Objectives

- Gametogenesis
- High points of normal embryologic and fetal development from fertilization until term
- Early placenta development
- Development of the female GU systems
- Include how ambiguous genitalia, Mullerian anomalies and vaginal septa develop
- Short description on ureter duplication anomalies otherwise no need to get into the urinary system

Urogenital system overview

- Develops from the intermediate mesenchyme on the dorsal body wall of the embryo.
- A longitudinal ridge of mesenchyme develops on either side of the dorsal aorta called the urogenital ridges.
- The urinary system develops from the nephrogenic cord
- The gonadal ridge gives rise to the genital system
Genital System

Female gamete development – Oogenesis

- Large number of primordial cells (oogonia) are formed by mitosis (~40,000)
- Cell growth until meiosis can occur → 1st oocyte → arrest in prophase until menstrual cycle begins → FSH triggers continued division of some of the 1st oocytes
- Meiosis results in two cells of unequal size (1st oocyte with all cytoplasm & the polar body which remains trapped within the follicle until it eventually degenerates) → secondary oocyte begins the second meiotic division but is arrested in metaphase II
- Ovulation occurs and 2nd oocyte enters the oviduct → follicular cells surrounding the oocyte form a corona radiata which nourish the 2nd oocyte
- Fertilization triggers the completion of meiosis II and the formation of another polar body (1st polar body may also undergo a second division to form a 3rd polar body)
- Once meiosis is complete the mature egg forms an ovum, before fusing its nucleus with the sperm nucleus to form a zygote

Comparison of oogenesis and spermatogenesis
Meiosis Overview

• Provides for constancy of the chromosome number from generation to generation by reducing the chromosome number from diploid to haploid, thereby producing haploid gametes.
• Allows random assortment of maternal and paternal chromosomes between the gametes.
• Relocates segments of maternal and paternal chromosomes by crossing over of chromosome segments, which “shuffles” the genes and produces a recombination of genetic material.

Chromosomal defects

• Can be numerical or structural in nature
• Estimated that 50% of conceptions end in spontaneous abortion and 50% of those are 2nd to major chromosomal abnormalities (25% of conceptions has major chromosomal defects)
• Most common in abortuses are:
  – Turner (45,X), trisomy 16, & triploidy
• Nondisjunction – homologous chromosomes fail to separate during meiosis → one gamete receives 24 and one 22 → results in an individual having either 47 or 45 chromosomes
• Translocation – chromosomes break and pieces of one attach to another; common in chromosomes 13, 14, 15, 21, and 22 because they cluster during meiosis.

Chromosomal Defect examples

• Down Syndrome – Trisomy 21 – most are the result of nondisjunction but can be from a translocation (4%) or mosaicism (trisomy in only some cells) (1%).
• Trisomy 18 – 85% lost between week 10 and gestation. Only 5% survive to a year.
• Klinefelter (47, XXY) – 1 in 500 males; unusually 20 to nondisjunction of the XX chromosome
• Turner (45,X) – the only monosomy compatible with life but 95% still spontaneously aborted.
Ovulation and Oocyte Capture by Oviduct Fimbriae

Fimbriae move to cover the ovary surface and the oviduct initiates rhythmic contractions to move the oocyte toward the uterus.

Fertilization typically occurs in the ampulla

Total number of sperm/ejaculation range between 280-500 million
Total number of sperm reaching upper oviduct for fertilization range from 1500-3000

Steps in Fertilization

Langman's Medical Embryology, 14e, Fig 3.5
Fertilization Releases the Oocyte From Meiosis II Block

- Restoration of the diploid number of chromosomes, half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents.
- Determination of the sex of the new individual. The chromosomal sex of the embryo is determined at fertilization. An X-carrying sperm → female (XX) embryo, and a Y-carrying sperm → male (XY) embryo.
- Initiation of cleavage. Without fertilization, the oocyte usually degenerates 24 hours after ovulation.

Early Cell Division and Formation of the Blastocyst

- 2 cell zygote undergoes several mitotic divisions → blastomeres
- Remain loosely clumped until 8 cell stage where they then undergo compaction where they are held together by tight junctions.
- This process segregates the inner cells (which communicate via gap junctions) from the outer cells
- The inner cells of the morula are the Inner Cell Mass which becomes the embryo proper
- The outer cells form the trophoblast which later contributes to the placenta
- The morula is now known as the blastocyst and implantation has begun.

Overview of Early Development Leading to Blastocyst Implantation

- Secretes progesterone, estradiol, inhibin A
Abnormal Implantation Sites – Associated with Early Embryo Hatching From the Zona Pellucida

Normal implantation usually occurs along either the posterior or anterior wall of the uterine body.

