Histology Female
Reproductive System
Lecture Objectives

• Describe the histological features of the ovaries, uterine tube, uterus and vagina
• **Ovaries** produce 2nd oocytes & hormones
• **Uterine tubes** transport fertilized ova
• **Uterus** where fetal development occurs
• **Vagina & external genitalia** constitute the vulva
• **Mammary glands** produce milk
The Ovary: Anatomy

- Pair of organs, size of unshelled almonds found in upper pelvic region
- Regional histology
  - **tunica albuginea** is capsule of dense connective tissue
  - **cortex** is region just deep to tunica, containing ovarian follicles
  - **medulla** is deeper region composed of connective tissue, blood vessels & lymphatics
  - **germinal epithelium** is simple cuboidal epithelial covering over the ovary
  - **Ovarian follicles** lie in the cortex and consist of oocytes in various stages of development
Follicular Stages

- primordial
- primary
- secondary
- graafian
- ovulation

- **Corpus luteum** is an ovulation wound
  - fills in with hormone-secreting cells

- **Corpus albicans** is a white scar left after corpus luteum degenerates (when it is not needed.)
Oogenesis and Follicular Development

- *Oogenesis* occurs in the ovaries. It results in the formation of a single haploid secondary oocyte.
- The oogenesis sequence includes reduction division (meiosis I), equatorial division (meiosis II), and maturation.
- While oogenesis is occurring, the follicle cells surrounding the oocyte are also undergoing developmental changes. The sequence of follicular cell changes is: *primordial, primary, secondary, and mature (Graffian) follicles, and corpus luteum and corpus albicans.*
Life History of Oogonia

- Germ cells from yolk sac migrate to ovary & become oogonia
- As a fetus, oogonia divide to produce millions by mitosis but most degenerate (atresia)
- Some develop into primary oocytes & stop in prophase stage of meiosis I
  - 200,000 to 2 million present at birth
  - 40,000 remain at puberty but only 400 mature during a woman’s life
- Each month, hormones cause meiosis I to resume in several follicles so that meiosis II is reached by ovulation
- Penetration by the sperm causes the final stages of meiosis to occur
Primordial Follicles

- Structure – **primary oocyte** surrounded by a single layer of flattened follicular cells
- Location – just beneath the tunica albuginea
- **Primary oocyte** - ~25 μm diameter; arrested in prophase (diplotene) stage of meiosis I
  - Balbiani body – localized accumulation of Golgi, ER, mitochondria, lysosomes
  - Annulate lamellae – stacks of membranes with pores similar to nuclear envelop
Primary Follicles

- **Unilaminar** – primary oocyte (100-250 μm diameter) surrounded by a single layer of cuboidal follicular cells

- **Multilaminar** – more than one layer of cuboidal cells. The multilaminar follicular cells are called *granulosa cells* and form the *granulosa layer*
  - Granulosa cells/granulosa layer – *avascular*
  - Cells have FSH receptors
  - Convert androgens to estrogen

- Oocyte and cortical granules – contains multiple Golgi complexes and secretory vesicles known as *cortical granules*

- **The perivitelline space** – between the oocyte and granulosa cells

- **Zona pellucida** – acidophilic refractile layer in the perivitelline space
  - Secreted by the oocyte
  - Rich in glycosaminoglycans and glycoproteins
  - Microvilli from the oocyte and processes from the granulosa cells extend into the zona pellucida enabling contact between cells

- **Theca interna** – inner, highly vascular layer of cuboidal cells
  - Separated from the granulosa cells by basal lamina
  - Steroid producing cells; secrete androgens (estrogen precursors)
  - Have receptors for luteinizing hormone (LH)

- **Theca externa** – outer layer of CT cells, smooth muscle cells and bundles of collagen fibers
Secondary (Antral) Follicles

• Structure – appearance of fluid filled cavities
  – Cavities form antrum containing liquor folliculi
  – Size of the oocyte (~125 μm) does not change due to the presence of the peptide oocyte maturation inhibitor (OMI) secreted by the granulosa cells
  – Follicle increases in size starting at ~200 μm and reaching a size up to 10 mm in diameter prior to ovulation

• Antrum/ liquor folliculi – rich in hyaluronic acid
• Cumulus oophorus – thickened area of granulosa cells that contains the oocyte and projects into the antrum
• Corona radiata – cells of the cumulus oophorus immediately surrounding the oocyte and released with the oocyte at ovulation
• Call-Exner bodies– PAS positive material found among granulosa cells, function unknown
Graafian (Mature) Follicle

Structure – 10 mm diameter
- Thinner stratum granulosa
- Expansion of the antrum
- Prominent thecal layers
- Extends through the thickness of the cortex
Graafian (Mature) Follicle

Function

• *Hormonal activity*
  – LH stimulates the theca interna cells to secrete androgens
  – Androgens transported to granulosa cells where they converted to estrogen in response to FSH
  – Estrogen stimulate granulosa cell proliferation causing follicle to increase in size
  – 24 hours prior to ovulation, estrogen influence the release of a surge of LH and FSH from the adenohypophysis
  – The LH surge induce the completion of the first meiotic division prior to ovulation. This produces the secondary oocyte and the first polar body
  – LH also induces ovulation
Ovulation

• The factors responsible for ovulation include:
  – Follicular fluid pressure
  – Proteolysis
  – Decreased blood flow – area pellucida or stigma
  – Deposition of GAG
  – Smooth muscle contraction
Fertilization

- Normally occurs in the ampulla of the oviduct. After fertilization, the second meiotic division is completed forming the mature ovum and the second polar body.

