Chapter 28
Reproductive System

The goal of the reproductive system is to produce a new, unique organism. But first, some terminology!

- Primary sex organs = gonads. They produce hormones and sex cells called gametes. The gametes are sperm and ovum.
- Accessory sex organs = ducts, glands and external genitalia. These organs deliver and receive sperm, and fertilize the egg.

The Male Reproductive System

The primary function of the male reproductive system is to produce and deliver sperm; produce and secrete sex hormones.

Pathway for Sperm

1. Seminiferous tubule (spermatogenesis here)
2. Tubulus rectus (the straight tube)
3. Rete testis (network of vessels)
4. Efferent ductile
5. Head of epididymus
6. Body of epididymus
7. Tail of epididymus
8. Ductus deferens
9. Spermatic cord
10. Ampulla (enlargement of ductus deferens)
11. Sperm meet up with vesicular fluid at the ejaculatory duct
12. Prostatic urethra (prostatic fluid mixes in here)
13. Urogenital membrane
14. Membraneous urethra
15. Spongy urethra (starts at root/bulb of penis)
16. Bulbourethral gland (secretes at arousal phase into spongy urethra)
17. External urethral orifice

Semen is composed of:

Testicular fluid
Vesicular fluid
Prostatic fluid

Some random notes on the anatomy of the male system

- The Pampiniform plexus is a network of vessels that cools arterial blood
- The Dartos Muscle is between the dermis and epidermis
- The Tunica Albuginea has fibers that run inside to form septa.
- The Ductus Deferens goes behind the bladder
- The Root is connective tissues that support the penis
- The Crus is the origin of the corpus cavernosa
- The Bulb is specific to the corpus spongiosum
- The Corpus Spongiosum enlarges at the glans
- The Seminal Vesicles are near the ampulla
- The job of the Corpus Spongiosum is to keep the urethra open during ejaculation
- The two tunics are membranes that surround the testes
    - Tunica albuginea deepest layer

- Tunica Vaginalis has two layers because it is a serous membrane…it is actually an extension of the serous membrane of the abdominal cavity.
- From superficial to deep, the layers are:
    i. Epidermis
    ii. Dermis (contains the dartos muscle)
    iii. Fascia
    iv. Cremaster muscle
    v. Tunica vaginalis
    vi. Tunica albuginea

The seminiferous tubules
There are a few different types of cells in the seminiferous tubues:
1. Developing sperm cells
2. Sertoli cells
3. Leydig cell (interstitial cells that produce testosterone)

Glands
The bulk of semen comes from vesicular fluid (2/3) and the prostatic fluid (1/3). Only about 3-5% is sperm. The vesicular and prostatic fluids transport and support the sperm cells on their journey. The reason for this is that sperm travel light. They basically only carry their nucleus and mitochondria. So they have to get nutrients from the fluids. These fluids each come from glands in the male reproductive system. Vesicular fluid comes from the SEMINAL VESICLES, and prostatic fluid comes from the PROSTATE GLAND.

Glands have smooth muscle to help them secrete, and ducts have it for transporation and propulsion. For example, the ductus deferens is almost all muscle, the lumen is small.

The seminal vesicles are paired. They have secretory pockets that are filled with seminal fluid. The pockets excrete outside of the tract, which is technically outside the body, so these are exocrine glands…they secrete into the ejaculatory duct.

The composition of this secretion **"vesicular fluid"** is alkaline, fructose (fuel), and prostaglandins. This fluid breaks down the cervical mucus plug and stimulates reverse uterine peristalsis.

The **prostate gland's** secretion is prostatic fluid, and it joins the mixture at the prostatic urethra during emission/ejaculation. The fuel source of prostatic fluid is citrate (it can go into the Kreb's cycle.) Enzymes in the fluid activate sperm! Now they can swim!!!

The **bulbourethral gland's** secretion is a clear mucus that acts as a lubricant that also neutralizes urine from the urethra. It secretes into the spongy urethra prior to ejaculation…during the arousal phase.

