Disorders of Sex Development and The Basis of the Gender Identity Crisis

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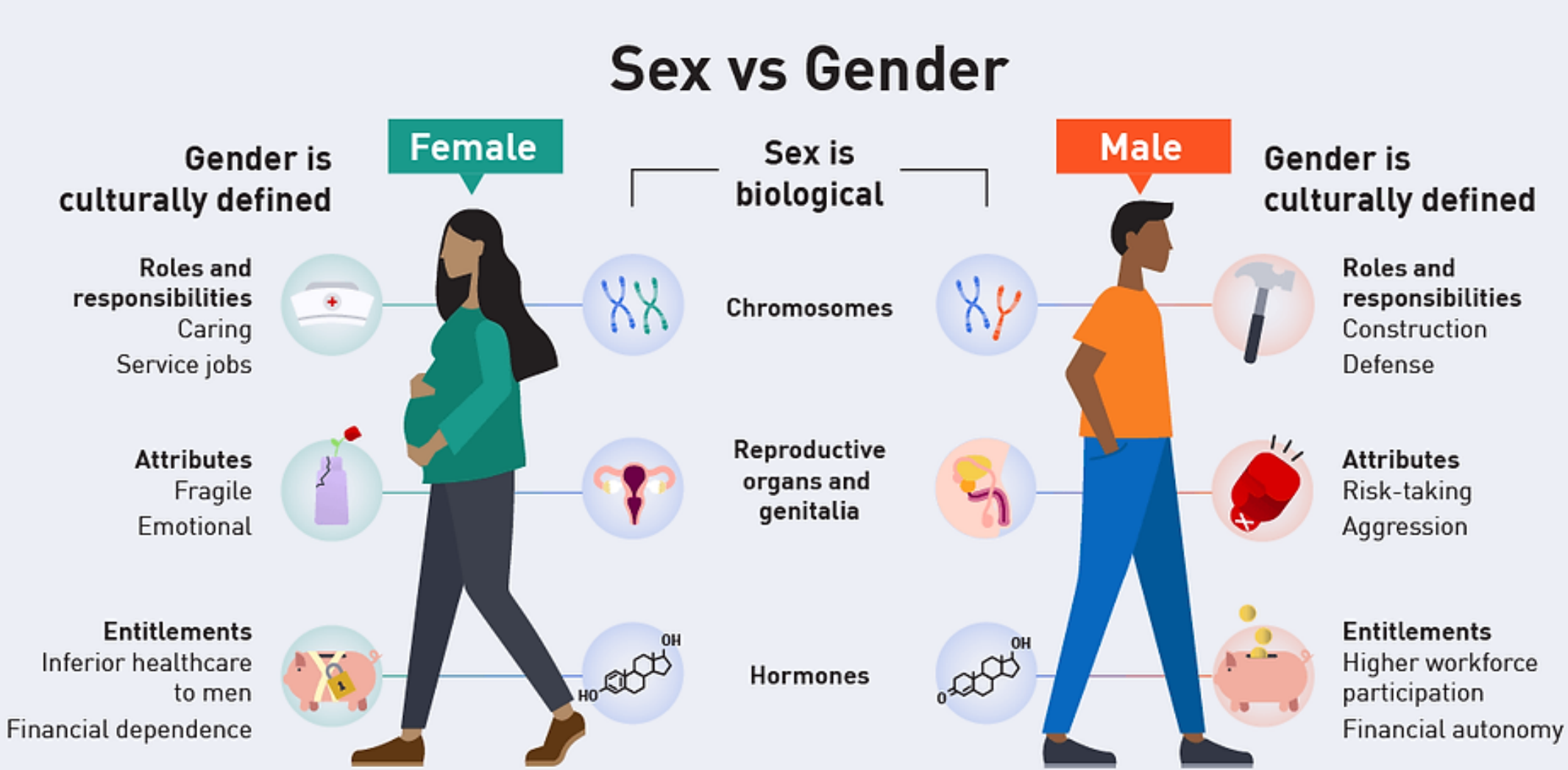
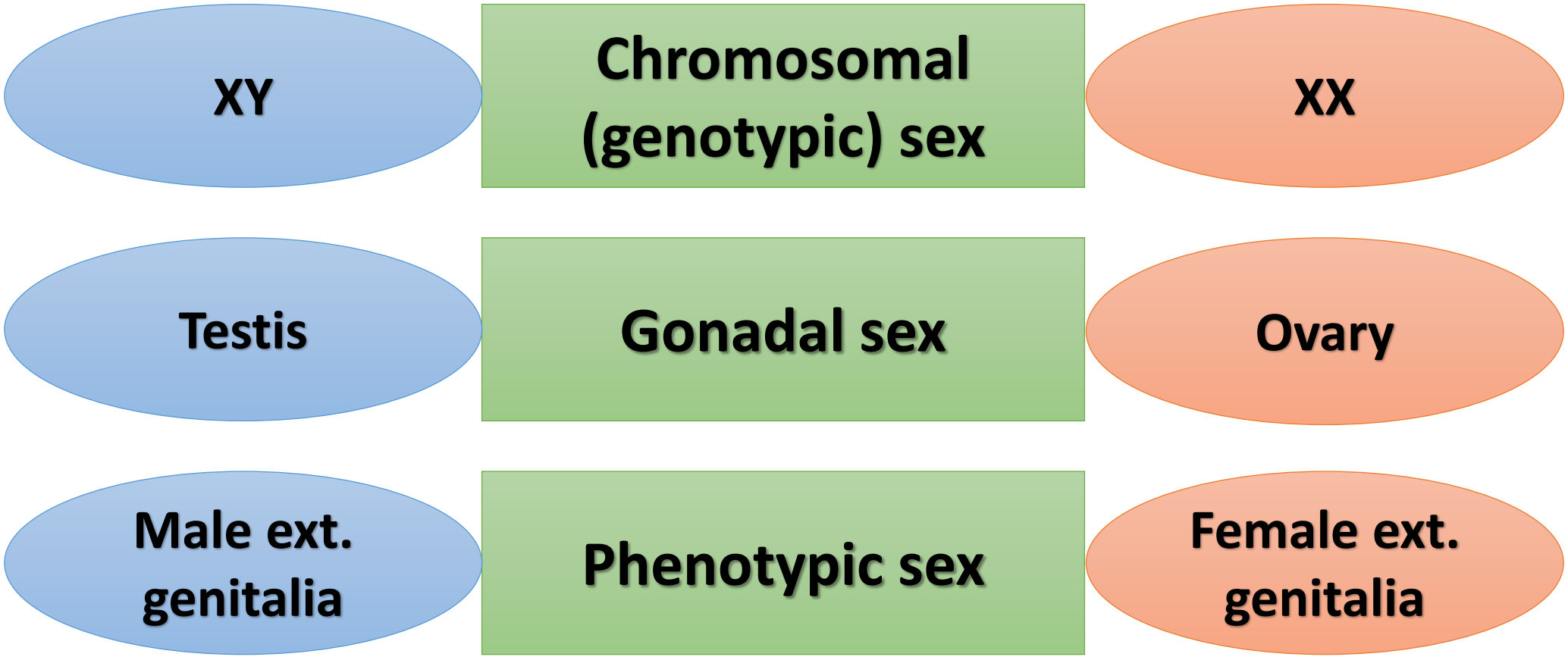
Sex vs. gender

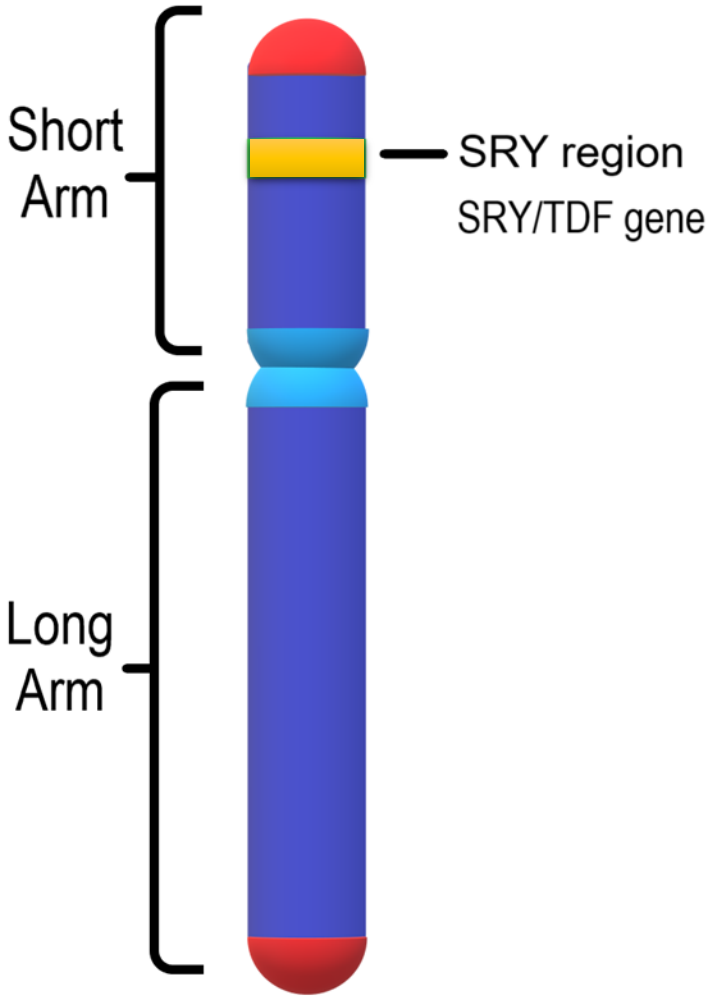


Sex


XY
Chromosomal (genotypic) sex
XX
Testis
Gonadal sex
Ovary
Male ext. genitalia
Phenotypic sex
Female ext. genitalia

Key to sexual dimorphism

- Y chromosome
- **SRY region**
- **SRY** (sex-determining region on Y)**/TDF** (testis-determining factor) **gene** on its short arm.
- **SRY protein/TDF** (the protein product of SRY/TDF gene) is a transcription factor.
  - Under the influence of TDF, **male** development occurs.
  - In the absence of TDF, **female** development occurs.



Genital system

- **2 basic processes** are involved in the development of the genital system:

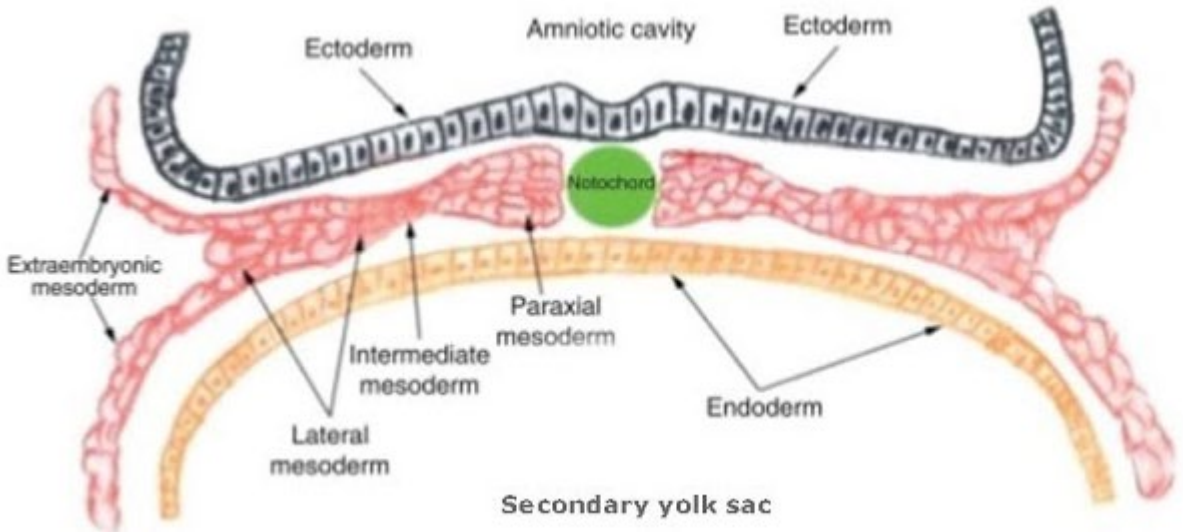
Sex determination	Sex differentiation
Determination of Chromosomal (genotypic) sex	Establishment of Gonadal and Phenotypic sex
At the time of fertilization	A complex process involving many genes

