Development of the Reproductive System

Thomas A. Marino, Ph.D.
Department of Anatomy & Cell Biology
Temple University School of Medicine
Question

• What does it mean to be female?
Question

• What does it mean to be male?
Question

• Are humans sexually dimorphic?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not XX and not XY</td>
<td>One in 1,666 births</td>
</tr>
<tr>
<td>Klinefelter (XXY)</td>
<td>One in 500-1,000 males</td>
</tr>
<tr>
<td>Androgen insensitivity syndrome</td>
<td>One in 20,000 births</td>
</tr>
<tr>
<td>Hypospadius</td>
<td>One in 125 male births</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>One in 15,000 births (classic)</td>
</tr>
<tr>
<td></td>
<td>One in 1,000 births (non-classic)</td>
</tr>
<tr>
<td>XX testicular disorder</td>
<td>One in 20,000 births</td>
</tr>
<tr>
<td>Swyer syndrome</td>
<td>One in 30,000</td>
</tr>
<tr>
<td>Turner’s syndrome (XO)</td>
<td>One in 2,500 girls</td>
</tr>
<tr>
<td>Kallmann syndrome</td>
<td>One in 10,000 to 86,000 births</td>
</tr>
<tr>
<td>Ambiguous genitalia</td>
<td>One in 5,000 births</td>
</tr>
</tbody>
</table>

This slide makes the following point. “Estimates from specialists working in major medical centers suggest that about one in every 2,000 births at a hospital involves a child whose genitals are atypical enough to make the child’s sex unclear. But, as noted above, if we count all types of sex anomalies, DSD must be considered much more numerous than 1 in 2,000.” [http://www.accordalliance.org/learn-about-dsd/faq.html](http://www.accordalliance.org/learn-about-dsd/faq.html)
When talking about an individual one needs to consider:

- Genetic sex – number of X and Y chromosomes
- Sex determining genes
- Gonadal sex – ovaries or testes
- Gonadal Hormones
- Phenotypic sex
  - Duct system
  - External genitalia
- Brain
  - Gender identity - an individual’s self identification as male or
Development of the Reproductive System

Two X - female
The ovaries will develop.

XY = male
The Y chromosome has sex-determining region
In the sex-determining region there is the testis determining factor that is encoded.
If present then the testes will develop.
Development of the Reproductive System

1921 - males had XY; females XX
1959 - Y determined maleness; lack of Y femaleness
1966 - short arm of Y carried information necessary for testis development
Development of the Reproductive System

Short arm

XX males

XY Males

XY Females

Long arm deletions

Long arm
Development of the Reproductive System


SRY
Development of the Reproductive System

Primary Sex Determination
Y needed to become male
Second X needed to become female
X0 = female without ovarian follicles
This is Turner’s syndrome with female hypogonadism (gonadal dysgenesis).
Development of the Reproductive System

Two X - female
XY = male

The sex-determining region of the Y chromosome.

The Y chromosome has the Testis determining factor on it.
If present then male develops
Development of the Reproductive System

Primordial germ cells migrate from yolk sac.
Populate the posterior body wall in the fifth week.
Get there via the dorsal mesentery.
Development of the Reproductive System

Germ cells arrive at the T10 vertebral level.
Induce the coelomic epithelium to form primitive sex cords.
Sex cords proliferate and a swelling is produced called the genital ridges.
Sulik website
Development of the Reproductive System

Sex cords have:
   Medullary region
   Cortical region

After six weeks they begin the develop differently in males and females.
Development of the Reproductive System

Sex cords surround the germ cells and will become:

- ovarian follicles in the female.
- Sertoli cells of the germinal epithelium of the seminiferous tubules in the male.

Without sex cords - no germ cell maturation
Without germ cells - no sex cords.
Development of the Reproductive System

Lateral to mesonephric ducts the coelomic epithelium invaginates.

Longitudinal ducts form that start in the thoracic region and end medial to the point where the mesonephric ducts empty into the pelvic urethra.

The ends of the ducts fuse in this region.

These are the paramesonephric ducts.

Sulik Website
Development of the Gonads

- Genetic males have testis determining factor on the sex determining region of the Y chromosome (SRY).

- SRY upregulates Steriodogenesis factor 1 (SF1) which acts through SOX9 in the sex cords.

- + SRY medullary sex cords differentiate into Sertoli Cells

  Sertoli cells produce anti-mullerian hormone

- In genetic females Wnt4 is upregulated

- Dax1 – upregulated by Wnt4

- Cortical sex cords differentiate into oogonia and follicle cells.

- FoxL2 – expressed in ovary in pregranulosa and granulosa cells.