Semen is the final product. It measures about 2-5 mL. It acts as a transport medium with nutrients, antibacterial factors and enzymes that protect and activate sperm.

The pH of sperm is 7.2 – 7.6, which is slightly basic. It neutralizes the acidic female duct system.

THE PHYSIOLOGY OF INTERCOURSE

The Arousal Phase (engorgement)

ERECTION is a parasympathetic reflex, stimulated by NO from the PANS. NO activates a cGMP 2nd Messenger pathway. (FYI, Viagra inhibits breakdown of cGMP).

This leads to DILATION of the arterioles which causes engorgement of the erectile bodies.

- expansion of the corpora cavernosa collapsing the veins and trapping the blood
- expanding the corpus spongiosum to keep the urethra open.

In this phase the bulbourethral glands secrete their lubricants.

EJACULATION (orgasm) is a sympathetic reflex that involves both smooth and skeletal muscles. The smooth muscle contracts of the duct system act peristalsis to move sperm/seminal fluid from the epididymus through the urethra. Along the way the sperm picks up glandular secretions from the seminal vesicles and prostate gland.) This reflex also constricts the bladder sphincter leading into the urethra. It also consists of skeletal muscle contractions along the base of the penis.

POST EJACULATION

In this phase the constriction of the arterioles resumes so the system resumes venous drainage and the blood flows out of the erectile bodies. There is a variable latent period during which the penis cannot be stimulated to orgasm.

SPERMATOGENESIS

Spermatogenesis is the production of gamets. Recall that a gamete is either a sperm or an ova (egg). In females the process is called oogenesis (oh-oh-genesis). While we use mitosis for the creation of new cells, we use meiosis to make gametes.

Haploid (n) = single set of chromosomes (23)

Diploid (2n) = number of chromosomes in most cells (46)

Haploid vs Diploid

A human sperm or egg cell is haploid, meaning it only contains of each of the 23 chromosomes of the human genome. Gametes are haploid, and the union of two haploid cells creates a diploid zygote with one set of chromosomes from mom, and one from dad.

Meiosis	Mitosis
Goal is to produce gamete	Goal is for growth and repair
Occurs in gonads	Occurs everywhere in the body
# of cell divisions in each cycle:	# of cell divisions: one cycle 1 cell becomes 2 cells
Begins with parent cell (2n)	Chromosome replication prior to division

Replicates DNA prior to meiosis	Parent cell has 46 chromosomes
Tetrad forms, crossing over occurs	Daughter cell has 46 chromosomes (one copy from each parent)
2nd cycle is same as mitosis	Product is 2 daughter cells that are identical to each other and identical to the parent.
After the complete process, have 4 daughter cells that are all unique	
Creates haploid cells	
Ensure genetic variability	

Phases of mitosis are prophase, metaphase, anaphase, telophase and cytokinase.

Meiosis and the sperm cell
This process starts with stem cells in seminiferous tubules. Mitosis of the stem cells keeps the supply constant…it's like those airplanes that refuel while flying. The stem cells (which are diploid) are on the outside near the basement membrane (aka: primary spermatocytes). They form in the basement compartment (formed by Sertoli cells) and migrate through BTB and complete meiosis I. Prior to migrating out, the primary stem cell divides by mitosis…one migrates out (Type B) to begin meiosis and one stays (Type A) to keep the supply steady.

The sperm cells of spermatogenesis are:

- Spermatogonia (diploid); Type A and Type B
- Primary Spermatocytes (diploid); They form in the basal compartment, migrate through Blood Testis Barrier, complete meiosis I.
- Secondary Spermatocytes (haploid);
  They complete meiosis II
- Spermatids (haploid); under differentiation
  & shedding = spermiogenesis
- Spermatozoa (haploid); incapable of fertilization
  at this point in their development.