Components of genital system

- **The genital system consists of:**
  - A pair of **gonads** (testes or ovaries)
  - **Genital ducts** (duct system of gonads) that carry the germ cells
  - **External genital organs** (external genitalia)
- **Genital system development is studied under 3 headings:**
  - Development of **gonads**
  - Development of **genital ducts**
  - Development of **external genital organs** (external genitalia)

Sources of development

- **3 sources:**
  - Intermediate mesoderm
  - Part of cloaca
  - Celomic epithelium covering the intermediate mesoderm



Stages of development

- **2 stages:**
  - Indifferent/primitive stage
  - Definitive stage

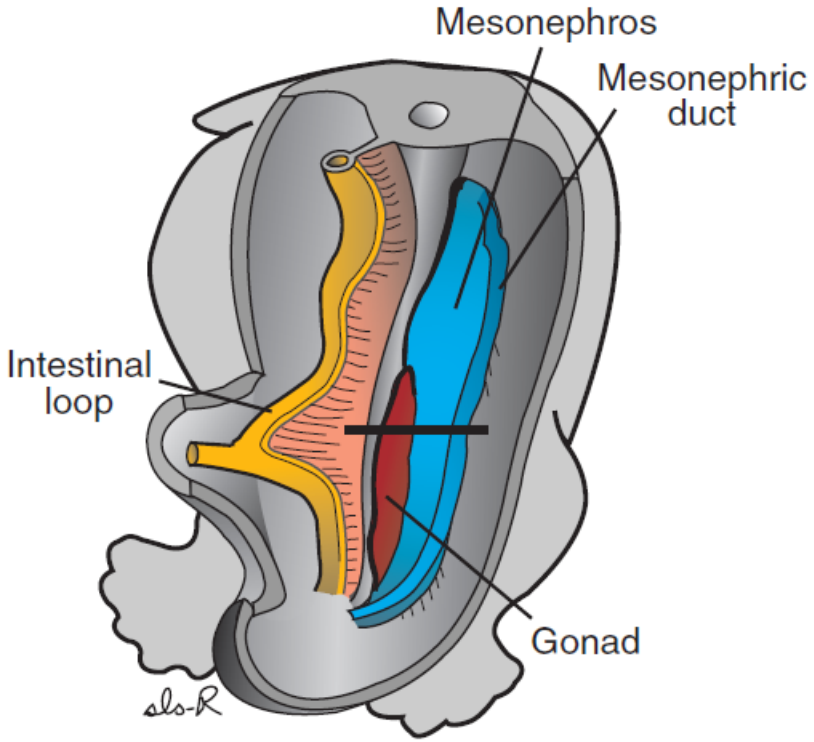
Development of gonads

Indifferent stage

- The gonads do not acquire male or female morphological characteristics until the **seventh week** of development, although the chromosomal sex of the embryo is determined at the time of fertilization.

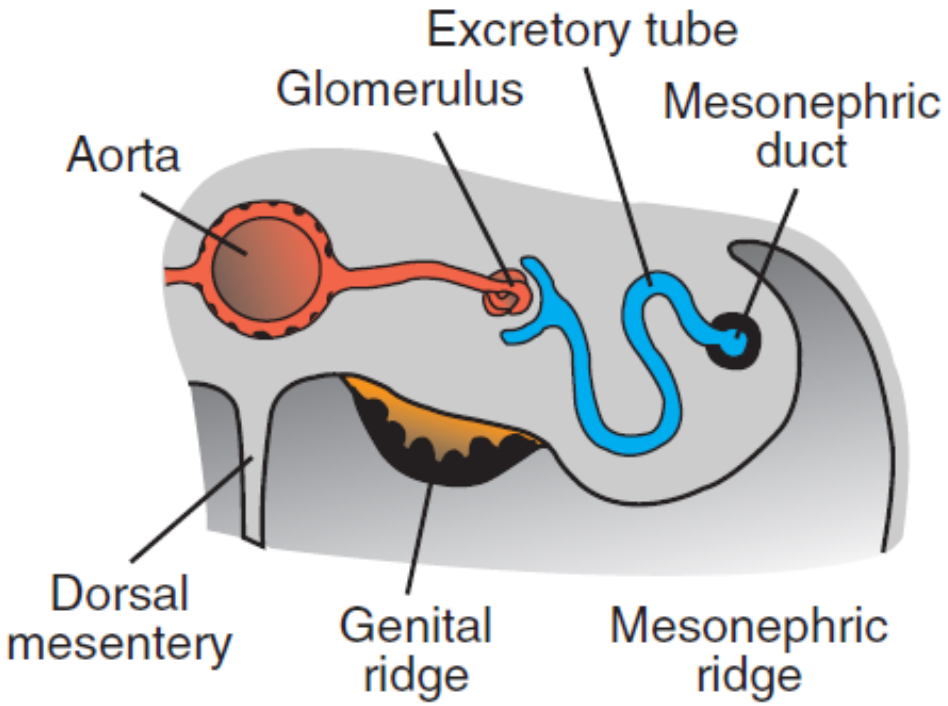
Indifferent stage-Formation of gonadal (genital) ridge

- Gonads appear initially as a pair of longitudinal ridges, **gonadal (genital) ridges**, just medial to mesonephric ridges.



Indifferent stage-Formation of gonadal (genital) ridge

- Formed by the **proliferation** of the surface (celomic) epithelium and **condensation** of underlying mesenchyme.

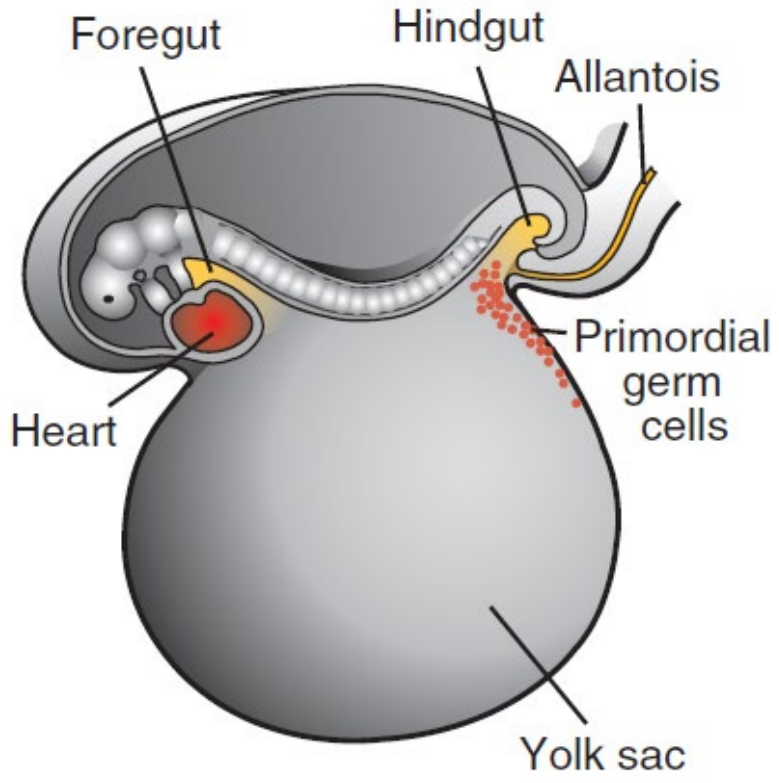


Indifferent stage-Formation of gonadal (genital) ridge

- Germ cells do not appear in the gonadal (genital) ridges until **the sixth week** of development.

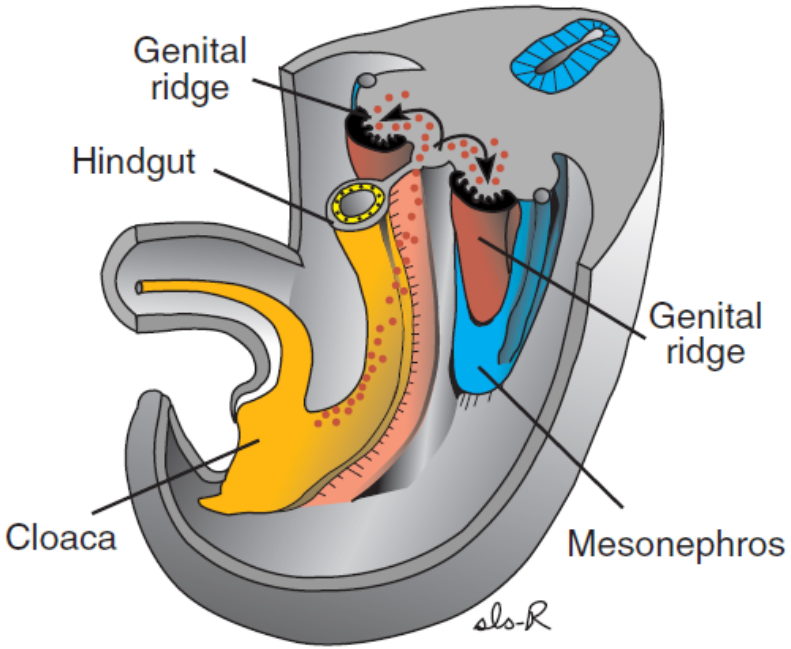
Indifferent stage-Entry of germ cells

- **Primordial germ cells (PGCs)** first appear in the wall of the yolk sac close to the allantois.



Indifferent stage-Entry of germ cells

- Migrate by **ameboid movement** along the dorsal mesentery of the hindgut.
- Arrive and invade the gonadal (genital) ridges at the beginning of **the sixth week.**

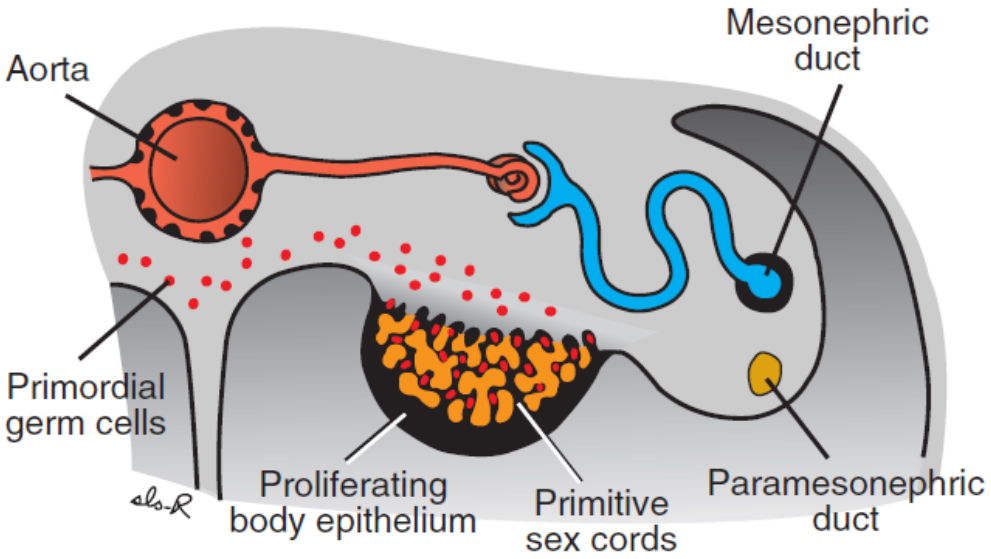


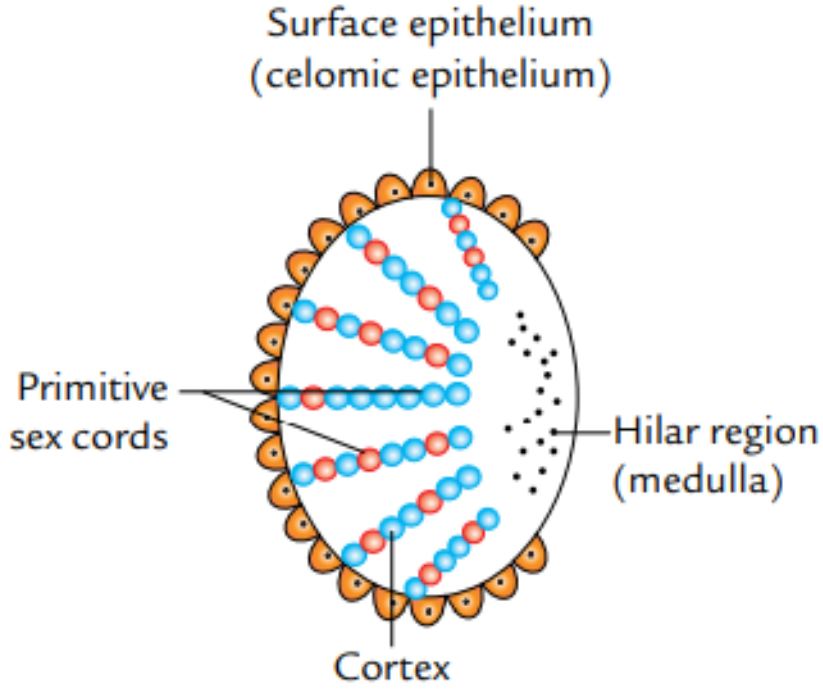
Indifferent stage-Entry of germ cells

- The primordial germ cells have an **inductive influence** on the development of the definitive gonad.
- If they fail to reach the ridges, the definitive gonads do not develop.