Review of week 2 and the rule of twos

- Embryoblast splits into two layers – epiblast and hypoblast
- Trophoblast divides into two layers – cyto and syncytiotrophoblast
- Two yolk sacs form
- Two new cavities form – amniotic and chorionic

Representative Stages of Blastocyst Implantation into the Endometrium

- Two layers of the trophoblast: inner cytotrophoblast, outer syncytiotrophoblast, which surrounds the embryo and yolk sac. The syncytiotrophoblast secretes several hormones: human placental lactogen (HPL), human chorionic somatomammotropin (HCS), estrogen, progesterone, and human chorionic gonadotropin (hCG). The latter is the basis of pregnancy testing as it is present in sufficient amounts to detect by the end of the 2nd week.
- Cells are also beginning to differentiate by now.
Week Three: Gastrulation and primitive streak

- Process that establishes the germ layers (endoderm, ectoderm, and mesoderm)
- Begins with the formation of the primitive streak
- The embryo begins differentiation into distinct cell lineages and axes (dorsal-ventral, cranial-caudal) begin to form.

Germ Layers

- The ectoderm gives rise to epidermis, the nervous system, and to the neural crest in vertebrates.
- The endoderm gives rise to the epithelium of the digestive system and respiratory system, and organs associated with the digestive system, such as the liver and pancreas.
- The mesoderm gives rise to many cell types such as muscle, bone, and connective tissue. In vertebrates, mesoderm derivatives include the notochord, the heart, blood and blood vessels, the cartilage of the ribs and vertebrae, and the dermis.

Reproductive Organogenesis
Embryogenesis of the Female Reproductive Tract

- Origin of reproductive structures is closely tied to early renal development because both are derived from the intermediate mesoderm that occupies the region between the somite and lateral plate mesoderm.
- Forms the longitudinal urogenital ridge that divides into the nephrogenic ridge and the genital ridge.
  - By gestational weeks 3-4 the mesonephric ducts have extended down to merge with the cloaca.
  - By approximately week 5 the uterine buds form from the mesonephric (Wolffian) duct near the cloaca and migrate cranially into the metanephric mesenchyme to form the ureter and induce the metanephric kidney.

Sex Differentiation

- Complex process that involves many genes
- The key element though is the presence or absence of the Y chromosome as it contains the testis-determining gene SRY
  - It's influence → male development
- The gonads initially appear as a pair of genital ridges
- Gonad development is dependent on the presence of primordial germ cells (PGCs), which begin to populate the ridges during the 6th week

PGC Origin and Migration into the Genital Ridge

- PGCs begin in the epiblast, migrate through the primitive streak into the endoderm cells within the yolk sac near the allantois and split into two migratory cell populations.
- These move caudally from the yolk sac wall through the hindgut endoderm (diapedesis) and along and finally up the dorsal mesentery into their respective genital ridges.
- If the PGC's fail to reach the ridges the gonads do not develop
Formation of the primordial follicle

- The surface epithelium of the female gonad continues to proliferate and gives rise to the follicular cells that surround the oogonium → primordial follicle

Langman's Fig 16.22
Initially there are two pairs of ducts present: Müllerian (paramesonephric) and Wolffian (mesonephric).

The Müllerian ducts and urogenital sinus are essential to the formation of the female reproductive system.

Note that the cranial end of the Müllerian ducts are open (into the coelem), and that the caudal ends are fused (uterovaginal primordium).

In the early embryo the indifferent gonad stage precedes male and female differentiation.

In females, in the absence of the SRY genes, testosterone and AMH (MIS) the mesonephric ducts degenerate, and the gonad develops into an ovary.

The female mesonephric (Wolffian) ducts persist only in vestigial form and are detected either adjacent to the uterus as Gartner's cysts or as the tubular remnants epoöphoron and paroöphoron seen in the mesovarium.

In the developing ovary the primitive sex cords degenerate as the genital ridge mesothelium forms the secondary sex cords which will become the granulosa and follicle cells surrounding the oocytes.

The caudal merging of the two Müllerian ducts occurs at about 10 weeks gestation.

They terminate at the sinovaginal bulbs adjacent to what will become the urogenital sinus.

The uterovaginal primordium forms the uterus and the superior vaginal canal.

The urogenital sinus forms the inferior portion of the vaginal canal.

Mesenchyme surrounding the uterus condenses to form the myometrium.
Schematic Representations of Anatomical Abnormalities in Uterine Development

Most commonly formed by defects in Mullerian duct fusion and/or septal reabsorption. Various genetic abnormalities of the uterus that can be detected by a sonographic examination or MRI imaging.