The process of meiosis for sperm
Prior to entering meiosis, the primary cell replicates itself via mitosis. These diploid cells are in the basal compartment (diploid has 46 chromosomes). Once the cell is haploid, it is on the other side of the tight junction…now it is a primary spermatocyte. It now goes through meiosis I.

First, the cell must replicate its DNA so that the one cell has 92 chromosomes…it is a diploid cell, with two sets of DNA. This is the primary spermatocyte. The end result of meiosis is two daughter cells that are both haploid. These are called the secondary spermatocytes. These cells each have two sets of chromosomes [(2n x2) x 2].

In meiosis II, the 92 chromosomes are split up amongst 4 haploid daughter cells.
[n x 1) x 4

The Sertoli cells (AKA sustenticular cells)
are also called "nurse cells" because they help! They hug and surround every sperm cell…they are really big! The diploid cells are in the basal membrane, and the haploid cells are protected in the adluminal compartment. This is the Blood Testis Barrier! The Sertoli cell basically provides these cells with their nutrients and support so they never come in contact with the blood or immune system. The body would attack these cells because they would come across as foreign. For example, FSH does not go directly to the sperm cell…it binds with Sertoli cells. Sertoli cells also:

- Guide migration to lumen
- Secrete testicular fluid
- Secrete inhibin, ABP, MIH
- (ABP = Androgen binding protein…
  b/c testosterone needs a carrier.

During spermeogenesis there is a lot of shedding. Basically getting rid of everything that is not essential. The sperm cell keeps the nucleus, flagellum and mitochondria. The acrosomal cap contains lysosomes…these break down whatever it needs to break down to attach to the egg.

Hormone Regulation of Spermatogenesis
Recall the 3-Hormone pathway for sex hormones:

GnRH stimulates FSH goes to Sertoli Cells which secretes ABP
GnRH stimulates LH goes to Interstitial Cells which secrete Testosterone
(ABP + testosterone = spermatogenesis)

This pathway is regulated by Negative Feedback.

- Increased levels of Inhibin lead to reduced FSH/LH secretion. This is a short loop.
- Increased levels of Testosterone lead to reduced GnRH production, which leads to lowered FSH/LH. This is a long loop.

Hyposecretion of FSH/LH causes the testes to atrophy, and for a reduction of sperm and testosterone production.

The possible connection between steroid abuse and testicular atrophy is because the exogenous steroids create a strong negative feedback loop, so less GnRH is released and thus less FSH/LH are released. The tissues are therefore not nourished by the tropic hormone, and spermatogenesis is not happening without FSH (which produces ABP.)

Sexual maturation
Prior to puberty, the set point for testosterone is very low, which provides a strong negative feedback loop, to inhibit GnRH & FSH/LH. This keeps testosterone levels down.

At puberty, the set point for testosterone goes up to adult levels. This causes increased levels of testosterone to be released into circulation and sperm production begins.

Other effects of testosterone

- Maintenance of accessory glands and organs
- Sex changes/puberty
- Mascularization of skeleton
- Closes epiphyseal plate in males
- Masculanizes the brain (prenatal)
- Anabolic effects: stimulates growth of bone/muscle, thickens skin

Female Reproductive System

Anatomy notes…a few female structures are analogous to those found in the male. For example, the vestibular gland is analogous to the bulbourethral gland, and the paraurethral gland is analogous to the prostate gland.

The interal genetalia incude the duct system and the ovaries, while the external genitalia is the vulva.

Uterus: Top is the fundus, bulk is the body, end is the cervix and the isthmus is the narrowed region.

Vagina: Cervix protrudes into the vaginal canal. It forms a fornix, which is a shallow recess surrounding the cervix.

