-5 Development of the internal reproductive organs.

At birth: Female development
Sexual differentiation of reproductive system (cont.)

- External genitalia start to form in week 8
  - **Genital tubercle** becomes penis of male or clitoris of female
  - **Urethral fold** forms spongy urethra of male or labia minora of female
  - **Labioscrotal swellings** form scrotum of male or labia majora of female
  - If testosterone is absent, all embryos develop into females
Figure 27.25 Development of homologous structures of the external genitalia in both sexes.

(a) Sexually indifferent stage

Approximately 5 weeks

(b) Male development

(c) Female development

- Glans penis
- Labioscrotal swellings (scrotum)
- Anus
- Penis
- Scrotum

- Glans clitoris
- Labioscrotal swellings (labia majora)
- Anus
- Labia majora
- Labia minora

- Urogenital sinus
- Urethral folds (labia minora)
• *Pseudohermaphrodites*: individuals with external genitalia that do not “match” their gonads
• Caused by interferences of normal sex hormone production in embryo
  – If embryonic testes do not produce testosterone, a genetic male develops female accessory structures and external genitalia
– If genetic female is exposed to testosterone, embryo has ovaries but develops male ducts, glands, as well as a penis and an empty scrotum

• Many seek sex-change operations to match outer self (external genitalia) with inner self (gonads)
Descent of gonads

- About 2 months before birth, testosterone stimulates migration of testes toward scrotum
- Migration is mechanically guided by fibrous cord called **gubernaculum** from each testis to scrotum
- Ovaries also descend, but stopped by broad ligament at pelvic brim
Cryptorchidism: failure of testes to make their normal descent

Can cause sterility and increases risk of testicular cancer

Surgery is usually performed during early childhood to rectify this problem
Developmental Aspects of Reproductive System

Puberty

• FSH and LH are elevated at birth but drop and remain low during prepubertal years

• **Puberty**: period when reproductive organs grow to adult size and become functional

• Occurs in response to rising levels of gonadal hormones

• Secondary sex characteristics also appear

• Earliest time that reproduction is possible
Menopause

- Has occurred when menses have ceased for an entire year
- No equivalent to menopause in males
  - Males continue to produce sperm well into eighth decade of life, though numbers and motility decrease
Menopause (cont.)

• Declining estrogen levels cause:
  – Atrophy of reproductive organs and breasts
  – Irritability and depression in some
  – Hot flashes as skin blood vessels undergo intense vasodilation
  – Gradual thinning of skin and bone loss
  – Increased total blood cholesterol levels and falling HDL
Menopause (cont.)

- Treatment: estrogen-progesterone preparations has been given for years
  - Women’s Health Initiative research reported increased risk of heart disease (51%), invasive breast cancer (24%), and stroke (31%), and dementia risk doubled
  - Smallest doses for shortest time are allowable to reduce symptoms if no history of breast cancer and no presence of mutated BRCA gene