- Steps of fertilization
  - **Capacitation** – occurs after spermatozoon penetrate the corona radiata; involves the removal of the glycosides on the surface of the sperm allowing the sperm to bind to zona pellucida receptors.
  - Sperm to bind to zona pellucida receptors – triggers the **acrosome reaction**.
  - The acrosome reaction- the release of enzymes from the acrosome; degradation of the zona pellucida.
  - Entrance of the sperm into the oocyte – triggers three post-fusion reaction:
    - **Fast block to polyspermy** – depolarization of the oolemma.
    - **Cortical reaction** – release of calcium from ooplasmic stores and fusion of the cortical granules (containing proteases) with the oolemma.
    - **Zona reaction** – proteases of the cortical granules degrade the sperm binding receptors in the zona pellucida and form the perivitelline barrier.
Corpus Luteum

**Function** – to produce and release hormones that prepare the lining of the uterus for implantation of the embryo

**Structure**

- **Corpus hemorrhagicus** – bleeding from the capillaries of the theca interna into the follicular lumen forms a central clot
- **Granulosa lutein cells** – formerly the granulosa cells, centrally located, ~30 μm in diameter, secrete progesterone, convert androgens (secreted from the theca lutein cell) into estrogens
- **Theca lutein cells** – formerly the theca interna cells, peripherally located, smaller in size (~15 μm), secrete progesterone, some estrogen, and androgens
- **Corpus luteum of pregnancy** – maintained by paracrine secretions known as luteotropins produced by the ovary (estrogens and insulin-like growth factors I and II (IGF I & IGF II))
  - Also maintained by endocrine luteotropins secreted by other glands such as human chorionic gonadotropin (hCG) (secreted by the trophoblasts of the chorion), luteinizing hormone (LH) and prolactin (secreted by the pituitary gland) and insulin (produced by the pancreas)
  - Persists throughout pregnancy but its functions are taken over by the placenta by 8th week of pregnancy
- **Corpus luteum of menstruation** – remains active for 14 days; it’s degeneration forms the corpus albicans
Corpus Albicans
- Structure – fibrous CT; slowly disappears after several months

Atretic Follicles
- A follicle in any stage of maturation may undergo atresia
- Interstitial glands of the ovary – in some mammals (non-human) the lutein cells of atretic follicles do not degenerate immediately but form the interstitial glands of the ovary. These glands produce steroid hormones
- In humans, interstitial cells occur in large numbers in the first year of life and in the phases of puberty. It has suggested that these cells influence growth and development of the secondary sex organs during early puberty.
- Ovarian hilar cells – found in the hilum. They contain Reinke crystalloids and may secrete androgens. Tumors associated with these cells cause masculinization
Oviducts

Function – to transmit the ova from the ovaries to the uterus; to provide a suitable environment for fertilization and initial development of the conceptus to the morula stage

Structure – paired structures extending from the uterus to the ovaries; also known as the uterine or fallopian tubes; approximately 12 cm long; consists of four regions

• Regions
  – **Infundibulum** – funnel-shaped region adjacent to the ovary. The end of the infundibulum has fringed extensions known as fimbriae
  – **Ampulla** – longest segment of the oviduct where fertilization normally occurs
  – **Isthmus** – narrowest portion
  – **Uterine/intramural region** – segment opens into the uterine cavity
Layers of the walls of the oviduct

**Mucosa** with mucosal folds – folds which project into the lumen of the oviducts and are most pronounced in the ampulla

- Epithelium – **simple columnar** with two types of cells
  - **Peg cells** – non-ciliated; secretory; secretion facilitates capacitation of spermatozoa, provides nutrition for the ovum and early embryo, and inhibits movement of microorganisms to the oviducts and peritoneal cavity
  - **Ciliated cells** – beat toward the uterus thereby propelling the ovum toward the uterus
- The epithelium undergoes cyclic change in response to hormones; estrogen stimulates ciliogenesis and progesterone increases the number of secretory cells
- Lamina propria – loose CT

**Muscularis** – **inner thick circular layer and longitudinal layer**

- During ovulation, the contraction of the muscularis causes constriction of engorged veins. This leads to distention of the oviduct and a “bending” of the infundibulum toward the ovary. The fimbriae contact the ovary and captures the released secondary oocyte (and it’s surrounding cumulus)