Histology: The vagina is an elastic muscular tube…made up of a lot of smooth muscle and elastic connective tissue. The inner lining is epithelium…it is a mucus membrane, so the underlying CT is the lamina propria. The difference between the epithelial membrane of the vagina and the skin is that the vaginal stratified squamous are not cornified. The layer deep to the lamina propria is the smooth muscle. It is controlled by the autonomic nervous system for peristaltic contractions. The glands of the vagina secrete mucus. A the blood vessels become engorged, fluid from the vessels moves to the luminal side in a process called transudation. The glycogen in the secretions are what good bacteria use for fuel (anaerobic process)…this produces the low pH of the vaginal canal.

Uterine Tube: Transports the ova, and transports pre-embryo to the uterus via ciliated columnar epithelium. There are three regions of the tube…

1. Infundibulum (with fimbrae…they create currents and bring oocyte in)
2. Ampulla (this is where fertilization usually occurs)
3. Isthmus (narrow portion)

Histology: Ciliated columnar epithelim; secretory mucosa that moisten and nourish the egg and sperm (or fertilized egg); smooth muscle for peristaltic contractions that propel the oocyte toward the uterus. It takes about 4 days for the oocyte to reach the uterine cavity.

Uterus: Limited mobility…ligaments keep it in place. The **broad ligament** encloses the ovaries, uterine tubes and uterus, and attaches to sides & floor of pelvic cavity, continuous with the parietal peritoneum.

Mesosalpinx is the free edge that attaches to the uterine tubes
Mesovarium is the fold of broad ligament that supports ovary

Ligaments within broad ligament:
Suspensory ligament of ovary anchors to pelvic wall
Ovarian ligament anchors ovary to uterus
Round ligament of uterus goes through inguinal canal to CT of ext. genit.
Uterosacral ligament of uterus anchors it to the sacrum

Regions of the Uterus:
Fundus is the superior portion (top)
Body
Isthmus (constricted portion)
Cervix (extends from isthmus into vagina)
Internal Os leads to the cervical canal which ends at Cervical Os
Cervical glands secrete the "mucus plug" to protect the uterus from bacteria. This gets broken down at ovulation so sperm can pass.

Histology of Uterus:
Most of the uterus is smooth muscle. The uterine wall consists of three layers…the perimetrium, myometrium and endometrium.

Uterine wall layers cont'd

Perimetrium:	covering (think peritoneum)
Myometrium:	smooth muscle for uterine contractions
Endometrium:	mucosal lining for implantation and support of embryo.

Endometrium layers
Stratum basalis (basilar zone) is the deepest layer…it is next to the myometrium. Its function is to form new cells for the stratum functionalis.

The next layer is the stratum functionalis (functional zone). This is the layer that degenerates and regenerates under hormonal control. It is at its thinnest at the beginning of the uterine cycle (menses)…after the last cycle has caused a complete sloughing of the layer. The white spaces you see are Uterine Glands.

Blood vessels
The arcuate arteries follow the contour of the uterus, while the radial arteries run through the uterine wall toward the endometrium. The straight arteries are within the stratum basalis, while the spiral arteries go into the stratum functionalis…these spasm causing tissue death.

Ovaries
The ovaries are the primary sex organ. They are responsible for follicle maturation and the release of oocyte. The oocytes develop within granulosum cells, which are the follicles. This makes the granulosum cell analogous to the Sertoli cell of the male.

Top few layers
Germinal epithelium
Tunica Albuginea
Cortex

The ovaries are supported by ovarian and suspensory ligaments, the mesovarium. The hilum is where the ovarian veins enter the ovary.

It has two regions, the cortex and the medulla. Everything happens in the cortex, and the medulla is where blood/nutrients come in. The outside covering of the ovary is the tunica albuginea (DICT). Around this connective tissue layer is a layer of epithelial cells, inappropriately named the germinal epithelium (they are NOT stem cells.)

External Genitalia (aka "Vulva")
Labia Minora & Majora enclose the vestible, which contains the vaginal and urethral openings.