Indifferent stage-Formation of primitive sex cords

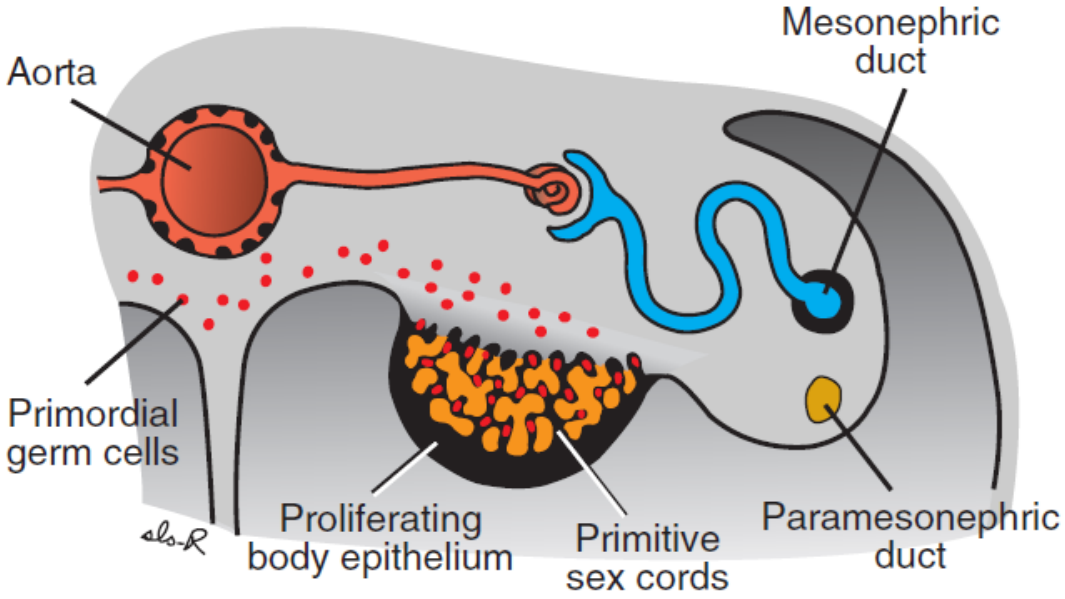
- On arrival of PGCs into the gonadal (genital) ridge, **the cells of celomic epithelium covering the gonadal ridge** proliferate and penetrate the underlying mesenchyme to form finger-like cords called **primitive sex cords**.

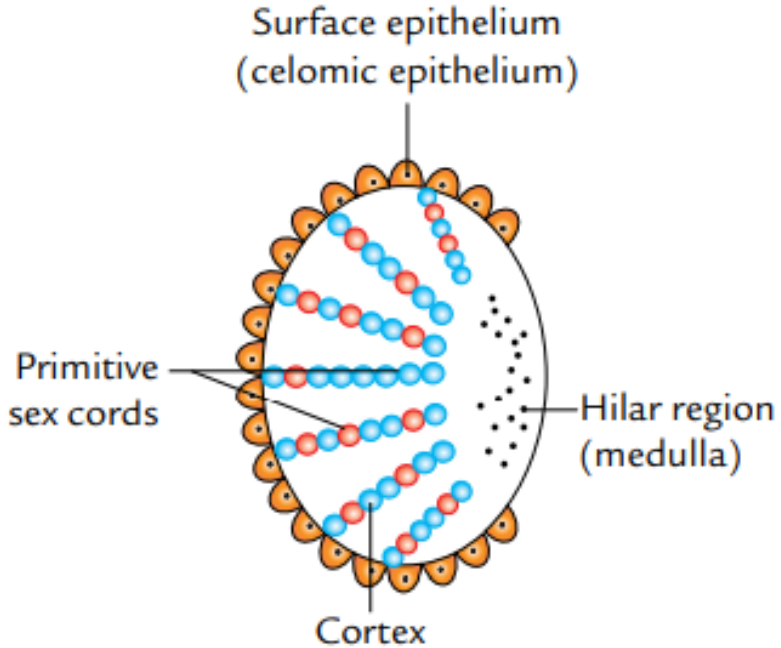




Indifferent stage-Formation of primitive sex cords

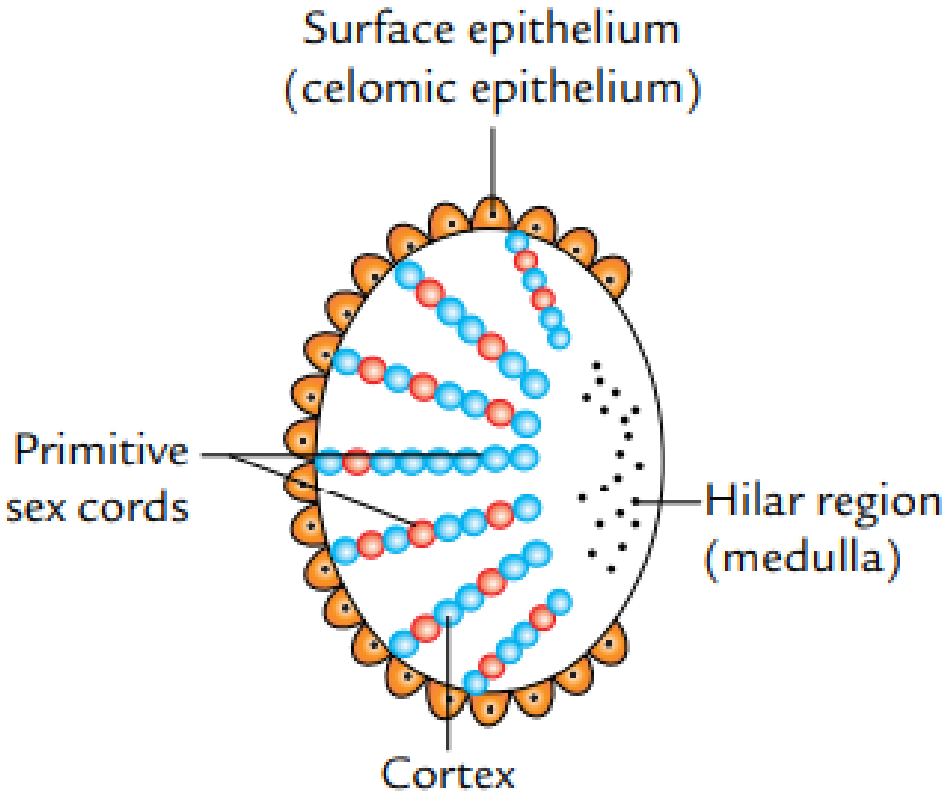
- In both male and female embryos, primitive sex cords are **connected** to celomic epithelium.
- The outer part of the gonadal (genital) ridge is called the **cortex,** and its central part is called the **medulla**.

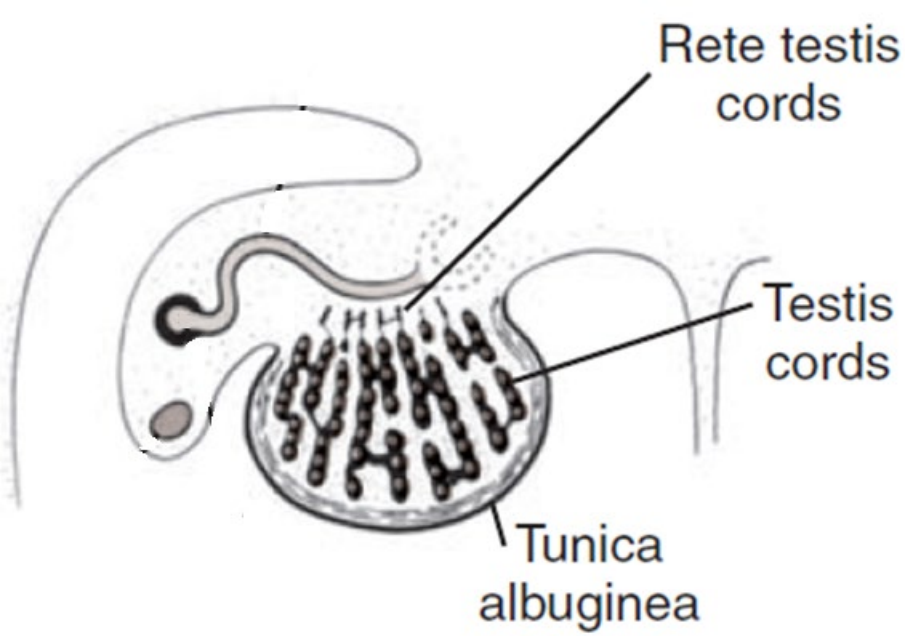


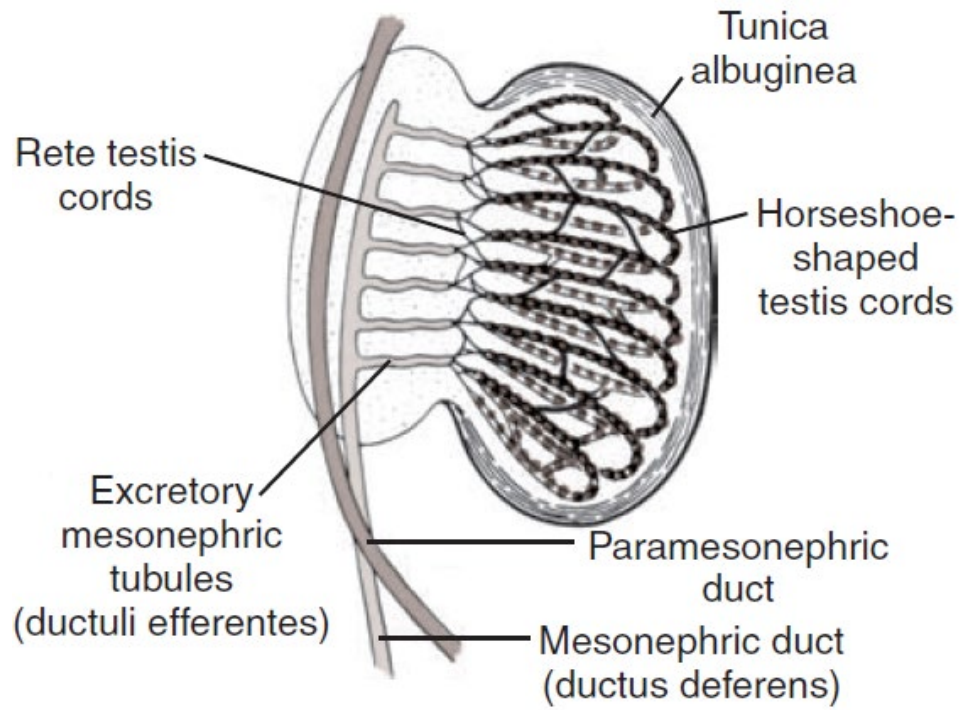


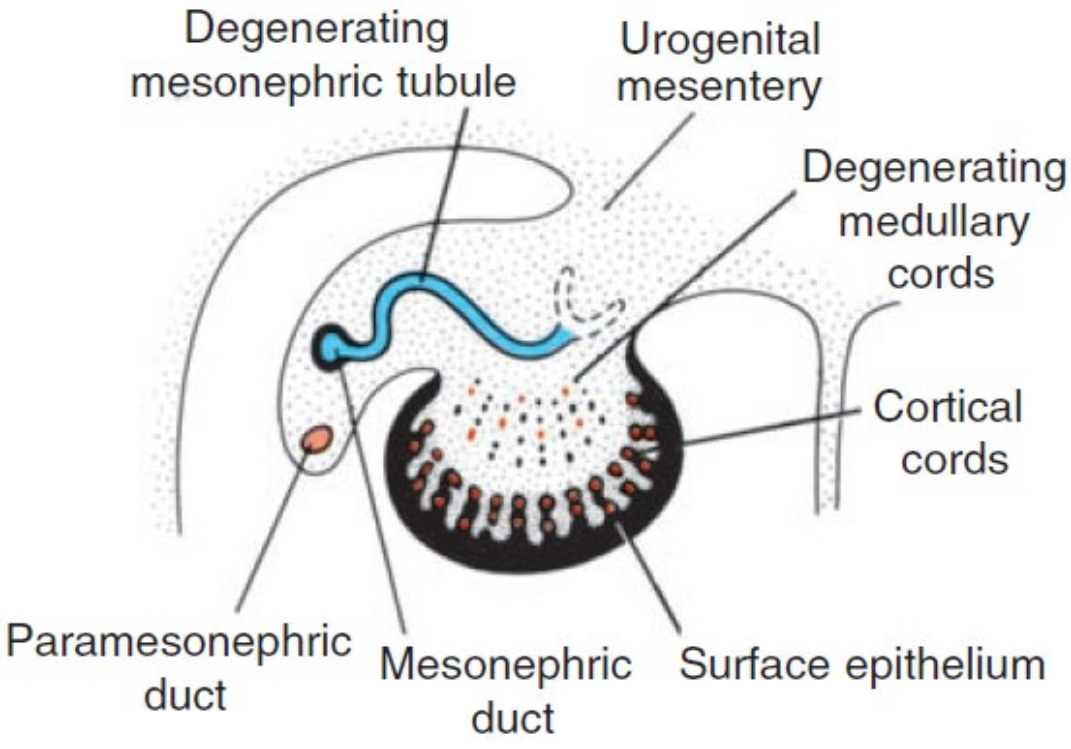
Indifferent stage-Formation of primitive sex cords