  Without Sertoli cells no anti-Mullerian hormone produced
DAX1 + WNT4 = FOXI2

SRY + SF1 = SOX9

Ovary
- Granulosa Cells
- Thecal Cells
- Follicles
  - Estrogen

Testis
- Sertoli Cells
  - SF1
  - MIH
- Leydig Cells
  - SF1
  - Testosterone
<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Function</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-1</td>
<td>9</td>
<td>Transcription factor</td>
<td>Gonad development and adrenal development</td>
</tr>
<tr>
<td>WT-1</td>
<td>11</td>
<td>Transcription factor</td>
<td>Gonad development and kidney development</td>
</tr>
<tr>
<td>SRY</td>
<td>Y</td>
<td>Transcription factor</td>
<td>Testis determining factor</td>
</tr>
<tr>
<td>DAX1</td>
<td>X</td>
<td>Transcription factor</td>
<td>Ovarian formation Testis repressor</td>
</tr>
<tr>
<td>SOX9</td>
<td>17</td>
<td>Transcription factor</td>
<td>Inhibits DAX1?</td>
</tr>
<tr>
<td>MIS (AMH)</td>
<td>19</td>
<td>Growth Factor</td>
<td>Inhibits paramesonephric duct development</td>
</tr>
<tr>
<td>Wnt-4</td>
<td>?</td>
<td>Growth factor</td>
<td>Ovary and paramesonephric duct differentiation</td>
</tr>
</tbody>
</table>
Development of the Reproductive System

At the end of the sixth week the indifferent stage comes to an end. Can not tell male from female: Medullary and cortical sex cords present. Germ cells present in both. Mesonephric and paramesonephric ducts present. After this point males & females diverge.
Development of the Gonads

Indifferent stage:
- Mesonephric ducts
- Paramesonephric ducts
- Gonads

Mesonephric ducts
- Paramesonephric ducts
- Gonads
- Primary Urogenital Sinus
Development of the Ducts

AMH induces degeneration of the paramesonephric ducts

AMH causes the cells in the gonadal ridge to become Leydig cells

Leydig cells produce:
- Testosterone
- Dihydrotestosterone

No AMH
paramesonephric ducts persist

DAX1 – Downregulates SF1
WNT4 - Contributes to ovarian differentiation
Development of the Reproductive System

Secondary Sex determination
body phenotype
determined by hormones
  Anti-Mullerian hormone
  Testosterone
Without the hormones the female phenotype appears.
Role of Testosterone

Induces development of male genital duct system.
Induces developmental changes in the brain.
At puberty causes seminiferous tubules to canalize, mature, and produce sperm.
Induces changes in primary and secondary sexual characteristics.
Week 6
Primitive Ducts
Development of Male Genital Ducts

8 weeks
Development of Male Genital Ducts
Development of the Female Genital Ducts

Estrogen is secreted from the ovaries.
Induces the Mullerian ducts to become:

- Uterine Tubes
- Uterus
- Cervix
- Upper 1/3rd of the vagina
Development of the Female Genital Ducts
Development of the Female Genital Ducts
Development of the Female Genital Ducts

- Paramesonephric ducts come into contact with the pelvic urethra.
- The posterior wall of the pelvic urethra thickens and becomes the sinovaginal bulbs.
Development of the Female Genital Ducts

- Fused paramesonephric ducts become genital canal or uterovaginal canal.

- Sinusal tubercle forms the sinovaginal bulbs.
Development of the Female Genital Ducts

Lower part of the uterovaginal canal becomes the superior part of the vagina (fornices).

Sinuvaginal bulbs become the vaginal plate, which elongates and becomes the lower vagina.

The tissue between the vaginal plate and the primary UG sinus remains as the hymen.
Development of External Genitalia

- By the fifth week there are swellings on either side of the cloacal membrane: cloacal folds.

http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital024.htm
Development of External Genitalia

- Indifferent stage lasts until week 12 or the end of the first trimester.
Role of Dihydrotestosterone

In fetus causes external genitalia to become a penis and scrotum.
Induces development of prostate.
# Development of External Genitalia

<table>
<thead>
<tr>
<th>Anlage</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital tubercle</td>
<td>Glans &amp; Shaft of Penis</td>
<td>Glans and Shaft of Clitoris</td>
</tr>
<tr>
<td>Def. UG sinus</td>
<td>Penile Urethra</td>
<td>Vestibule of the Vagina</td>
</tr>
<tr>
<td>Urethral Fold</td>
<td>Penis</td>
<td>Labia minora</td>
</tr>
<tr>
<td>Labioscrotal Fold</td>
<td>Scrotum</td>
<td>Labia Majora</td>
</tr>
</tbody>
</table>
Development of External Genitalia

Genital tubercle elongates = phallus
Pulls urethral folds to become urethral groove.
Urethral groove does not reach glans.
Urethral groove is lined by endoderm = urethral plate.
Urethral folds close urethral groove to become urethra.
Sexual Differentiation

• Phenotypic sexual development occurs over the first 2 months of pregnancy.
• Sexual differentiation of the brain occurs over the 2\textsuperscript{nd} half of pregnancy.