Erectile Tissues:
The erectile tissues of the female genitalia include the clitoris and the bulb of the vestibule. The portion of clitoris that is visible externally is the glans (which is covered by a prepuce). The crura connects the corpora cavernosa to the pelvic bone. The bulb of the vestibule is analogous to the corpus spongiosum in the male.

Accessory Glands:
The lesser vestibular glands keep the vestible moist, while the greater vestibular gland provides lubrication during sexual arousal. The Paraurethral glands may be involved in female ejaculation…they only secrete at orgasm.

<u>The Physiology of Intercourse</u>
Just like in the male, engorgement occurs during the AROUSAL PHASE, and is a parasympathetic reflex. It is mediated by NO (in a cGMP 2nd Messenger pathway) and dilates the arterioles. The clitoris and bulb become engorged, as do the vaginal mucosa, labia and breasts. With men, it's only the penis that becomes engorged. Women rock! The engorgement of the vaginal mucos allows for increased vaginal transudate across the mucos for lubrication. This reflex also stimulates the GREATER VESTIBULAR GLAND and the CERVICAL GLAND SECRETIONS for more lubrication.

ORGASM is a sympathetic reflex, with the main difference from males is that ejaculation does not have to occur (though there is some talk about female ejaculation). Orgasm consists of reverse peristaltic contractions, whose purpose it is to move the sperm toward the egg for fertilization. These contractions include the smooth muscle of the vagina and uterus. Though orgasm is not essential for fertilization, women do not have a latent

period. Sometimes, orgasm includes secretion of the paraurethral glands. Once over, the arterioles resume a constricted state and the tissue returns to its flaccid state.

Oogenesis

Oogenesis takes place in the ovarial follicles. There are several differences between oogenesis and spermatogenesis (S)

- **When it begins**. Oogenesis begins in the female embryo, whereas S begins at puberty for males. The oogonia goes through mitosis in utero, producing about 2-4 million oogonia that develop into primary oocytes. These all PAUSE IN PROPHASE I…note that each has a primodial follicle at this stage. By the time the little doll reaches puberty, there are about 400,000 left (due to atresia of the primordial follicles). The ovaries are "inactive" during childhood.
- **It stops and starts**. Males start producing sperm and never stop. Oogenesis resumes at puberty until menopause on a monthly basis (ovarian cycle). One primary oocyte completes Meiosis I each month to form a secondary oocyte. Then there is ANOTHER PAUSE in Metaphase II. At this time the secondary oocyte is ovulated. ONLY FERTILIZED OOCYTE COMPLETES MEIOSIS II to become an ovum.
- **Number Produced**. While S produces four unique daughter cells, oogenisis produces just one gamete and 2-3 polar bodies. The polar bodies take on the extra chromosomes so that the gamete has the right number. The unequal distribution of cytoplasm to the polar bodies makes for one huge oocyte.

Stages of Oogenesis & Follicular Development

Each month a few primary follicles develop. When there is just one layer of cells around the oocyte the cells are called follicle cells. When it's 2+ layers, they are granulosum.

Primordial follicle is a primary oocyte plus a single layer of follicle cells. Each month, FSH stimulates a few primordial follicles to mature into primary follicles.

Primary follicle is a primary oocyte plus granulosa cells (so more than one layer.) Note that **thecal cells** now surround the follicle, and the **zona pellucida** (a layer of glycoproteins) is formed by the oocyte and its granulose cells.

Secondary follicle is the primary oocyte plus granulosa cell plus fluid-filled sacs.

Tertiary follicle (AKA "Vesicular", or "Graafian") is the primary oocyte plus granulosa cells plus the complete ANTRUM. At this point the follicle is bulging from the surface of the ovary…ready to go! The tertiary follicle is surrounded by the CORONA RADIATA, which extends from the CUMULUS OOPHORUS. Only one secondary follicle will reach this stage about one day before ovulation. It will be the follicle that is the MOST sensitive to FSH.

