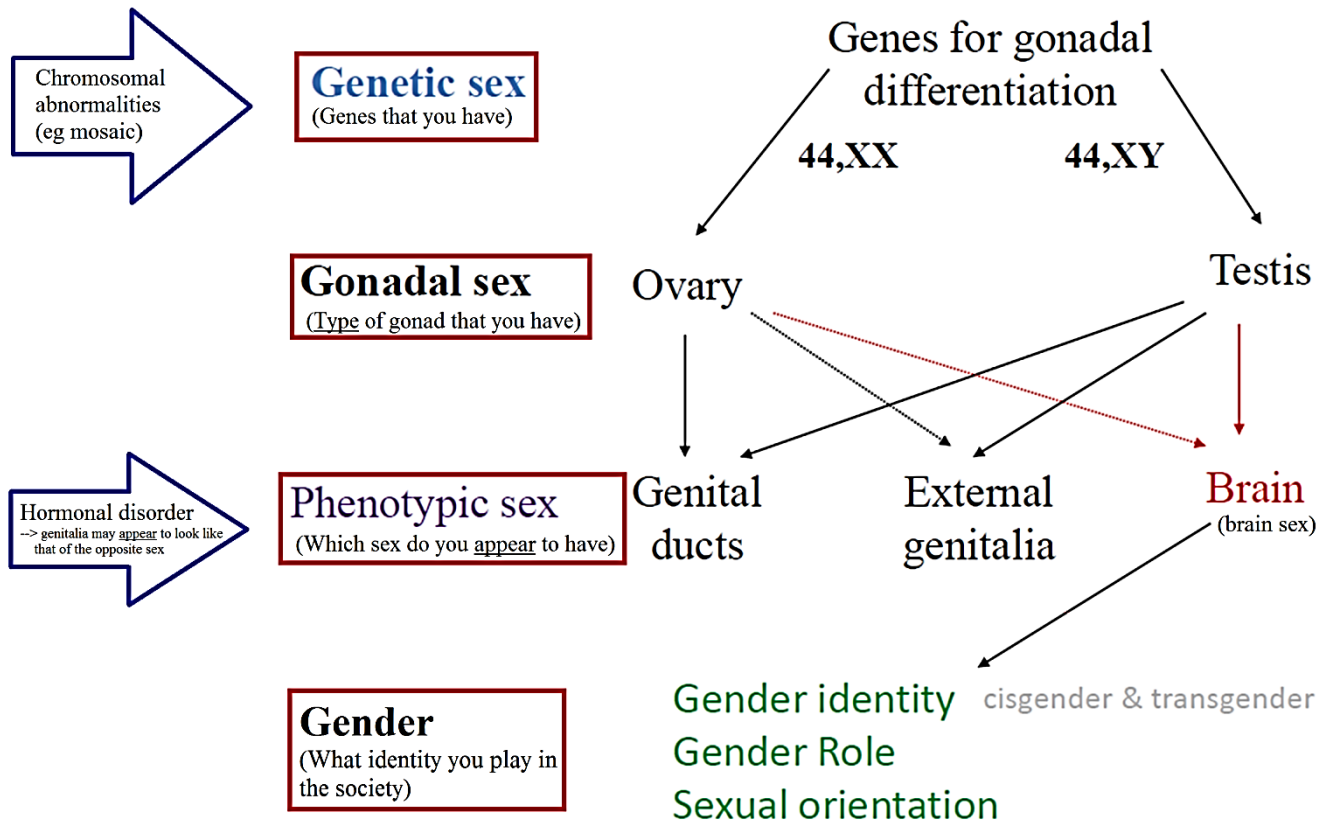


# L2 Development of the Reproductive System

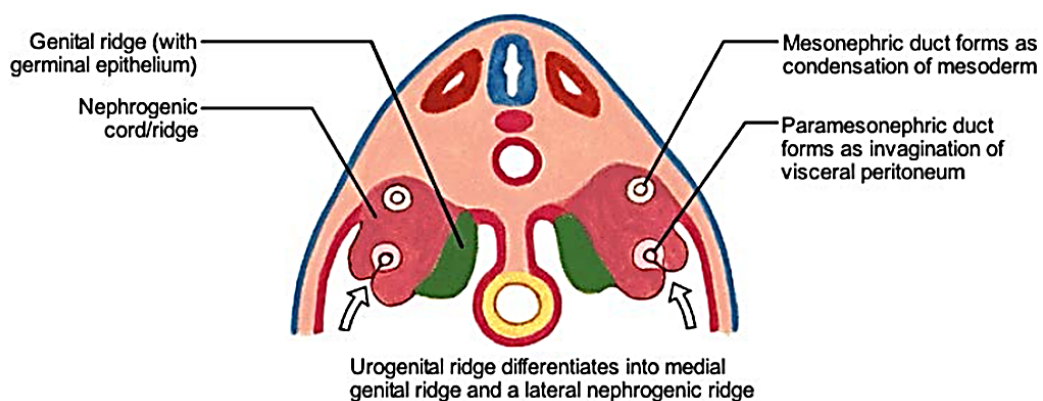
## A. Sexual Differentiation



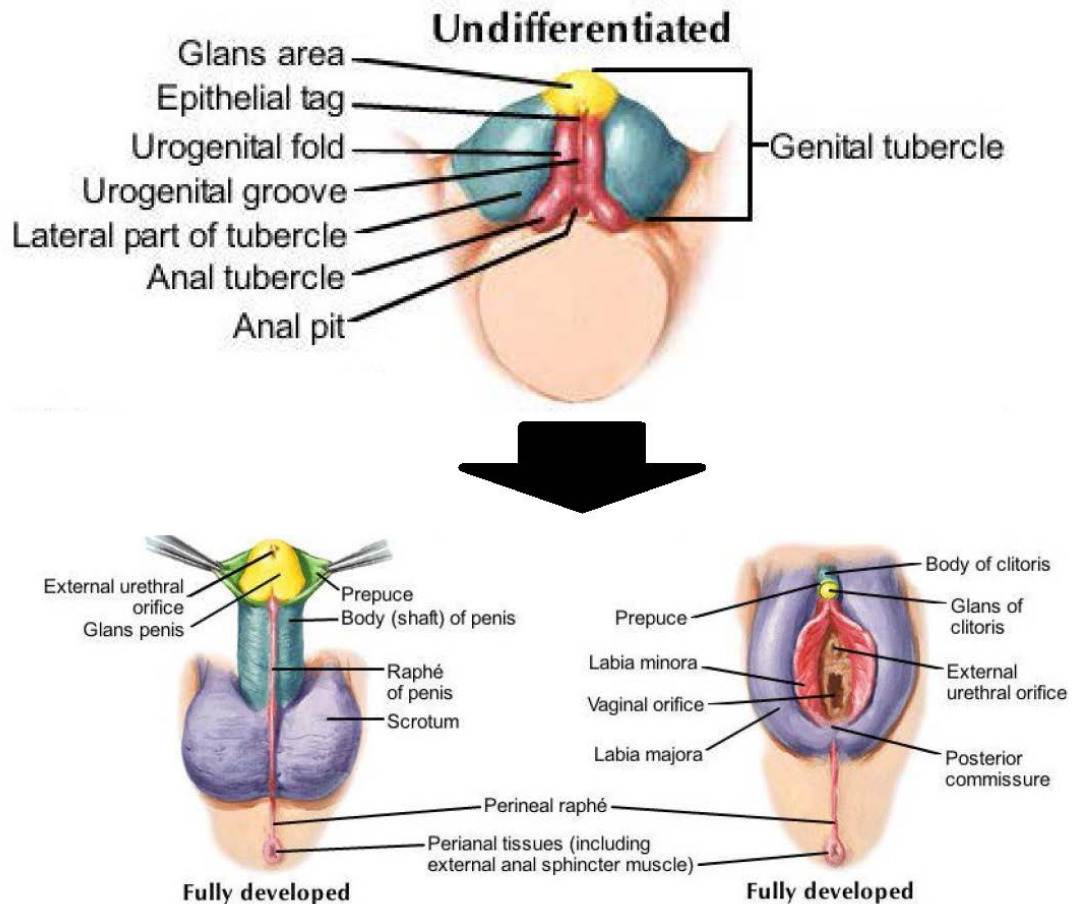
- ▶ **Sex:** biological sexual identity
- ▶ **Gender:** social sexual identity
- ▶ Sex of a person can be defined on various levels
- ▶ Various disorders in the course of development may lead to inconsistency in these types of sex
- ▶ **Genetic sex:** sex as determined by genes
  - Established at fertilization
  - Depends on whether an X-bearing or a Y-bearing sperm fertilizes the X-bearing oocyte
  - Generally dependent on presence of **sex-determining region on short arm of Y chromosome (SRY)**
  - Number of X chromosomes in abnormal sex chromosome complexes (eg. XXX, XXY) appeared to be unimportant in sex determination