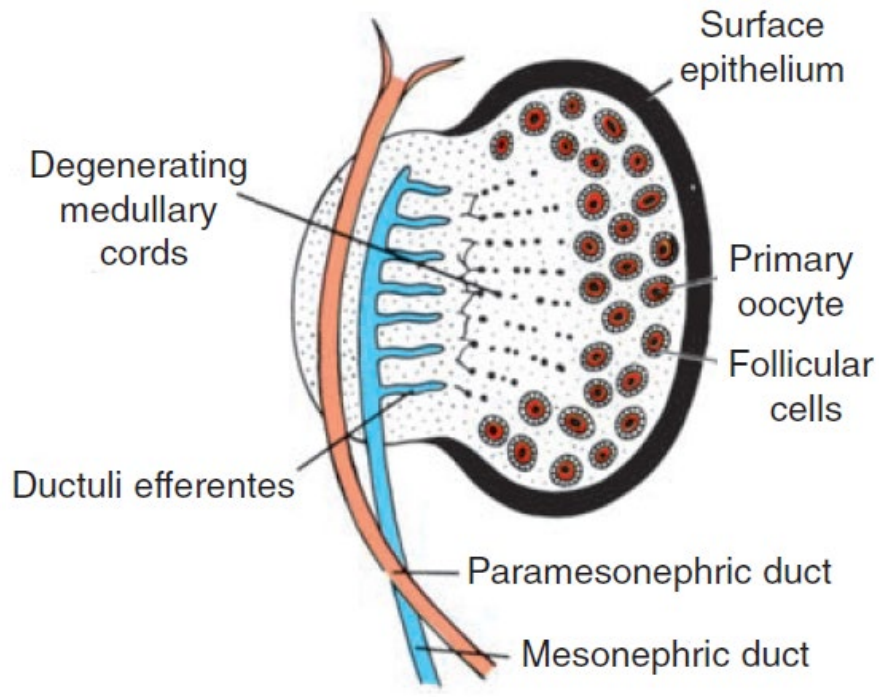
- Impossible to differentiate between the male and female gonad. Hence, the gonad is known as the **indifferent gonad**.

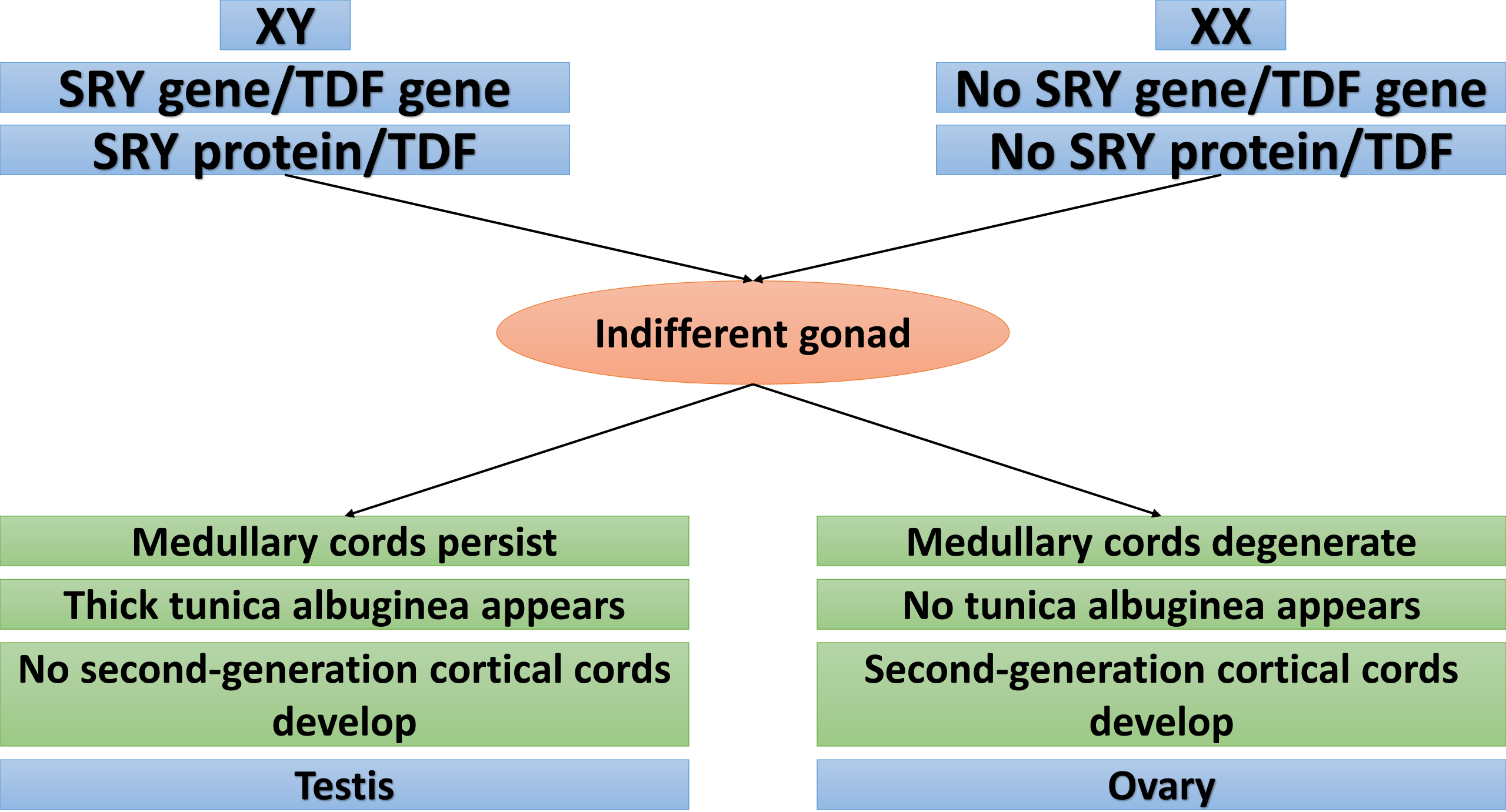



Rete testis cords
Testis cords
Tunica albuginea


Tunica albuginea
Rete testis cords
Horseshoe-shaped testis cords
Excretory mesonephric tubules (ductuli efferentes)
Paramesonephric duct
Mesonephric duct (ductus deferens)

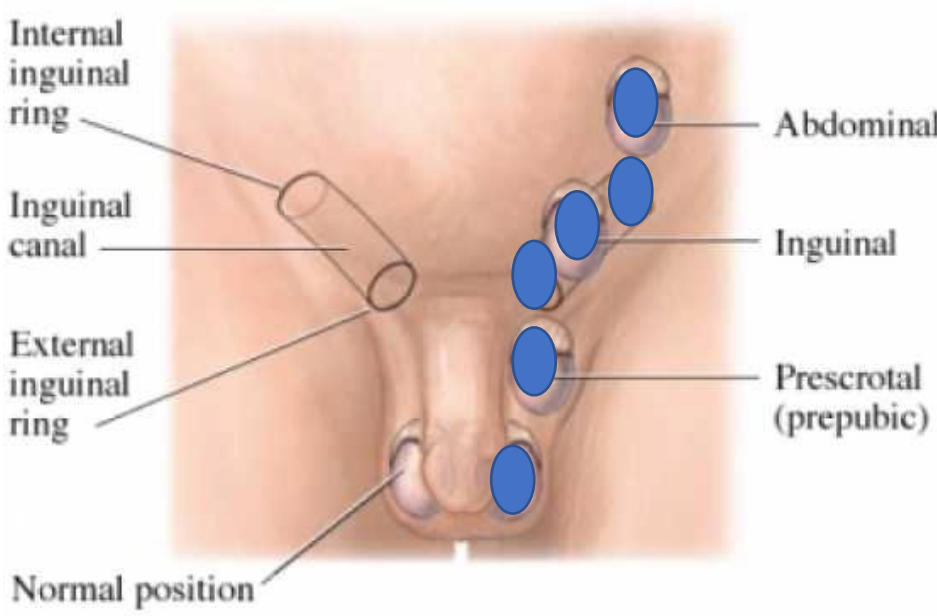

Degenerating mesonephric tubule
Urogenital mesentery
Degenerating medullary cords
Cortical cords
Paramesonephric duct
Mesonephric duct
Surface epithelium

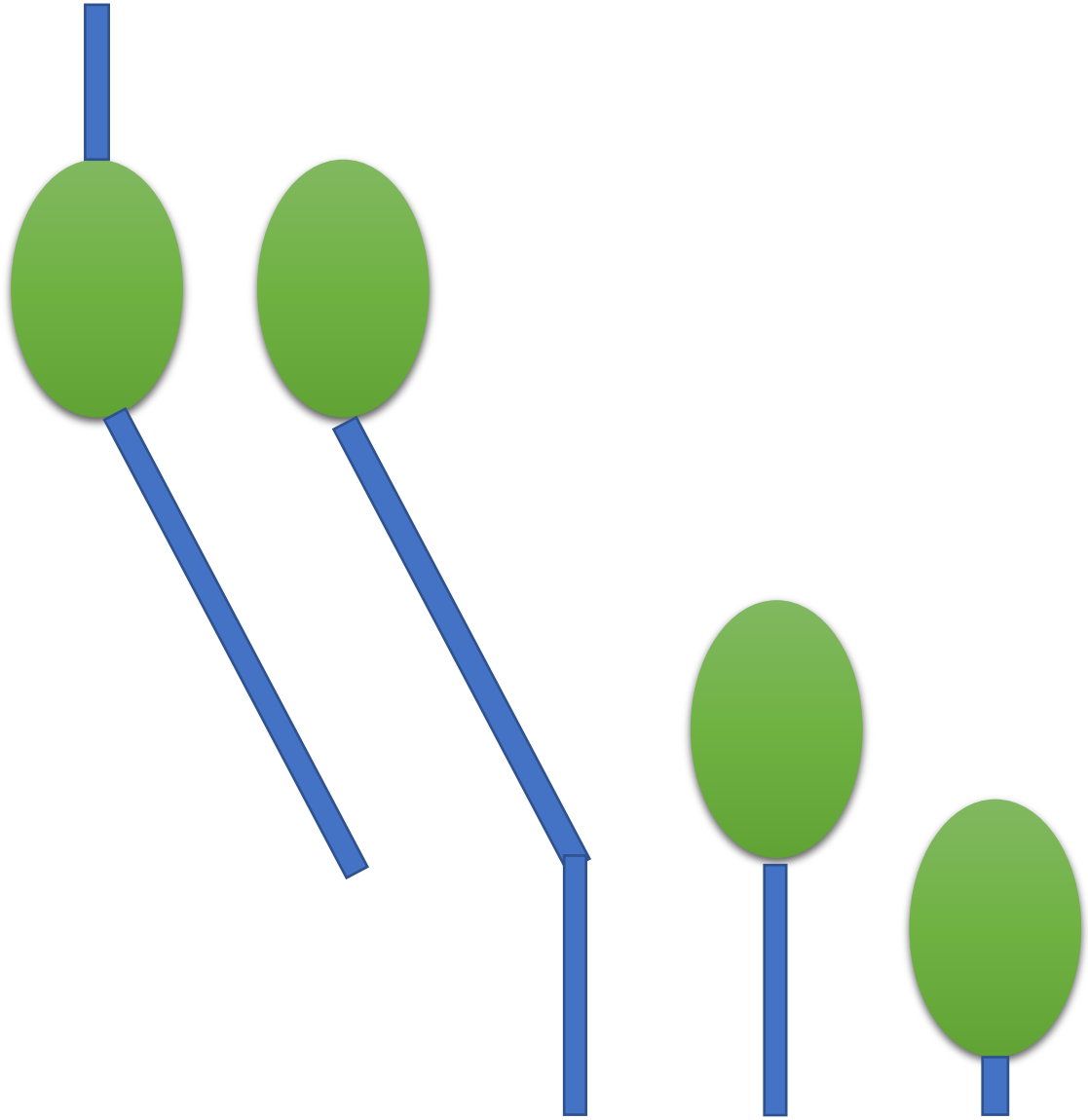

Surface epithelium
Degenerating medullary cords
Primary oocyte
Follicular cells
Ductuli efferentes
Paramesonephric duct
Mesonephric duct