- Hypoplasia
  - Agenesis
  - Bicornuate
- Unilobar
- Bicornuate
- Septate
  - Complete
  - Partial
- Uterus Didelphys
- Uterus Unica
- Uterus Anureta

Sonographic observations of abnormal uteri

- Didelphys uterus with fetuses
- Septate uterus with the septum (asterisk) separating the endometrial cavity in two.
- The uterine fundus (arrow) is convex.
- Unicorne uterus
- Bicornuate uterus with two uterine horns containing separate endometrial cavities and a pregnancy (arrow) in the right uterine horn.

Congenital Uterine Anomalies (CUAs)

- CUAs may lead to symptoms such as pelvic pain, prolonged or otherwise abnormal bleeding at the time of menarche, recurrent pregnancy loss or premature delivery.
- Increased risk of skeletal or abdominal wall abnormalities, & inguinal hernia.
- Renal anomalies occur in 20-30% of Mullerian defects (Oppelt, von Have, Paulsen et al., Fertil. Steril. 87:232, 2007)
- When a renal anomaly is present it is typically ipsilateral to the CUA.
- Anomalies may be congenital or acquired; karyotypes are usually normal (92%).
- Absence of symptoms \rightarrow true incidence of anomalies is unknown
- 57% of women with uterine defects have successful fertility and pregnancy.
- The mean incidence of uterine malformations has been reported as 4.3% for women with normal reproductive outcomes (Grimbizis et al., Hum Reprod. Update. 2001 Mar-Apr. 7(2):161-74.)
- Some form of mullerian hypoplasia or agenesis affects one in every 4,000 - 5,000 females.
Clinical Significance of CUAs

- **Arcuate uterus** – Is typically classified as a normal variant and is not associated with adverse pregnancy outcomes.
- **Septate/subseptate uterus** – Most common uterine anomaly (30-90%) of all identified uterine malformations. Is more likely to be associated with adverse pregnancy outcomes than other uterine anomalies. Increased risk for spontaneous abortion (21-44%) and preterm delivery (12-33%) Associated with an increased risk of breech presentation and abruption. Pregnancy loss often occurs in 2nd trimester. Live birth rate ranges from 50-72%.
- **Bicornuate uterus** – Literature reports indicate spontaneous abortion is 36%, preterm birth in 21-23% and fetal survival in 50-60% of patients. Fetal growth restriction and malpresentation in labor also increase. Pregnancy loss often occurs in 2nd trimester. Live birth rate ranges from 50-72%.
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- **Unicornuate uterus** – Associated with a high incidence (40%) of renal abnormalities. Higher risks for endometriosis, premature labor and breech presentations. This condition may be associated with an ectopic ovary. Associated obstetric complications include ectopic pregnancy (3%), first trimester abortion (24%), second trimester abortion (10%), preterm delivery (20%) fetal demise (4%). Live birth rate is 51%.

Mayer-Rokitansky-Küster-Hauser syndrome

- Uterine agenesis – a condition whereby the vagina and uterus are underdeveloped or absent due to a failure of Mullerian duct formation. Frequency ~ 1:5,000 female births; poorly studied (Human Reprod. 2016 Dec;31(12):2384-90. doi: 10.1093/humrep/dew220. Epub 2016 Sep 8) Third most common cause of primary amenorrhea after pregnancy and gonadal failure (such as from Turner syndrome).

The first noticeable sign of MRKH syndrome is that menstruation does not begin by age 16 (primary amenorrhea)

- Females with MRKH have a normal chromosome pattern (46, XX) and normally functioning ovaries. They also have typical female external genitalia, breast, and pubic hair development.

Inheritance pattern is unclear - signs and symptoms of the condition frequently vary among affected individuals in the same family. However, in some families, there is an indication for an autosomal dominant pattern of inheritance.

Urogenital Sinus

- By the 7th week the cloaca is divided by an upper urorectal septum (Tourneux fold) that meets the medial Rathke’s folds forming a separate rectum and urogenital sinus.

- The urogenital sinus can be considered as having three parts:
  - Cephalad (cranial; vesicle) portion which gives rise to the urinary bladder.
  - Pelvis (middle) portion that gives rise to the female urethra.
  - Caudal (phallic) portion giving rise to distal vagina, greater vestibular (Bartholin), urethral and paraurethral (Skene) glands (also known as the lesser vestibular glands).
Vaginal Development

- The upper 1/3 develops from the uterovaginal primordium
- The epithelium of the vaginal canal forms from the endoderm of the urogenital sinus.
- The vaginal plate is derived from fusion of the sinovaginal plates which form when the uterovaginal primordium and urogenital sinus fuse.
- Central cells of the vaginal plate break down, forming a lumen.
- Failure of this fusion can result in a variety of malformations of the female reproductive system.
- Dissolution of the midline septum is usually completed by 20 weeks.
- The hymen is the partition that remains between the dilated canalized fused sinovaginal bulbs and the urogenital sinus, becoming perforated either shortly before or after birth.