- ▶ **Gonadal sex:** type of gonads that is developed
  - Determined by sex chromosome complex of embryo
  - Ovaries (female) and testes (male) developed from **indifferent gonads** (before 7<sup>th</sup> week)
- ▶ **Phenotypical sex:** sex shown by differentiation of internal and external genitalia
  - Hormonal disorders during development may lead to changes in phenotypical sex
- ▶ **Brain sex:** sex shown by differentiation of the brain and hypothalamus

## B. Overview on Development of Reproductive System

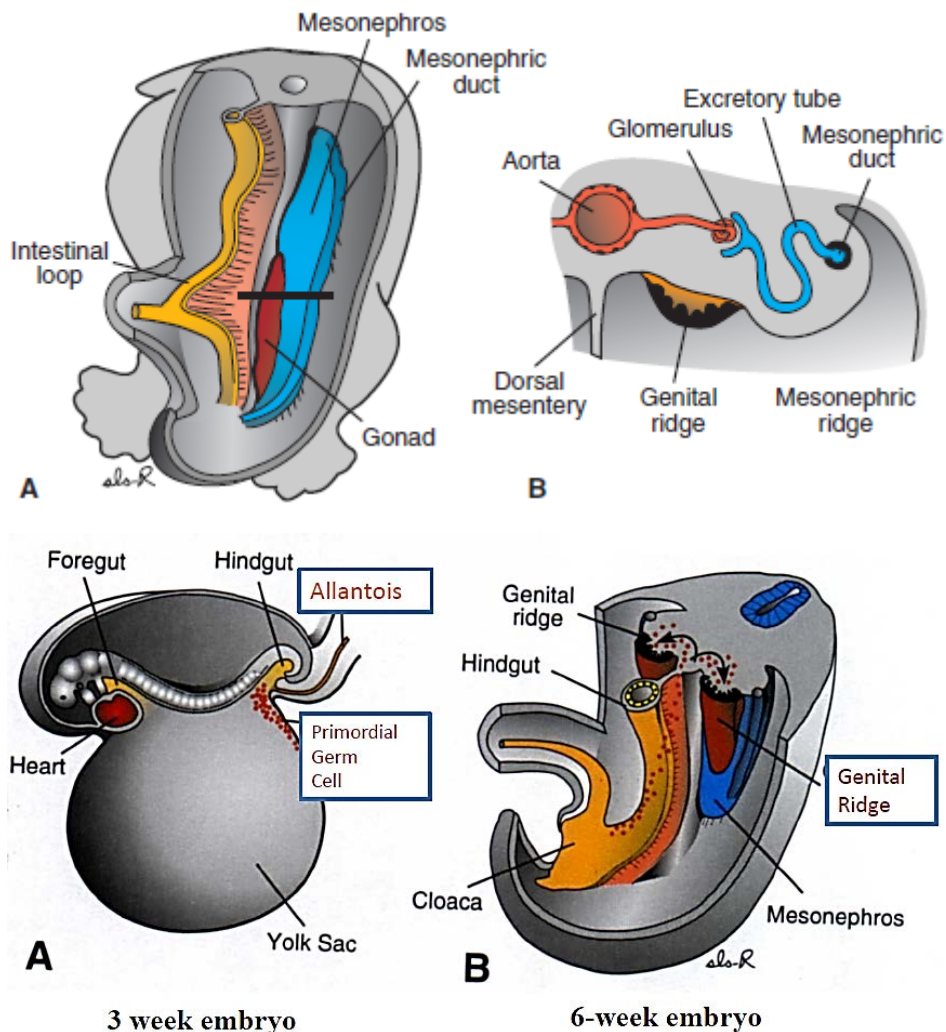


- ▶ **Genital system** arises from medial part of **urogenital ridge** called **genital ridge**
- ▶ **Gonads** developed from:
  - **Primordial germ cells (PGC)** → oocytes or sperms
  - **Genital ridge:** mesenchyme → gonadal somatic cells (**Sertoli cells** for males)
    - **Sertoli cells:** a kind of sustentacular cell in **seminiferous tubules** that aids in spermatogenesis
- ▶ **Genital ducts** from two sets of ducts at indifferent stage:
  - **Mesonephric (Wolffian) ducts:**
    - Male: differentiate into ducti efferentus, epididymis, vas deferens and seminal vesicles
    - Female: regresses
  - **Paramesonephric (Müllerian) ducts:**
    - Male: regresses
    - Female: differentiate into uterus (caudal) and oviducts (cranial)