XY
SRY gene/TDF gene
SRY protein/TDF
XX
No SRY gene/TDF gene
No SRY protein/TDF
Indifferent gonad
Medullary cords persist
Thick tunica albuginea appears
No second-generation cortical cords develop
Testis
Medullary cords degenerate
No tunica albuginea appears
Second-generation cortical cords develop
Ovary

Descent of the testes

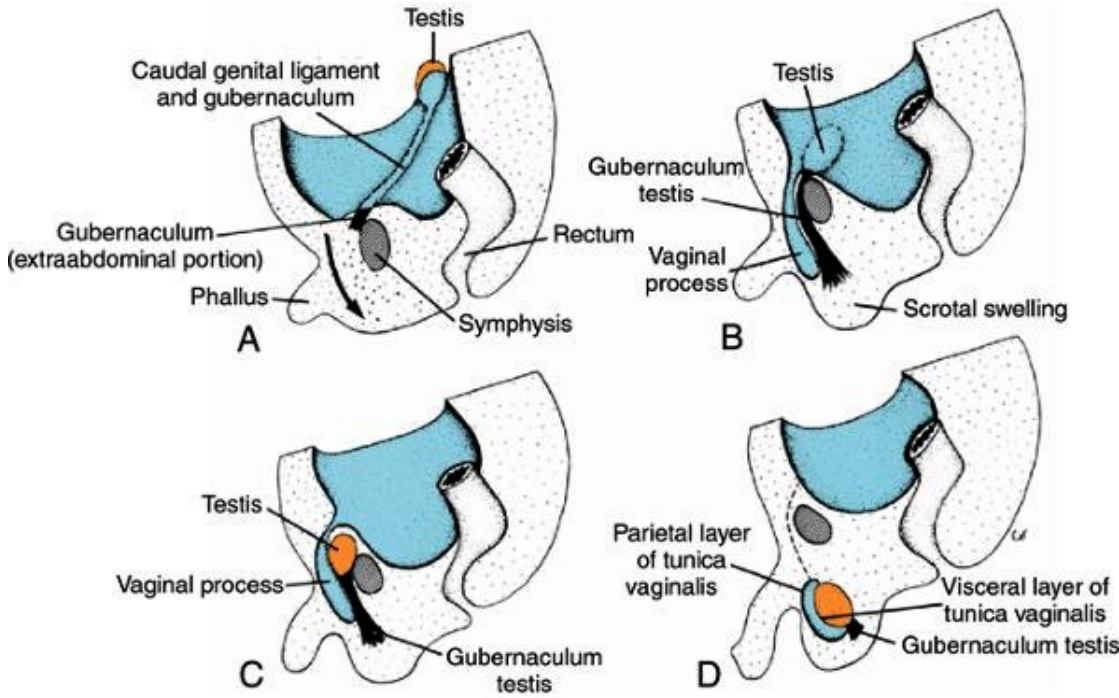
- The testis develops in the abdominal cavity where the temperature is high and unsuitable for proper spermatogenesis.
- Hence, it migrates into the scrotum.
- At or just after birth, it reaches the base of the scrotum.





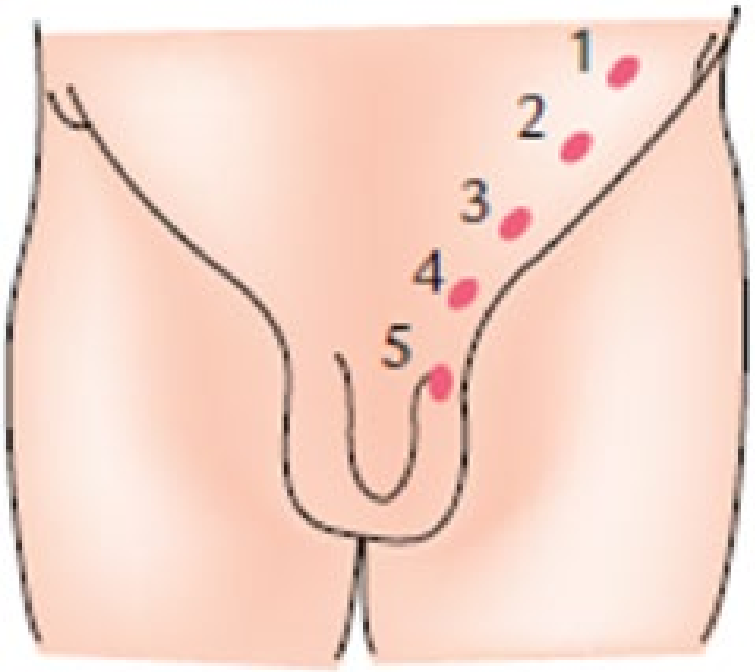
Factors controlling descent of the testis

- **Outgrowth of the extra-abdominal portion** of the gubernaculum produces intra-abdominal migration.
- **An increase in intra-abdominal pressure** due to organ growth produces passage through the inguinal canal.
- **Regression of the extra-abdominal portion** of the gubernaculum completes the movement of the testis into the scrotum.
- **Differential growth of the body wall.**
- **Hormones** (male sex hormones produced by the testis, and maternal gonadotrophins).
- **Calcitonin gene-related peptide (CGRP)**, a neurotransmitter secreted by the genitofemoral nerve.



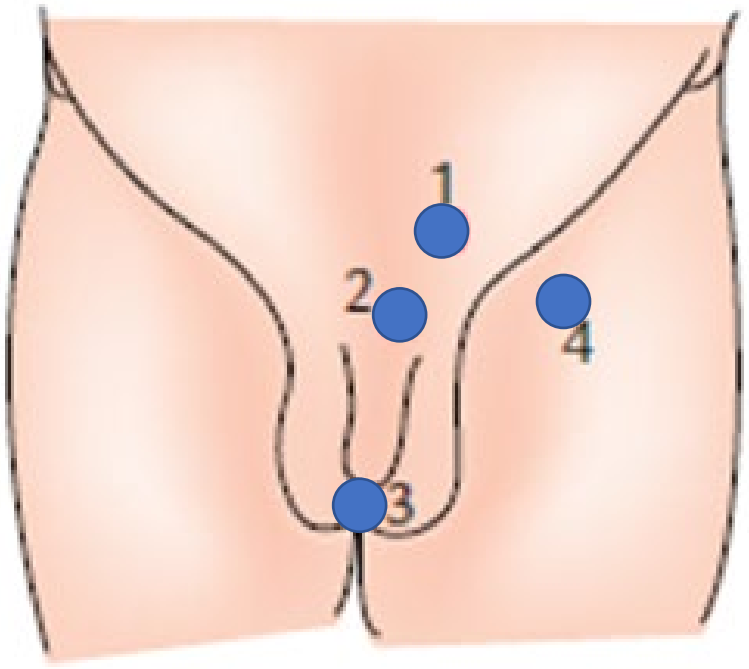
Cryptorchidism (incomplete descent of testis)

- In this condition, the testis travels through its normal path but fails to reach the base of the scrotum during its descent.
- Thus, it may be found
  - within the abdomen
  - at the deep inguinal ring
  - within the inguinal canal
  - at the superficial inguinal ring
  - high up in the scrotum
- **Complications**:
  - It may fail to produce spermatozoa (**infertility**).
  - It is prone to undergo **malignant change**.



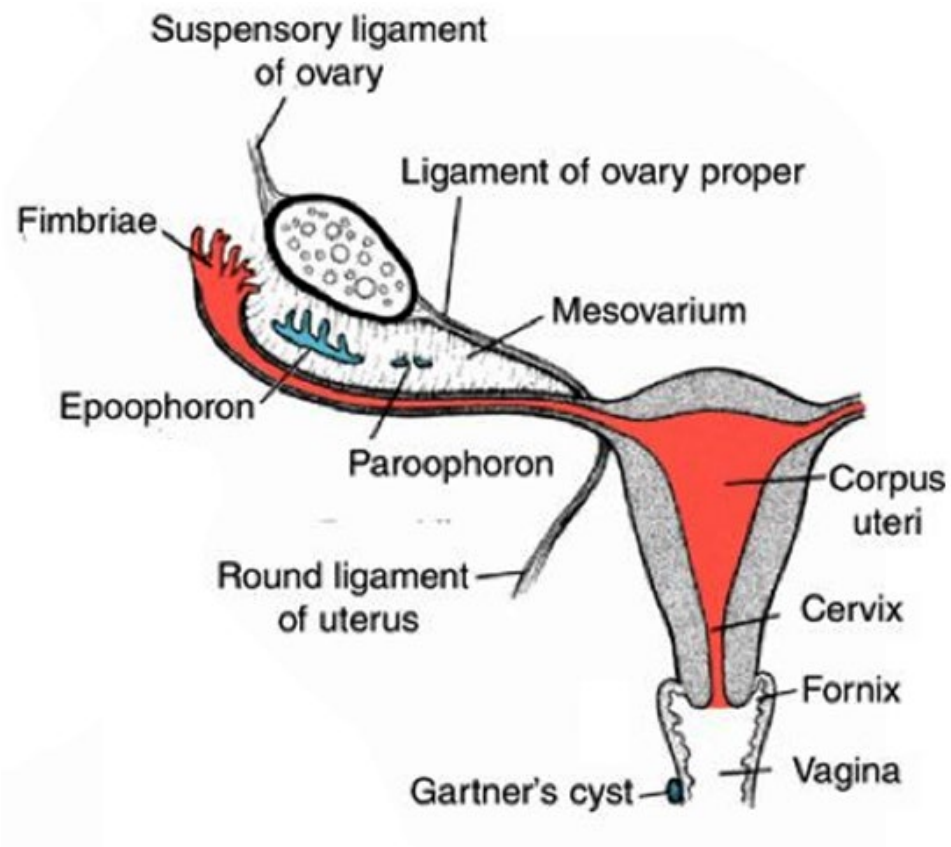
Ectopic testis (maldescent of the testis)