Vaginal Anomalies

- In vaginal atresia the urogenital sinus fails to contribute the caudal portion of the vagina. The lower fifth to third of the vagina is replaced by 2–3 cm of fibrous tissue, above which lies a well-differentiated upper vagina, cervix, uterine corpus, and fallopian tubes.
- Transverse vaginal septa occur at several locations and may be complete or incomplete. These septa are usually about 1 cm thick (but can be thicker) and located near the junction of the upper third and lower two-thirds of the vagina, however, septa may be present in the middle or lower third of the vagina. Occurrences have been reported as 46%, 35%, and 19% in the upper, middle, and lower portion of the vagina (Rock, et al., Obstet. Gynecol. 59:448, 1982). Perforations are usually central but may be eccentric in location.
- Vaginal septa may also be longitudinal (sagittal or coronal). Longitudinal septa, which rarely produce clinical problems, probably result from abnormal mesodermal proliferation or persisting epithelium.

Phenotypic differentiation of the female external genitalia

- During week 3 mesenchyme cells from the primitive streak migrate around the cloacal membrane forming a pair of slightly elevated cloacal folds.
- Cloacal folds unite anteriorly forming the genital tubercle.
- In week 6 the cloacal membrane sub-divides into the urogenital and anal membranes, subdividing the cloacal folds into the urethral and anal folds. Another pair of elevated swellings, the genital swellings, appear on each side of the urethral folds. At this point the indifferent stage of external genitalia development has been reached.
- From this point the following changes occur. The genital tubercle develops into the clitoris. The genital swellings become the labia majora. Urethral folds develop into labia minora. The labiostis (vaginal orifice) develops between the urethral folds.

Phenotypic differentiation of the female external genitalia occurs due to the lack of the SRY region of the Y-chromosome and the lack of TGF.
21-hydroxylase Congenital Adrenal Hyperplasia (CAH), is the most common form (90-95% of cases) of this genetic condition causing the adrenal glands to make excess male hormones (androgens). In this case, ovaries, the uterus, fallopian tubes, upper vagina, and other müllerian structures are normally formed.

Prenatal exposure to substances with male hormone activity. Certain drugs, including progesterone (taken in the early stages of pregnancy to stop bleeding) and anabolic steroids, can cause developing female genitalia to become more masculinized.

Depending on the severity of hyperandrogenism, a female infant can be mildly affected, obviously ambiguous, or so severely virilized as to appear to be a male. (see Prader scale)

Prader-Willi Syndrome – Disorder Due in Part to Imprinting on the Long Arm of Chromosome 15

- Prader-Willi Syndrome (PWS) is a genetic disorder and the most common syndromic cause of obesity. (1:10,000 – 30,000 worldwide) Occurs equally in both sexes and all races.
- The genetic defect is lack of expression of the paternally inherited region of chromosome 15 (15q11-q13).
- Normally this region is expressed from the paternal allele, while the maternal allele is hypermethylated, thus “silencing” the transcription of genes on the maternal chromosome.
- Clinical manifestations involve primary neuropsychiatric and endocrine defects with secondary involvement in many different systems including hypogonadism:
  - Incomplete, delayed or abnormal pubertal development.
  - Men are thought to be infertile; there are two known case reports of a female PWS patient reproducing.

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or of part of a chromosome, from one parent and no copies from the other parent—a non-disjunctional event that can occur during meiosis.
Overview of kidney development

- 3 sets of kidneys develop
  - Pronephroi – rudimentary and non-functional; pronephric ducts used by mesonephroi
  - Mesonephroi – well-developed with function during weeks 6-10; most degenerate after this but the mesonephric ducts (from pronephric ducts) have several adult derivatives, including Gartner’s duct
  - Metanephroi – permanent kidneys; become fully functional around 9 weeks; urine is secreted into the amniotic cavity, forming part of the amniotic fluid

Metanephroi

- 2 sources for development
  - Ureteric bud – metanephric diverticulum; primordium of the ureter, renal pelvis, calyces, and collecting tubules
  - Metanephrogenic blastema – mesenchyme from the nephrogenic cord; forms the nephrons

Positional changes of the kidneys

- Begin adjacent to each other in the pelvis
- As the body grows the kidneys ascend until they contact the suprarenal glands during about week 9
- They also rotate medially, which places the hilum medially
- Note the alteration in blood supply as the kidneys ascend – 25% or more adults have accessory renal arteries; a polar renal artery can cause hydronephrosis
Common renal malformations

- Horseshoe kidney is the number one malformation (0.2% of the population)
- Fusion of the kidney causes its ascent to halt at the IMA
- Ectopic kidneys – simply a failure to ascend fully
- Duplicate ureter – early splitting of the ureteric bud

Langman's, fig 16.11

Langman's, fig 16.9