Embryology of Genital System

Basics:
- The urogenital system consists of: urinary & genital systems.
- Both develop from the intermediate mesoderm (mesodermal ridge).
- The ducts of both two systems opens in a common cavity, the cloaca.

Development of the Genital System

- The sex is determined after fertilization; either female (XX) or male (XY).
- However, initially the genitalia are identical in morphology in both sexes and this is known as indifferent stage.
- The key of sexual dimorphism (differentiation) is the Y chromosome which contains a gene called SRY gene (sexual determining region) on its short arm Yp11.
- The protein product of the SRY gene, testes-determining factor, stimulates the development of male genitalia.
- In absence of SRY gene (as in female XX), the female genitalia are developed.
- The gonads appear initially as a **gonadal** or **genital ridge**.
- Primordial germ cells appear at the early stages of development (3rd week) around the wall of yolk sac close to allantois.
- These germ cells migrate and reach the genital ridge by the 6th week.

  ![Diagram of External Genitalia Development](image)

  **External Genitalia Development**

**Undifferentiated State:**

- Genital tubercle "phallus".
- Labioscrotal swellings.
- Urogenital folds.
- Urogenital sinus.

  - The genitalia become differentiated by the 12th week of gestation.
  - Under the effect of Androgens, male hormones, male external genitalia develop.
  - In absence of Androgens, female external genitalia develop.
The most important required androgen for development of male genitalia is **Dehydrotestosterone (DHT)**.

\[
\text{Tostesterone} \xrightarrow{5 \alpha - \text{reductase}} \text{DHT}. \quad (5\alpha - \text{reductase} \text{ is the key enzyme}).
\]

**Differentiation of Genitalia in Both Sexes**

<table>
<thead>
<tr>
<th>Embryologic Structure</th>
<th>The Corresponding Part of the External Genitalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital tubercle &quot;phallus&quot;</td>
<td>Glans Penis</td>
</tr>
<tr>
<td>Labioscrotal swellings</td>
<td>Scrotum</td>
</tr>
<tr>
<td>Urogenital folds</td>
<td>Ventral Portion of the Penis</td>
</tr>
<tr>
<td>Urogenital sinus</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Bladder.</td>
</tr>
<tr>
<td></td>
<td>Prostate.</td>
</tr>
<tr>
<td></td>
<td>Prostatic utricle.</td>
</tr>
<tr>
<td></td>
<td>Bulbourethral glanda.</td>
</tr>
<tr>
<td></td>
<td>Seminal colliculus.</td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Bladder.</td>
</tr>
<tr>
<td></td>
<td>Urethral &amp; preurethral glands.</td>
</tr>
<tr>
<td></td>
<td>Vagina.</td>
</tr>
<tr>
<td></td>
<td>Greater vestibular glands.</td>
</tr>
<tr>
<td></td>
<td>Hymen.</td>
</tr>
</tbody>
</table>

---

**Embryologic Structures**

- **Ectoderm**
- **Endoderm**
- **Glandular plate**
- **Urethral groove**
- **Urorectal folds**
- **Pancreatic bud**
- **Corpus cavernosum**
- **Penile urethra**
- **Spongiosum**
- **Penile raphe**
- **Vestibule of vagina**
- **Scrotal raphe**
Development of Internal Genitalia

Remember:
- They develop from the gonadal ridge.
- The undifferentiated gonads begin to develop on the 5th week.
- In presence of Y chromosome (where SRY gene), testes develop.
- In absence of Y chromosome, ovaries develop.
- In female:
  - The ovary develops from the cortex whereas the medulla regresses.
  - At birth, ovary has around 2 millions oocytes.
- In male:
  - The testes develop from the medullary sex cord and the cortex regresses.

Undifferentiated stage:
- Gonadal ridge.
- Genital ducts: mesonephric (Wolffian) and paramesonephric duct (Mullerian).
Male Pathway

Internal genitalia:
- The SRY gene is activated in the 6th week and stimulates undifferentiated gonads to form testes.
- The modullary sex cord forms sertoli cells and seminiferous tubules.
- Sertoli cells secrete antimullerian hormones AMH (inhibit the growth of Mullerian duct) which is a functional marker for sertoli cells.
- Then AMH causes differentiation of Leydig cells.
- Leydig cells produce tostesterone.
- Tostesterone stimulates Wolfian ducts to form:
  - Epididymis.
  - Vas deferens.
  - Seminal vesicles.

External genitalia: develop under the effect of androgen as mentioned above.

Female Pathway

Internal Genitalia:
- Absence of SRY gene causes undifferentiated gonads to form ovary.
- Since there is no sertoli cells, so there is no AMH.
- Therefore, the Mullerian duct continuous to differentiate into:
  - Fallopian tube (the cranial ends; which remains separated).
  - The pelvic ends of the two ducts fuse together forming one tube which forms:
    - Uterine canal: endometrium, glands and myometrium.
    - Cervix.
    - Upper vagina.
- The wolfian ducts in absence of tostesterone (no leydig cells), regresses and disappears at the 10th week.
- Development of the Vagina:
  - Mullerian duct is connected with the thickened area of the urogenital sinus.
  - Fusion of these two structures form the Vaginal Plate.
- The cranial end of this plate proliferates increasing the distance between the uterus and the urogenital sinus.
- So, the uterus has a dual origin:
  - The upper portion is derived from the uterine canal.
  - The lower portion is derived from the urogenital sinus.