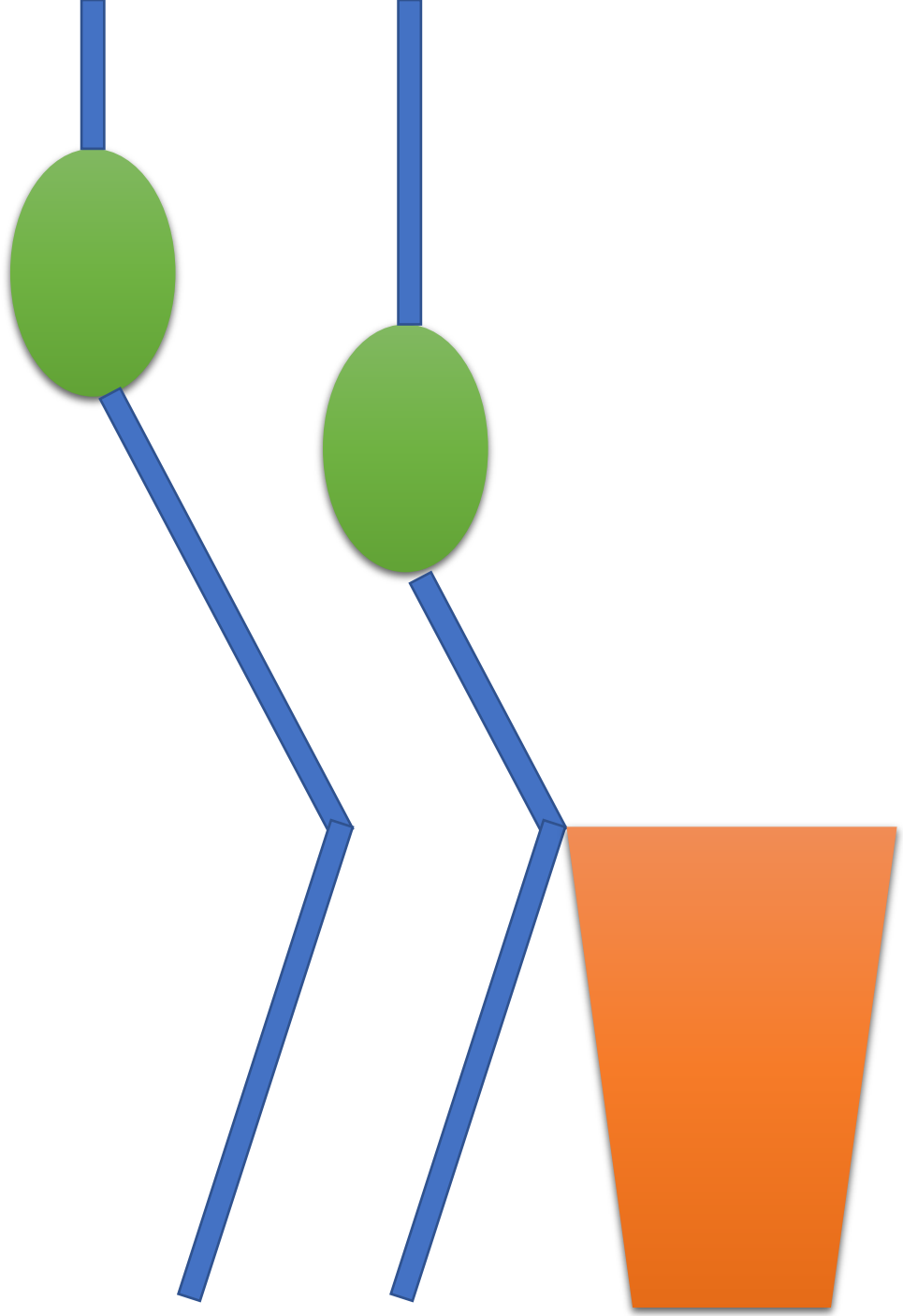
- In this condition, the testis travels down along an abnormal path, and therefore fails to reach the scrotum.
- Thus, it may be found
  - in the superficial fascia of the lower part of the anterior abdominal wall
  - in front of the pubis
  - in the perineum
  - in the thigh
- **Complication:**
  - An ectopic testis is susceptible to **trauma**.



Descent of the ovaries

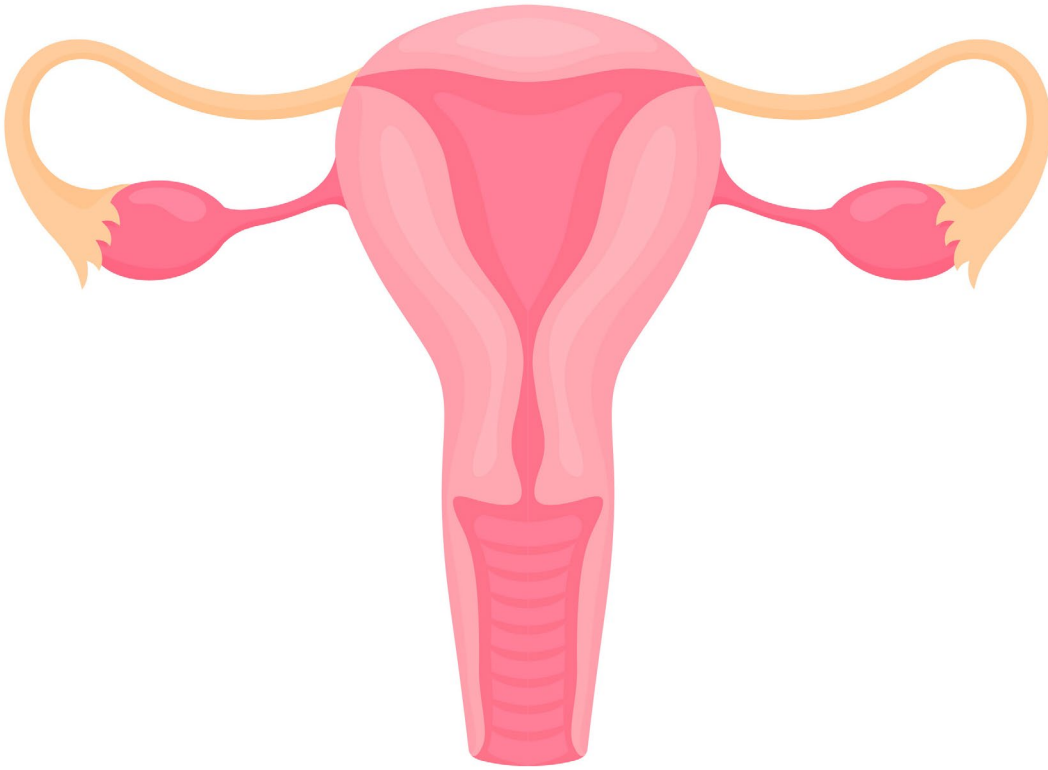
- The descent of the ovary is **considerably less** than the descent of the testis.
- The **cranial genital ligament** forms the suspensory ligament of the ovary.
- The **caudal genital ligament (gubernaculum ovary)** forms the ligament of the ovary proper and the round ligament of the uterus.
- The latter extends into the labia majora.





Genital ducts and external genitalia

- **Genital ducts**
  - **Male**
    - Efferent ductules
    - Duct of epididymis
    - Vas deferens
    - Ejaculatory duct
  - **Female**
    - Fallopian tube
    - Uterus
    - Vagina
- **External genitalia**
  - Male external genitalia
  - Female external genitalia

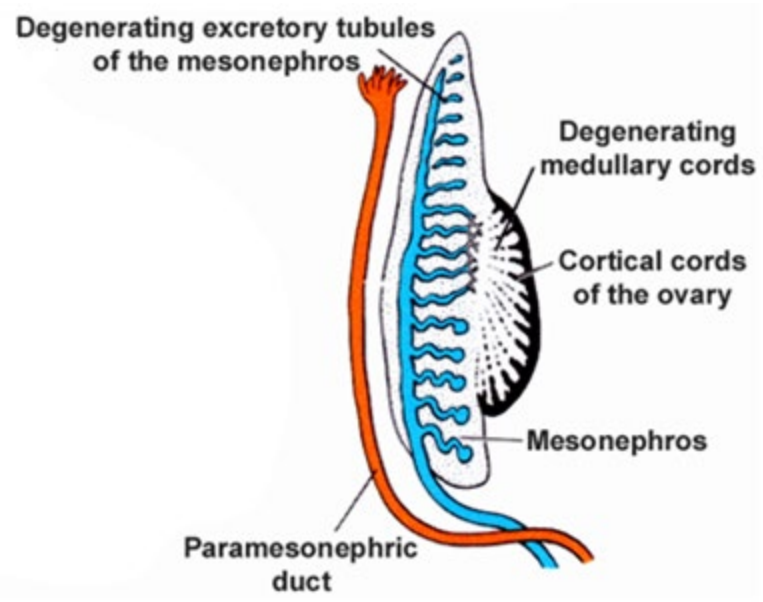


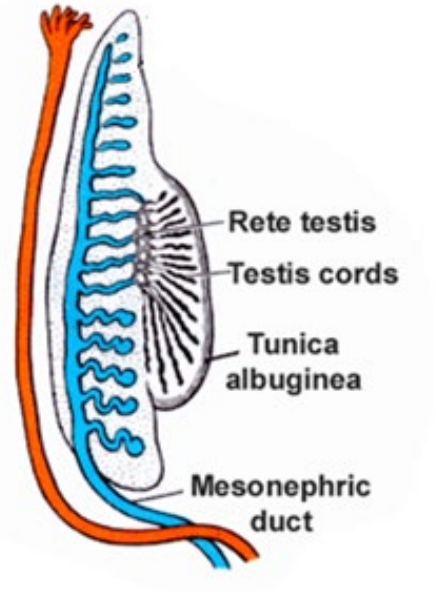
Stages of development

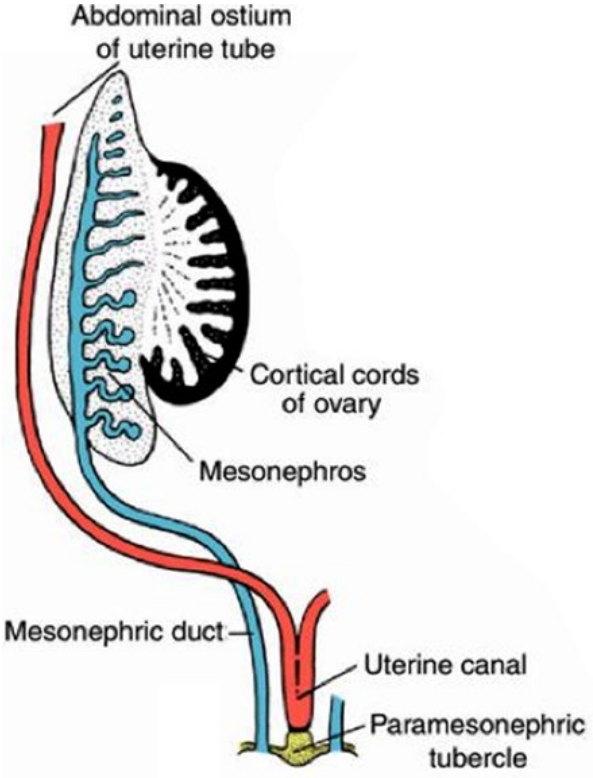
- **2 stages:**
  - Indifferent/primitive stage
  - Definitive stage

Indifferent stage of genital ducts

- Initially, both male and female embryos have two pairs of genital ducts:
  - **mesonephric (Wolffian) ducts**
  - **paramesonephric (Müllerian) ducts**





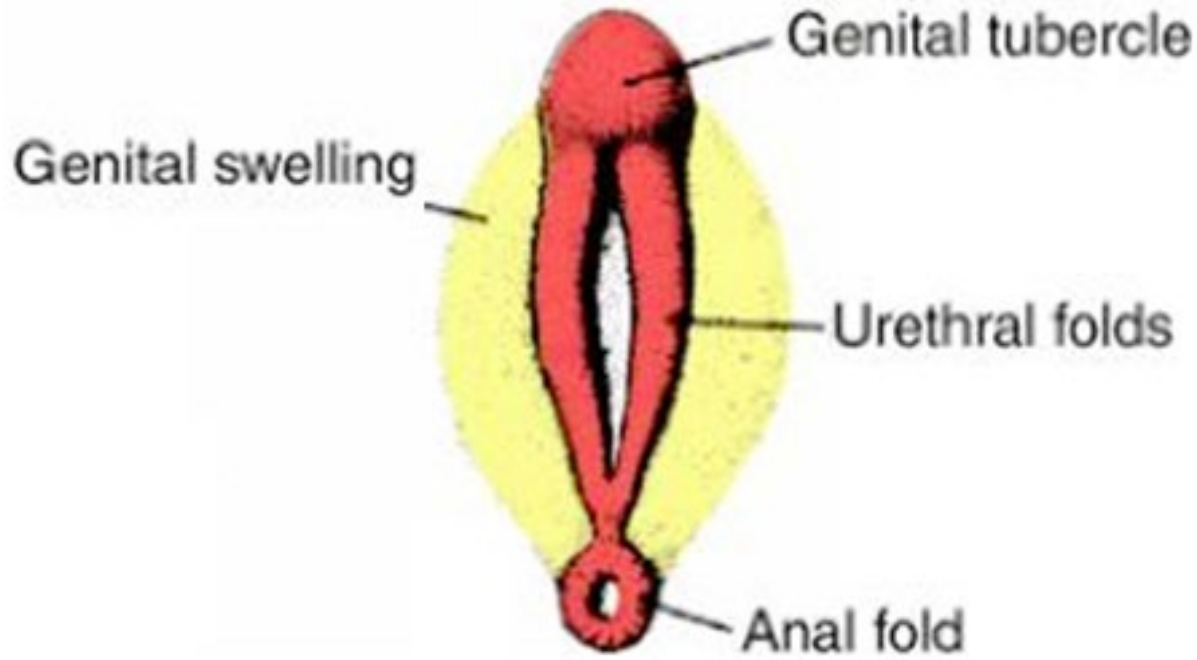


Indifferent stage

- **In male:**
  - Mesonephric (Wolffian) ducts form the male genital ducts.
  - Paramesonephric (Mullerian) ducts **mostly disappear**.
- **In female:**
  - Paramesonephric (Mullerian) ducts form the female genital ducts.
  - Mesonephric (Wolffian) ducts **mostly disappear**

