Urogenital Development

Intermediate Mesoderm
Interconnective - Urinary and Genital Systems
Recapitulation of Kidney Development
Epithelial-Mesenchymal Interactions
Indifferent Stage of Sexual Differentiation
Genetic vs. Environmental Factors

Kidney Architecture

Renal Cortex:
- Renal corpuscle
- Convoluted tubules
Renal Medulla:
- Collecting ducts
- Loop of Henle
Each Minor calyx drains a tree of collecting ducts within a renal pyramid
Pyramids are separated by columns of cortical tissues called renal columns
The Renal pyramids converge to form the renal papilla

Urinary System - Kidneys

Kidneys, Ureter, Bladder, Urethra
Intermediate Mesoderm

Early Development – 3 successive stages
Pronephros, Mesonephros, Metanephros

Pronephros- Most primitive Kidney
Cervical nephrotomes- 5 pairs of small hollow balls of epithelium – connected to the primary nephric duct (pronephric duct)

Non functional in mammals
Transient – nephrotomes degenerates by 24-25 days
Primary nephric duct extends caudally to become the Mesonephric duct
**Mesonephros**

Functional embryonic kidney

**Mesonephric tubules** form in each segment
- Cranial to caudal sequence
- First 4-6 bud out from the primary nephric duct
- Remaining form in the intermediate mesoderm and connect with the Mesonephric duct
- Mesonephric tubule differentiates a cup-shaped **Bowman’s capsule** that wraps around the **Glomerulus**
- Glomerulus is a knot of capillaries
- Bowman’s capsule and Glomerulus make up the **Renal Corpuscle**
- Mesonephric tubules connect to Mesonephric duct (Wolffian duct)
- Mesonephric kidney is the functional adult kidney of fish and some amphibians

**Mesonephric Duct**

Initially a solid rod that grows caudally
- Diverges from intermediate mesoderm and fuses with the ventrolateral cloacal wall (future bladder)
- Mesonephric duct undergoes canalization – transformation from mesenchyme to epithelium
- Mesonephros is functional until 10 weeks
- Mesonephric Duct regression depends on sex (Genital Development)
- Mesonephric is also called the Wolffian duct

**Metanephros**

**Ureteric Bud** (Metanephric diverticulum) – outgrowth of the distal mesonephric duct
- **Metanephric blastema** is the mesenchyme surrounding the ureteric bud
- Ureteric bud – multiple events of **elongation** and **bifurcation**
- Bifurcation results in two ampulla each with its blastema
Ureteric Bud/Metanephric Blastema

Ureteric Bud is induced by surrounding mesenchyme

- **GDNF** – Glial-Derived Neurotrophic Factor (metanephric blastema)
- **C-ret** – Tyrosine kinase receptor family (mesonephric duct)
- **WT-1** – Wilms tumor suppressor gene – controls GDNF

Elongation and Branching is controlled by cross-talk between the metanephric blastema and the tips of the branches

- Ureteric buds produce FGF2, BMP7, Wnt11
- Metanephric blastema produces Wnt4 and Pax2

Ureteric bud forms the collecting duct system

Metanephric blastema forms the renal tubules (note: mesenchyme to epithelium transition required)

Ureteric Bud Branching

Branching of the Ureteric bud gives developing kidney a lobular appearance, Sulcus separates the lobes

- First 4 bifurcations (16 branches) coalesce to form the Renal Pelvis and the Major Calyces
- Next 4 bifurcations coalesce to form the Minor Calyces
- 11 more branches forms 1-3 million collecting tubules
Nephron formation
metanephrogenic blastema forms
the nephric vesicle that elongates
and associates with a glomerulus
The tubules differentiates into the
1) Bowman’s capsule
2) Proximal convoluted tubule
3) Loop of Henle
4) Distal convoluted tubule
The distal convoluted tubule fuses with the collecting duct.