**Serosa** – mesothelium and thin layer of CT
Uterus

Function – receives the morula from the oviduct and provides the environment for fetal development

Structure – hollow pear-shaped organ; consists of three regions:

- **Regions of the uterus**
  - Body – large upper portion
  - Fundus – upper, rounded part lying above the attachment of the oviduct
  - Cervix – lower, barrel-shaped portion
Layers of the uterine wall

- **Endometrium** – mucosa of the uterus lined by *simple columnar epithelium* containing secretory and ciliated cells; undergoes cyclic changes during the menstrual cycle to prepare it for the implantation of the fetus. It consists of:
  - **Stratum functionalis** – thick part of the endometrium sloughed off during menstruation
  - **Stratum basale** – part which is retained during menstruation and serves as a source of regeneration of the functionalis
  - **Lamina propria** – contains simple branched tubular glands
- **Myometrium** – thickest layer of uterine wall. It consists of three muscle layers: an \textit{inner and outer longitudinal} layers oriented parallel to the long axis of the uterus and \textit{middle circular} layer which is highly vascularized. This layer is known as the stratum vasculare
  - Blood supply – paired uterine arteries branch into 6-10 arcuate arteries in the stratum vasculares. The arcuate arteries give rise to two sets of arteries: straight arteries to the stratum basale and coiled arteries to the stratum functionalis
- **Perimetrium** – covers the posterior surface of the uterus and part of the anterior surface; remaining is covered by adventitia
Cervix

Function – secretory

Gross Structure – terminal end of the uterus

• **Internal os** – communicates with the uterine cavity

• **External os** – communicates with the vagina

• **Portio vaginalis** – protrusion into the vagina, lined by *stratified squamous epithelium*

• **Fornix** – extension of the vagina around the portio vaginalis
Microanatomy

• **Mucosa**
  – Epithelium – lined by *mucus-secreting columnar epithelium* except at the portio vaginalis where it is lined by stratified squamous epithelium
  – Glands – *branched cervical glands*
  – Wall of the cervix – *mostly dense CT* (smooth muscle makes up approximately 15% of total)

• **Glandular secretions** – two types of secretion under the influence of the ovarian hormones:
  – **Serous** – produced during ovulation
  – **Viscous** produced at other times and during pregnancy. The viscous secretion forms a mucus plug

• **Cervical erosions** – patches of columnar cells extending into the portio vaginalis; may become inflamed and lead to cervical cancer

• **Nabothian cysts** – mucus-filled cysts due to the obstruction of the lumen of the tubular glands

• **Pap smears** – clinical test of the exfoliated cervical cells
Vagina

Gross structure – muscular tube, 8-9 cm in length, extending from the cervix to the external genitalia

Microanatomy

• Three layers of the vaginal wall:
  – Mucosa – stratified squamous epithelium supported by a fibroelastic, richly vascularized CT. Estrogen stimulates the production and storage of glycogen by epithelium. The vaginal bacterial flora metabolizes the glycogen to form lactic acid. Lactic acid lowers the lumenal pH thereby restricting pathogenic invasion and growth
    • There are no glands in the vaginal mucosa
  – Muscularis – outer longitudinal bundles (continuous with muscle layer of uterus) and inner circular bundles. A skeletal sphincter is present at the vaginal opening
  – Adventitia – thin layer of dense to loose CT that joins the vagina to the urethra and bladder anteriorly and rectum and anal canal posteriorly
The Vulva

Labia Majora

- Structure – folds of skin containing adipose tissue and a thin layer of smooth muscle
  - External surface has coarse hairs
- Glands – sweat and sebaceous glands on inner and external surfaces
- Developmental analogue – scrotum

Labia Minora

- Structure – folds of skin containing a core of spongy (erectile) tissue
  - No adipose tissue or hairs
- Glands – numerous sebaceous and sweat glands
- Developmental analogue – corpus spongiosum
The Vulva

Vestibule

- Structure – cleft between the labia minora, lined with stratified squamous epithelium
  - Receives the vaginal and urethral opening
- Glands
  - Bartholin (greater vestibular glands) – two large tubuloalveolar glands that secrete a lubricating mucus; homologues of the bulbourethral glands
  - Skene – minor vestibular glands (paraurethral glands)

Clitoris

- Structure - two erectile bodies, the corpora cavernosa surrounded by a fibrocollagenous sheath
  - Covered by stratified squamous epithelium
  - Contains numerous blood vessels and sensory nerves
- developmental analogue - penis
Overview of Female Reproductive Cycle

Ovarian cycle
- Primordial follicles
- Primary follicles
- Secondary follicle
- Mature (graafian) follicle
- Ovulation
- Corpus luteum

Uterine (menstrual) cycle
- Menstruation
- Proliferative phase
- Secretory phase
- Menstruation

(a) Hormonal regulation of changes in the ovary and uterus