Indifferent stage of external genitalia

- In the third week of development, mesenchyme cells originating in the region of the primitive streak migrate around the cloacal membrane to form a pair of **cloacal folds**.
  - **Genital tubercle**
  - **Urethral (urogenital) folds** anteriorly
  - **Anal folds** posteriorly
  - **Urethral (urogenital) groove**
  - **Genital swellings**

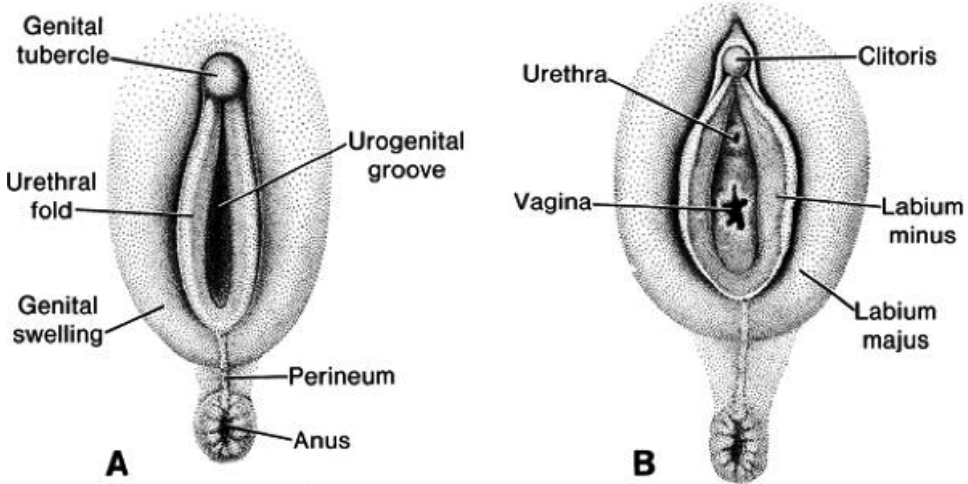


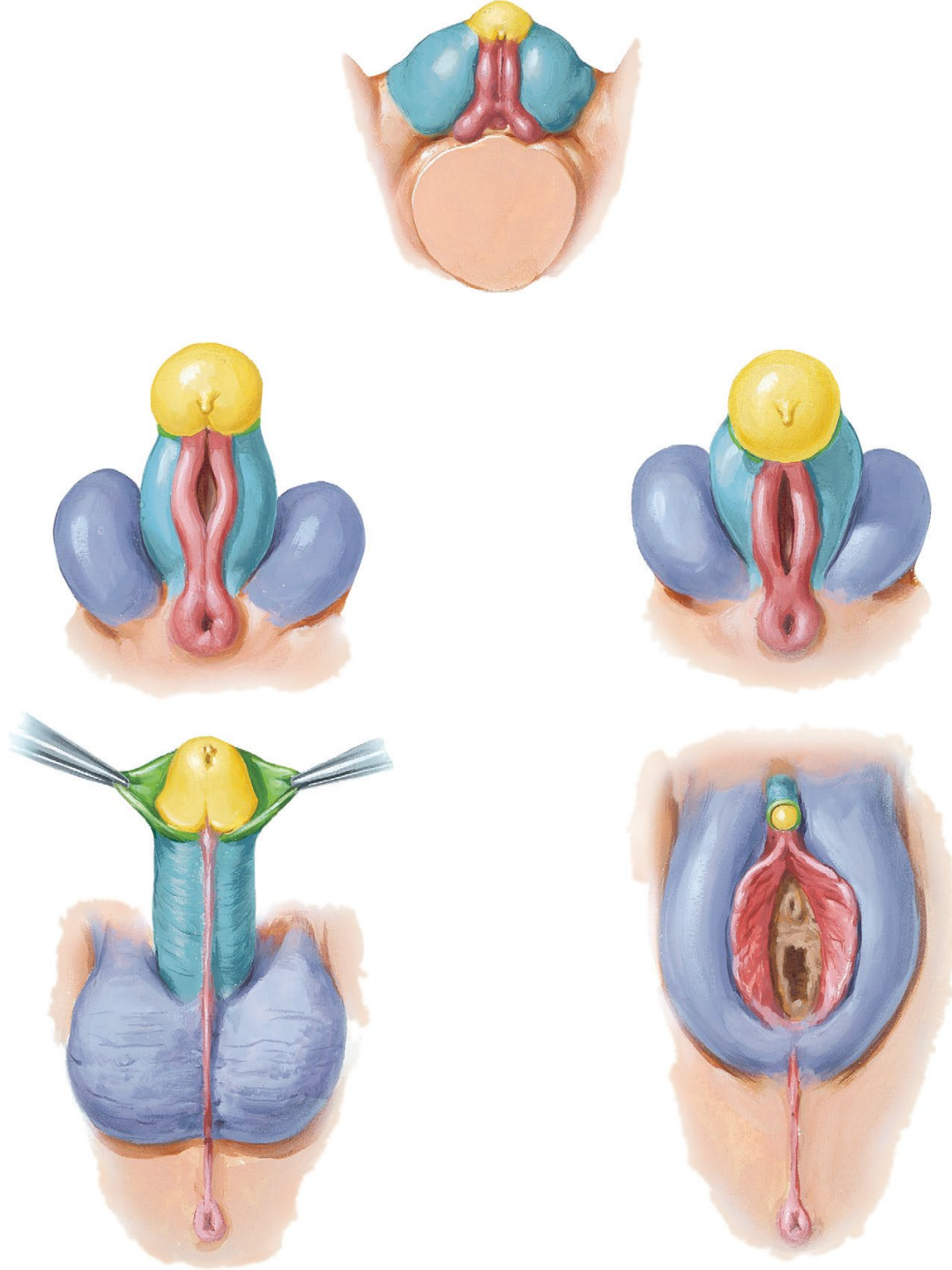
Definitive stage

- The differentiation of genital ducts and external genitalia into male and female direction is influenced by the hormones secreted by the gonads.

External genitalia in the female

- Estrogens stimulate the development of the external genitalia of the female.
- **The genital tubercle** elongates only slightly and forms the clitoris.
- **Urethral (urogenital) folds** do not fuse but develop into the labia minora.
- **Genital swellings** remain unfused, enlarge, and form the labia majora.
- **The urethral (urogenital) groove** is open and forms the vestibule.





XY

SRY gene/TDF gene

SRY protein/TDF

Testis

Sertoli cell

AMH/AMS/MIH/MIS

Suppression of paramesonephric (Mullerian) duct

Failure of progression of female genital ducts

Leydig cell

Testosterone

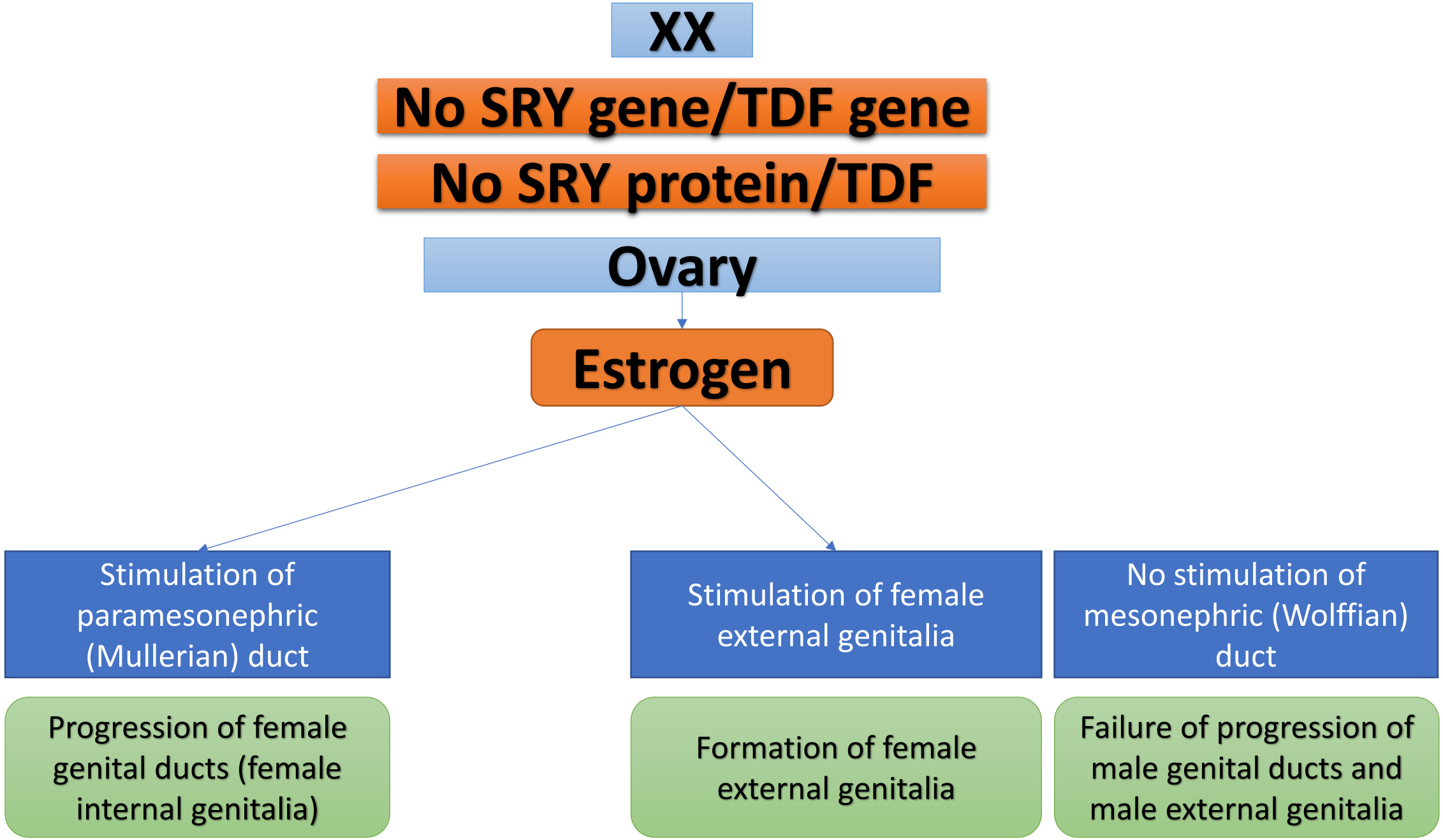
Stimulation of mesonephric (Wolffian) duct

Progression of male genital ducts (male internal genitalia)