Renal corpuscle = Bowman’s capsule/glomerulus. The nephron is
the metanephric excretory unit.
The origin of the Renal corpuscle and tubules is distinct from the
collecting duct (Metanephric duct)
Duct systems merge
Renal duct – sequence of differentiation
renal corpuscle → proximal tubule → distal tubule
Loop of Henle elongates into the medulla
Late Changes

Branching system becomes larger forming the pelvis and calyces.
Kidneys undergo a cranial shift from the pelvic region to the abdominal region.
Kidneys also undergo a lateral displacement that brings them in contact with the developing Adrenal glands that fuse to the cranial pole.
Kidneys rotate 90° so that the renal pelvis is facing the midline.

Urogenital Sinus

Urogenital sinus forms:
- Bladder
- Pelvic urethra
- Definitive urogenital sinus

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Urethra</td>
<td>Membranous &amp; Prostatic Urethra</td>
<td>Urethra</td>
</tr>
<tr>
<td>Definitive Urogenital Sinus</td>
<td>Penile Urethra</td>
<td>Vagina</td>
</tr>
</tbody>
</table>

Bladder Formation

The ureter drains into the mesonephric duct that drains into the bladder.
The wall of the bladder expands and the mouth of the mesonephric duct flares so the mesonephric duct blend into the bladder wall.
The mesonephric duct contributes to the formation of the Trigone of the bladder.
The ureter gains a separate connection to the bladder.
The connections of the ureter to the bladder begins lateral to the mesonephric ducts and ends up at a superior position (the mesonephric duct migrates).
Urinary System Anomalies

3-4% of all newborns have a developmental abnormality of the urinary tract - most do not cause problems.

Renal agensis – unilateral or bilateral
Supernumerary kidney
Crossed ectopia – migration problem
Horseshoe kidney – fusion of kidneys fails to ascend
Bifid ureter - bifurcation of the ureteric bud
Genital System

Develops in conjunction with urinary system
Germ cells migrate from yolk sac to intermediate mesoderm medial to the developing mesonephros.
The Genital ridge forms at the 10th thoracic level medial and ventral to the mesonephros.
Early development of males and females are similar
Indifferent Phase

Gametogenesis

Spermatogenesis, oogenesis
Germ cells originate from yolk sac of embryo (parent)
Migration into genital ridge
Primary sex cords (compact strands of tissue)
Mitosis
Female - ovary, sex cords cells → ovarian follicle
Male - testis, sex cord cells → Sertoli cells of the seminiferous tubules
Sex cord cells are essential for gametogenesis.

Gametogenesis – Germ Cells

From BM Carlson, 1999

Genital Ridge

Supporting cells from the mesonephros and coelomic epithelium invade the genital ridge and aggregate around the primordial germ cells to form the primary sex cords.
Germ cells are required for invasion of supporting cells
Supporting cells are required for survival of germ cells
Genital ridge enlarges and forms a cortex and medulla—these regions have different fates in males and females
After 6 weeks—males and females diverge—prior to this is called the Indifferent phase of genital development.
Mullerian Duct

During week 6- paramesonephric duct (Mullerian duct) forms lateral to the mesonephric duct

Mullerian ducts is an invagination of coelomic epithelium
- Cranially at the 3rd thoracic segment
- Caudally they elongate, join and fuse with the urogenital sinus (medial to the mesonephric ducts)

At this time the mesonephric duct opens into the pelvic urethra
- The site of fusion with the pelvic urethra is called the Mullerian tubercle

The bilaterally fused region of the duct is the Uterovaginal canal
- At the cranial end there is an opening into the coelom that is funnel-shaped

Female Reproductive Tract

Ovary - Oogenesis
- Uterine (Fallopian) Tube
  - Fimbriare (finger like projections of Infundibulum)
  - Infundibulum
  - Ampulla – Fertilization
  - Isthmus
- Uterus - endometrium, myometrium, perimetrium
- Cervix
- Vagina

Ovary

Primitive (medullary) sex cords degenerate and secondary sex cords form from cortical tissues
- called Cortical sex cords