The LH surge stimulates the primary oocyte to complete Meiosis I just before ovulation. The ovulated follicle releases the secondary oocyte, which is surrounded by corona radiata. Don't forget that the secondary oocyte will only complete Meiosis II if it is fertilized. Otherwise it does not become an ovum! The ruptured follicle stays behind in the ovary to become the corpus luteum and it is nurtured by stimulation of LH.

The Ovarian Cycle and Hormonal Control

There are two phases in the ovarian cycle…the follicular phase and the luteal phase.

The FOLLICULAR PHASE begins when GnRH levels rise, causing levels of FSH to rise. FSH stimulates follicle develoment (so the primordial to primary to secondary, etc…). Also at this time LH stimulates the thecal cells to produce androegens, which are converted to Estrogen by the granulosa cells. The follicular phase involves negative feedback while estrogen levels are low.

The growing follicles (with more and more granulosa cells) secrete increasing levels of estrogen. Once the levels reach threshold, it switches over to positive feedback. This leads to a surge in LH!!!!!

The LH SURGE results in 3 things:

1. The secondary oocyte completes meiosis I
2. Ovulation of the secondary oocyte (about 9 hours after LH peak)
3. Conversion of the ruptured follicle to the corpus luteum

In THE LUTEAL PHASE the corpus luteum produces a lot of PROGESTERONE, plus Estrogen and Inhibin, which leads to a decrease in FSH/LH secretion. The purpose of this is to prevent the maturation or ovulation of other follicles during this time. Progesterone is the dominant hormone for this part of the cycle, and stimulates the continued growth of the stratum functionalis and the uterine glands.

Progesterone is the dominant hormone for this part of the cycle!

LH continues to maintain the corpus luteum for about 10-12 days. The phase ends once the corpus luteum degenerates (and becomes the corpus albicans), causing a crash in progesterone, estrogen and inhibin. This allows for GnRH to again stimulate a new cycle.

If pregnancy/fertilization occurs, then MEOISIS II is completed and you have an ovum. Also, the corpus luteum is maintained by hCG, which is secreted by trophoblasts of the conceptus.

The Uterine Cycle

Recall that the function of the uterus is to receive, house and nourish the conceptus. The uterine cycle involves changes to the uterus, mainly the stratum functionalis. This cycle is coordinated with the ovarian cycle.

It consists of three phases:

1. **Menstrual phase** (day 1-5) corresponds with the first part of the follicular phase. During this phase, progesterone and estrogen levels are very low since the corpus luteum has degenerated and is no longer secreting its hormones. The spiral arteries are constricted, which causes them to spasm leading to tissue necrosis of the stratum functionalis. As the cells die they rupture and spill out their lysosomes which further helps to break down the tissue.
2. **Proliferative phase** (day 6-14) corresponds with the second half of the follicular phase of the ovarian cycle. During this phase, increasing Estrogen levels from the growing granulosa cells results in growth of uterine epithelium/glands and spiral arteries. Also, the endometrial cells are sensitized to Progesteron (they have more Progesterone receptors), which is a permissive action. Further, the cervical mucus is thinned so sperm can pass through. This process results in regeneration of the stratum functionalis…just in case a conceptus wants a place to implant and grow!
3. **Secretory phase** (day 14-28) corresponds to the luteal phase of the ovarian cycle. It involves the continued preparation for possible implantation. In this phase Progesterone levels are very high (also Estrogen) due to the corpus luteum doing its thing. This results in:
    a. Further growth of spiral arteries and uterine glands. This leads to more secretion of the glycogen-rich mucus
    b. Reformation of the cervical mucus plug
    c. Inhibition of FSH/LH, which eventually leads to the degeneration of the corpus luteum if fertilization does not occur. (around day 26) The inhibition of FSH also ensures that another follicle does not develop. The inhibition of LH leads to the degeneration of the corpus luteum

The loss of the corpus luteum and thus the loss of Pregesterone and Estrogen is followed by menses and the start of a new cycle.

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