External genitalia: as mentioned before.
APPLIED EMBRYOLOGY

Congenital Anomalies of Uterus and Vagina (defects of Mullerian ducts):

- **Mayer-Rokitansky-Küster-Hauser Syndrome (or Rokitansky Syndrome):**
  - Agenesis of both uterus and vagina.
  - This is due to failure of development of Mullerian duct.

- **Uni-cornoate Uterus** (unilateral hypoplasia of one Mullerian ducts).

- **Failure of fusion:**
  - **Uterus didelphys.**
  - **Bicornuate uterus.**
  - **Septate uterus.**

- **Asherman's Syndrome:**
  - Uterine synechiae or intrauterine adhesion.

- **Transverse vaginal septum.**

- **Imperforate hymen.**
Ambiguous genitalia

- It is a birth defect in which the external genitalia do not have the typical appearance of either male or female.

- Causes:
  - Congenital Adrenal Hyperplasia CAH.
  - 5α-reductase deficiency.
  - 17β-hydroxysteroid dehydrogenase deficiency.
  - Hermaphroditism: a medical condition in which the baby is born with both ovarian and testicular tissue.
  - Chromosomal abnormalities: Klinefelter and Turner's syndromes.

- Investigations:
  - Keratotypy: XX, or XY??
  - Hormonal assay: FSH, LH, Testosterone, progesterone,..
  - Pelvic US.
  - Pelvic MRI.
  - DNA for genetic testing.

Congenital Adrenal Hyperplasia CAH

- Occurs in female XX.
- Autosomal recessive.
- Characterized by genetic defect in enzymes mediating the production of cortisone by the adrenal gland from cholesterol.

- Pathophysiology:
  - 21-hydroxylase enzyme deficiency → ↓ cortisone production → adrenal hyperplasia (to compensate) → ↑ Androgen production → Mascularization of external genitalia → Ambiguous genitalia.

- Management:
  - Correct cortisone.
  - Genital surgery: cosmetic, stenosis or obstruction.
Complete Androgens Insensitivity CAI

- Occurs in male XY.

- **Pathophysiology:**
  - Disruption of androgen receptors gene $\rightarrow$ Lack of body response to androgens $\rightarrow$ development of female external genitalia.
  - AMH is secreted $\rightarrow$ regression of mullerian duct $\rightarrow$ absence of internal female genitalia.
  - The baby has an intra-abdominal testes.

- The baby is born with female genitalia with normal morphology, normal breast, without any signs of muscularization but has no menses at puberty.

- **Management:**
  - Surgical removal of testes before puberty.
  - Vaginal dilatation, vaginoplasty.

Swyer's Syndrome

- Occurs in male fetus XY.

- **Pathophysiology:**
  - Mutation in the SRY gene $\rightarrow$ disruption of male pathway $\rightarrow$ XY fetus diverts to female pathway.
  - The gonads don't produce AMH or Testosteron.
  - So the external genitalia of female develop and Mullerian ducts develop into internal organs (uterus, cervix and vagina).
  - At puberty:
    - There is amenorrhea (primary amenorrhea) and abnormal breast development.
    - Hormonal assay reveals elevated gonadotrophin and low estradiol and testosterone.
  - Management:
    - Removal of gonads (gonadectomy).
    - Pregnancy is possible only with a donor oocytes.
5α-reductase and 17β-hydroxysteroid dehydrogenase deficiency

<table>
<thead>
<tr>
<th>Androstenedion</th>
<th>17β-hydroxysteroid dehydrogenase</th>
<th>Testosterone</th>
<th>5α-reductase</th>
<th>DHT</th>
</tr>
</thead>
</table>

- Both of the two conditions occur in XY (male fetus).
- Caused by deficiency of one of these two enzymes which are important for androgens production.
- Initially, the fetus develops normally under the effect of SRY gene with male gonads.
- But absence of androgens, the female external genitalia develop.
- AMH is present so the Mullerian duct regresses.
- Wolffian duct develop so epididymis, vas deferens and seminal vesicles are present.
- **Presentation:**
  - Ambiguous genitalia: Female with clitoromegally and poor breast development.
  - Pubic and axillary hair has a male distribution pattern.

**Hermaphroditism**

**True Hermaphroditism:**
- Presence of both ovarian and testicular tissues in one person.
- Occurs in majority (80%) of XX fetuses, and minority (20%) of XY fetuses.
- **Causes** is unknown.
- **Presentation:**
  - Most of cases present with ambiguous genitalia.
  - The degree of muscularization depends on the function of the testicular tissues.
  - 80% (the majority) have female internal organs and are potentially fertile.
- **Management** is unknown.

**Pseudohermaphroditism:**
- The genitalia are of one sex, but some physical characteristics of the other sex are present.