The germ cells in the degenerating medullary sex cords invade the cortical sex cords
- Germ cells differentiate into oogonia and enter 1st meiosis then arrest
- Cords break up into cell clusters = primitive follicles containing oogonia and follicle cells.
Mullerian Ducts Develop in Female

In the absence of testosterone:
- The mesonephric duct degenerates
- The Mullerian duct develops uninhibited
- Mullerian duct - cranial funnel-shaped opening to the coelom forms the fimbriated of the infundibulum
- The cranial Mullerian duct forms the uterine tubes
- The caudal end of the Mullerian ducts fuse to form the uterovaginal canal that later forms the uterus and the superior vagina

Urogenital Sinus

Urogenital sinus forms:
- Bladder
- Pelvic urethra
- Definitive urogenital sinus

<table>
<thead>
<tr>
<th>Pelvic Urethra</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous &amp; Prostatic Urethra</td>
<td>Urethra</td>
<td>Urethra</td>
</tr>
<tr>
<td>Definitive Urogenital Sinus</td>
<td>Penile Urethra</td>
<td>Vagina</td>
</tr>
</tbody>
</table>
Uterus and Vagina

The cranial end of the uterovaginal canal forms the uterus.
The caudal end of the uterovaginal canal forms the superior vagina.
The inferior vagina forms from the definitive urogenital sinus.
The uterus and vagina become occluded by tissue called the uterovaginal plate (forms from the Mullerian tubercle) that canalizes to form the lumen of the uterus and vagina.

External Genitalia

Initially the same in both sexes – Indifferent stage.
Genital folds flank the urogenital membrane.
The anterior genital folds form the genital tubercle.
Lateral to the genital folds are the genital swellings.
The genital tubercle elongates to form the phallus.

Genital Anomalies - Females

Phallus becomes the clitoris.
Genital folds become the labia minora.
Genital swellings become the labia majora.
Male Reproductive Tract

From Seeley, Stephens and Tate, 1989

Male Reproductive Tract

Testis (seminiferous tubules) - Spermatogenesis
Epididymis – biochemical maturation
Ductus deferens (vas deferens)
Ejaculatory duct and inputs:
  - seminal vesicle
  - prostate gland
  - bulbourethral gland
Urethra - out the penis

Testis Development

With the expression of Testosterone:
  - Primitive (medullary) sex cords of the genital ridge are maintained and the cortical tissues degenerate.
  - The medullary sex cord cells form the testis cords that contain Sertoli cells
  - Regions of the testis cords that contain germ cells will canalize and form the seminiferous tubules of the mature testis.
  - The inner portion of the testis cords form the Rete testis
  - The Rete testis connects with the efferent ductules of the Mesonephric duct
  - Seminiferous tubules become separated by mesenchyme that forms the interstitial cells of Leydig
Mesonephric Duct Develops in Males

The male utilizes the mesonephric duct while the paramesonephric (Mullerian) duct degenerates. Leydig cells produce testosterone and Mullerian-Inhibiting Substance (MIS). MIS induces Mullerian duct regression. The Rete testis connects with 5-12 residual efferent mesonephric tubules which connects the testis to the mesonephric duct system. The mesonephric duct becomes the epididymis in this region.

Male Duct System

Further caudally the mesonephric duct becomes the ductus deferens and drains into the urethra. Near the caudal end of the mesonephric duct the seminal vesicle develops as a lateral outgrowth. Caudal to the seminal vesicle the mesonephric duct becomes the ejaculatory duct. Prostate Gland forms from endodermal cells of the urethra and the surrounding mesenchyme, the glandular epithelium is endodermal. Bulbourethral gland - pea sized - endodermal outgrowths from urethra.