Dihydrotestosterone

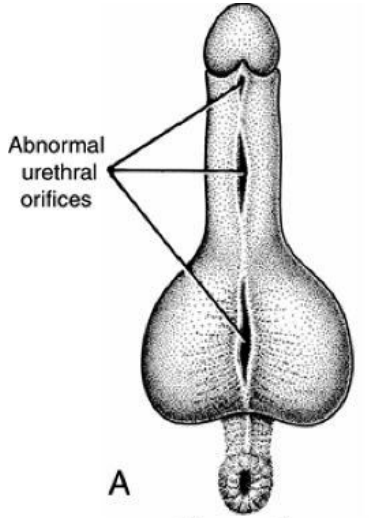
Stimulation of male external genitalia

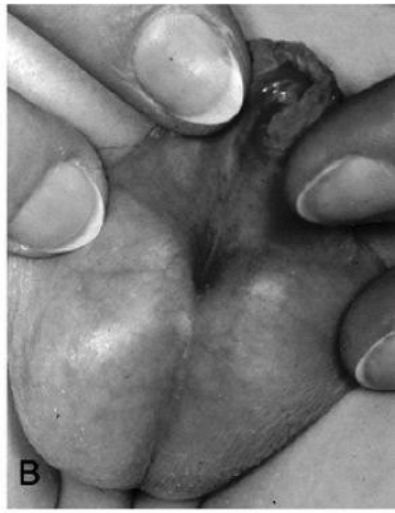
Formation of male external genitalia

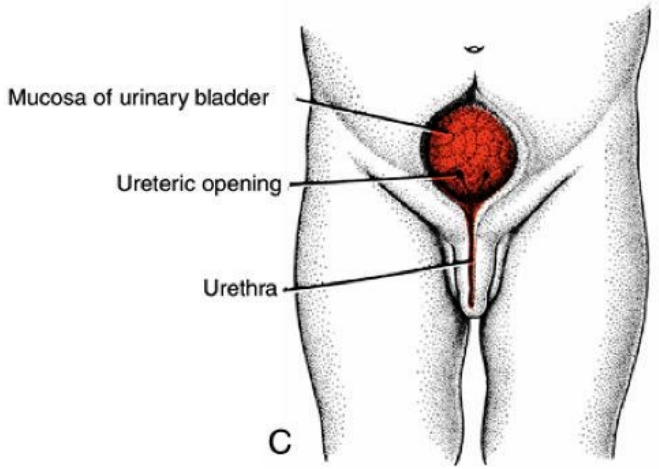

XX
No SRY gene/TDF gene
No SRY protein/TDF
Ovary
Estrogen
Stimulation of paramesonephric (Mullerian) duct
Stimulation of female external genitalia
No stimulation of mesonephric (Wolffian) duct
Progression of female genital ducts (female internal genitalia)
Formation of female external genitalia
Failure of progression of male genital ducts and male external genitalia

Anomalies of male external genitalia

- Hypospadias
- Epispadius
- Extrophy of bladder/ectopia vesicae
- Micropenis
- Double/bifid penis





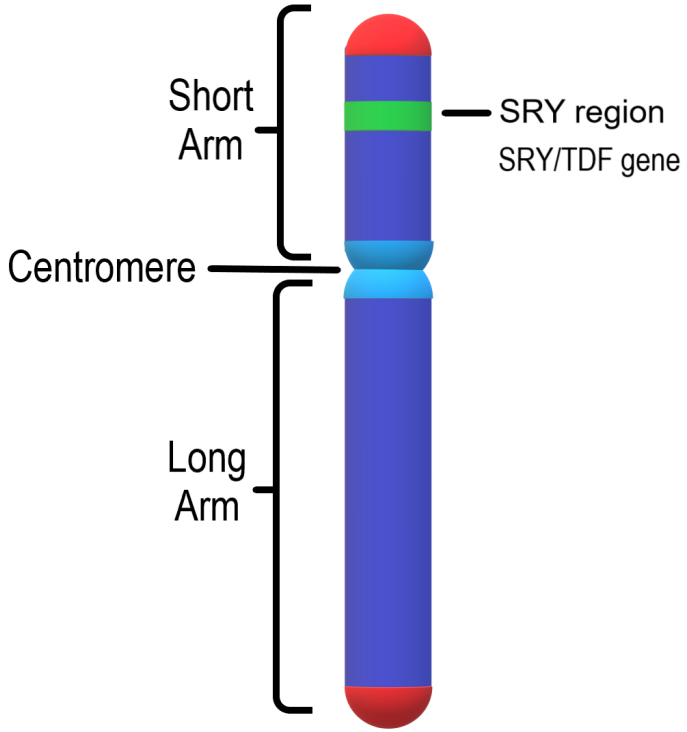


The central dogma of sexual differentiation

Chromosomal (genotypic) sex	→	Gonadal sex	→	Phenotypic sex
At fertilization		$7^{th}/8^{th}/9^{th}$ week		12^{th} week

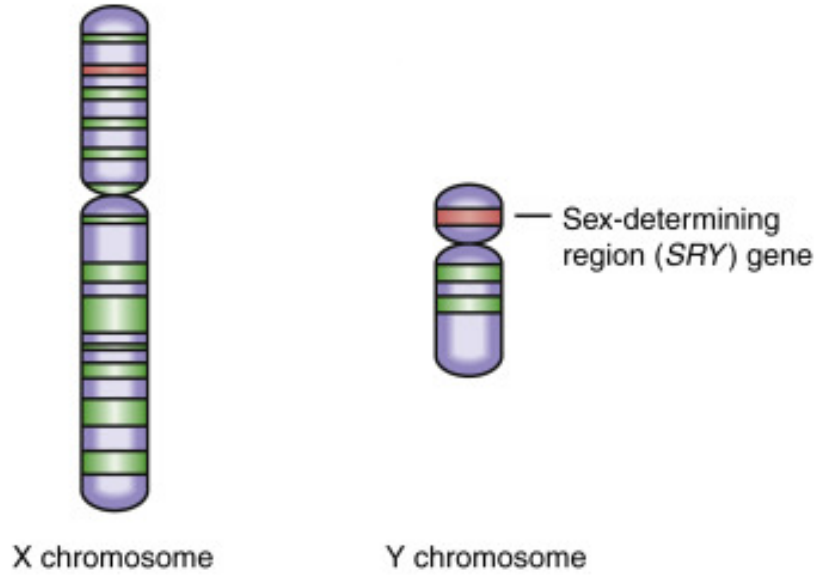
Deletion or point mutation of SRY region

- During spermatogenesis (meiosis)
- Deletion/point mutation of SRY region
- Y chromosome containing sperm (No SRY region)
- Fertilization
- XY containing zygote
- **Genotypic sex** male
- **Gonadal sex**?
- **Phenotypic sex**?



Translocation of SRY region to X chromosome during meiosis

- During spermatogenesis (meiosis)
- Translocation of SRY region to X
- Y chromosome containing sperm (No SRY region)
- X chromosome containing sperm (SRY region)
- Fertilization
- XY containing zygote
- XX containing zygote
- **Genotypic sex** male/female
- **Gonadal sex**?
- **Phenotypic sex**?



Congenital adrenal hyperplasia

- **Genotypic sex** female (XX)
- **Gonadal sex** female
- Hyperplasia of zonal reticularis of the adrenal gland
- Excess androgen secretion
- Virilization (masculinization) of the external genitalia
  - Clitoral enlargement/hypertrophy
  - Labial fusion
- **Phenotypic sex**?
- Also called adrenogenital syndrome

Deficiency of testosterone or MIH

- **Genotypic sex** male (XY)
- **Gonadal sex** male
- Deficiency of testosterone/MIH
- Disorder in the development of the duct system
- **Phenotypic sex**?

Androgen insensitivity syndrome

- **Genotypic sex** male (XY)
- **Gonadal sex** male
- Failure of androgen receptor to work
- Disorder in the development of the duct system
- Disorder in the development of external genitalia and secondary sexual characteristics
- **Phenotypic sex**?
- Also called TFS

5-a-Reductase deficiency (5-ARD)

- **Genotypic sex** male (XY)
- **Gonadal sex** male
- Failure of conversion of testosterone to DHT
- Disorder in the development of external genitalia and secondary sexual characteristics
- **Phenotypic sex**?

Klinefelter/Turner syndrome

- 47, XXY
- 45, X0

Disorders of sex development

- **Deletion** or **mutation** (XY female gonadal dysgenesis) or **translocation** of SRY region to X chromosome during meiosis
- Congenital adrenal hyperplasia (AGS)
- Deficiency of testosterone or MIH
- Androgen insensitivity syndrome (TFS)
- 5-a-Reductase deficiency (5-ARD)

Intersexuality or hermaphroditism

- When there is normal sexual differentiation, the appearance of the external and internal genitalia is consistent with the sex chromosome complement.
- **Errors in sex determination and differentiation** result in various degrees of intermediate sex-**intersexuality** or hermaphroditism.

Etymology

- The term **hermaphrodite** derives from the Latin: **hermaphroditus**, which derives from **Hermaphroditus**, the son of **Hermes** and **Aphrodite** in Greek mythology.
- According to Ovid, he fused with the nymph **Salmacis** resulting in one individual possessing physical traits of male and female sexes.
- According to the earlier Diodorus Siculus, he was born with a physical body combining male and female sexes.
- The word hermaphrodite entered the English lexicon as early as the late fourteenth century.

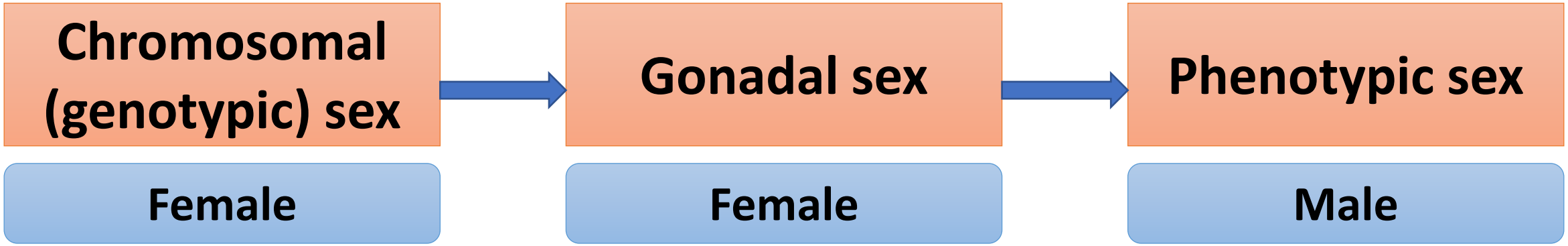
Thank you for your patience

True hermaphroditism

- Approximately 70% of them have a **46, XX chromosome** constitution; approximately 20% have **46, XX/46, XY mosaicism**, and approximately 10% have a **46, XY chromosome** constitution.
- Most true hermaphrodites have both testicular and ovarian tissue or an ovotestis.
- The phenotype may be male or female, but the external genitalia are always ambiguous

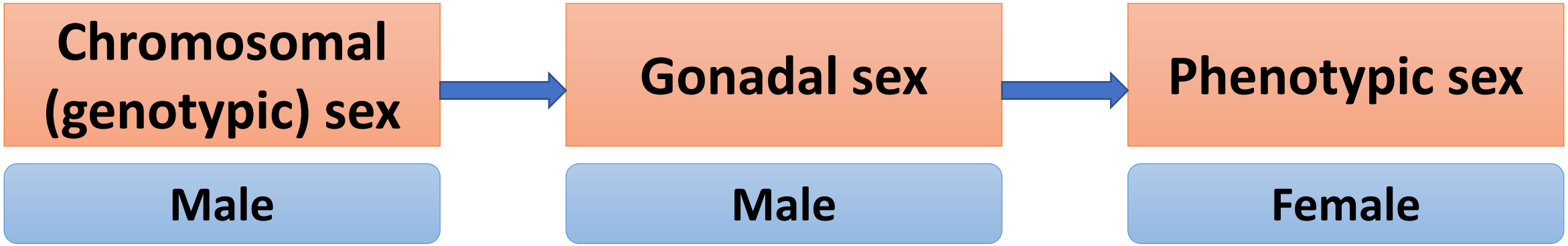
Female pseudohermaphroditism

- Persons with this condition have a **46, XX chromosome** constitution.
- This anomaly results from exposure of the female fetus to **excessive androgens secreted from the fetal suprarenal glands (CAH/AGS)**.
- This causes **virilization (masculinization) of the external genitalia** (clitoral enlargement/hypertrophy and labial fusion).



Male pseudohermaphroditism

- Persons with this condition have a **46, XY chromosome** constitution.
- These anomalies are caused by **inadequate production of testosterone and MIS by the fetal testes** or **AIS (TFS)**.
- The external genitalia are developmentally variable as is the development of the internal genitalia due to varying degrees of development of the paramesonephric ducts.



Disorders of sex development

- Ambiguous genitalia-Large clitoris or a small penis with hypospadias.
- Ovotesticular disorders of sex development [formerly called true hermaphrodism]
- 46, XX DSD-Congenital adrenal hyperplasia [CAH]/AGS
- 46, XY DSD-
  - XY female gonadal dysgenesis [Swyer syndrome]-results from point mutations or deletions of the *SRY* gene
  - Deficiency of MIH/AMS
  - Androgen insensitivity syndrome [AIS]/TFS
  - 5-a-Reductase deficiency [5-ARD]
  - Klinefelter syndrome
- Turner syndrome