Urogenital Sinus

Urogenital sinus forms:
- Bladder
- Pelvic urethra
- Definitive urogenital sinus

Pelvic Urethra
- Membranous & Prostatic Urethra

Definitive Urogenital Sinus
- Penile Urethra

Males | Females
--- | ---
Membranous & Prostatic Urethra | Urethra
Penile Urethra | Vagina

External Genitalia

Initially the same in both sexes – Indifferent stage

Genital folds flank the urogenital membrane. The anterior genital folds forms the genital tubercle. Lateral to the genital folds are the genital swellings. The genital tubercle elongates to form the phallus.
Male Genitalia

Phallus elongates
Genital swellings enlarge and fuse to form the scrotum
Genital folds fuse to form the penile urethra - note: penile urethra does not extend to the tip of the penis
An ectodermal invagination at the tip of the penis fuses with the penile urethra.

Genital Anomalies - Males

Hypospadias – Ventral opening of urethra

Descent of the gonads

Both male and female gonads descend from the 10th thoracic level
Females descend less than males
In Males there are 3 phases of the descent
1) Caudal displacement due to regression of the mesonephric kidneys
2) Transabdominal descent to the Inguinal ring caused by regression of the Mullerian ducts (MIS activity)
3) Transinguinal descent into the scrotum guided by the gubernaculum into the vaginal process (evagination of the caudal abdominal wall)
Sex Determination

Genetic determination:
- Female – XX
- Male – XY

Y Chromosome - SRY – Sex-determining Region on the Y chromosome. Testis determination gene - DNA binding protein
Expressed in Sertoli cells (not germ cells)
Results in the induction of Leydig Cell differentiation
Leydig Cell → Testosterone → Trigger male development (XX mice)

<table>
<thead>
<tr>
<th>Indifferent structure</th>
<th>Male derivative</th>
<th>Female derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital ridge</td>
<td>Testis</td>
<td>Ovary</td>
</tr>
<tr>
<td>Primordial germ cells</td>
<td>Spermatogonia</td>
<td>Ova</td>
</tr>
<tr>
<td>Sex cords</td>
<td>Seminiferous tubules (Sertoli cells)</td>
<td>Follicular cells</td>
</tr>
<tr>
<td>Mesonephric tubules</td>
<td>Epithelial ducts</td>
<td>Epithelial ducts</td>
</tr>
<tr>
<td>Mesonephric (male) ducts</td>
<td>Appendix of epididymis</td>
<td>Appendix of ovary</td>
</tr>
<tr>
<td></td>
<td>Epididymal duct</td>
<td>Gartner's duct</td>
</tr>
<tr>
<td></td>
<td>Rectal duct</td>
<td>Rectal duct</td>
</tr>
<tr>
<td></td>
<td>Excretory duct</td>
<td>Excretory duct</td>
</tr>
<tr>
<td></td>
<td>Microwave duct</td>
<td>Microwave duct</td>
</tr>
<tr>
<td></td>
<td>Parameocyte (male) ducts</td>
<td>Appendix of testis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine tubes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vagina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td>Definitive urogenital sinus (lower part)</td>
<td>Perineum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower vagina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper vagina</td>
</tr>
<tr>
<td></td>
<td>Early urogenital sinus (upper part)</td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td>Genital tubercle</td>
<td>Prostatic urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clitoris</td>
</tr>
<tr>
<td></td>
<td>Genital folds</td>
<td>Root of penile-urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Labia majora</td>
</tr>
<tr>
<td></td>
<td>Genital swellings</td>
<td>Scrotum</td>
</tr>
</tbody>
</table>

Genital Anomalies - Genetics

Hermaphroditism - ambiguous external genitalia
- True hermaphrodite - both ovarian and testicular tissues
- Generally 46,XX (crossing over, X with short arm of Y)
- Ovotestes formation - medullary and cortex development
- Male pseudohermaphroditism - 46,XY
- External genitalia and ducts are intersex
- Inadequate testosterone or abnormal MIS production
- Female pseudohermaphroditism - 46,XX
- Overproduction of androgens
- Masculinization of genitalia - clitoral hypertrophy
- Androgen insensitivity syndrome (Testicular feminization syndrome) - 46,XY - female in all ways but with testis - results from androgen receptor defects