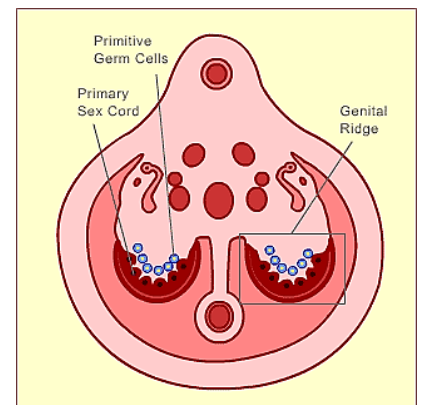


- **External genitalia** formed from three structures near cloacal opening:
  - **Genital tubercle** → penis (male) or clitoris (female)
  - **Cloacal (urogenital, urethral, genital) folds** → penile urethra (male) or labia minora (female)
  - **Genital swelling** → scrotum (male) or labia majora (female)

## B. Development of Indifferent Gonads (3-7w)

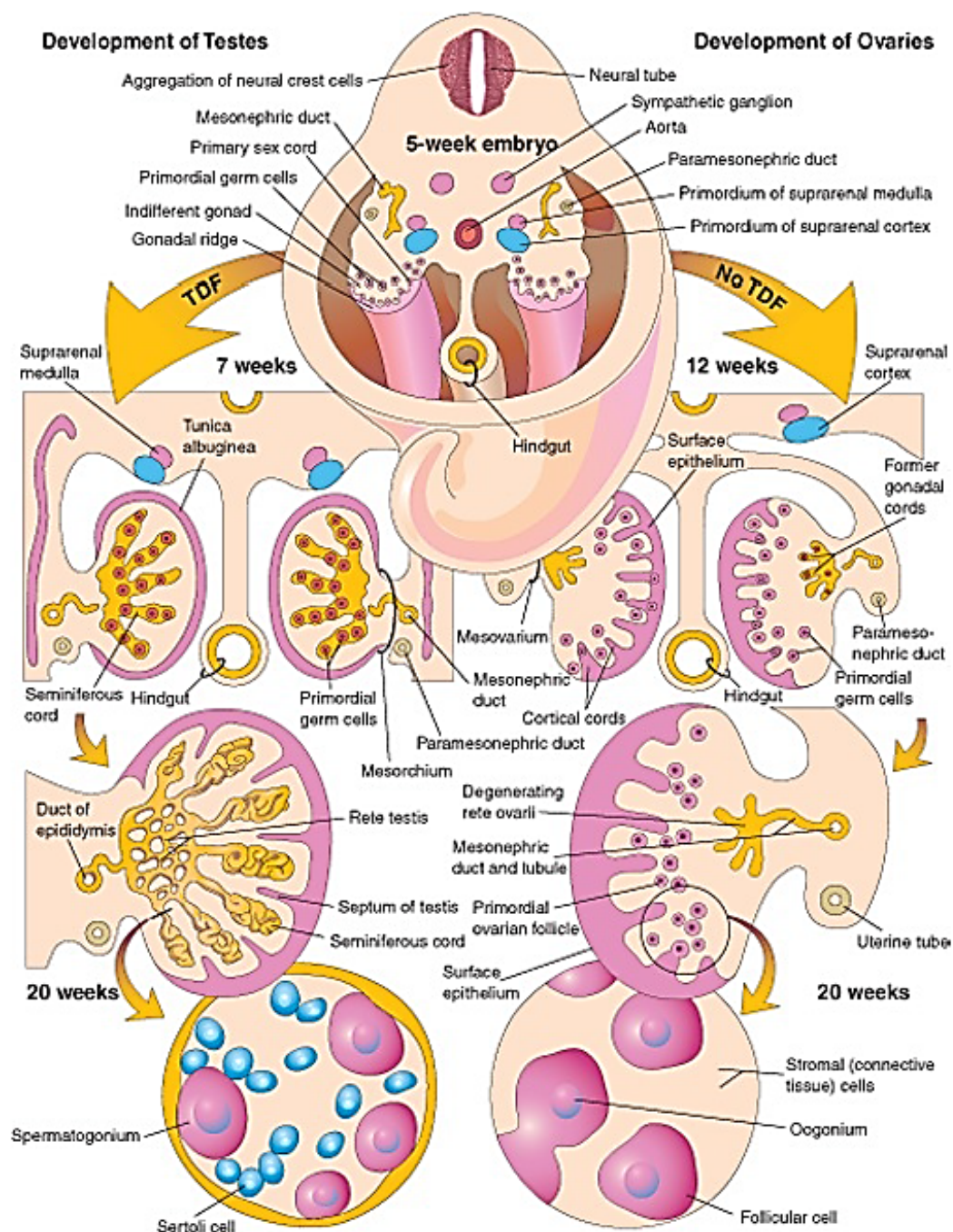


- ▶ **Primordial germ cells (PGC)** originate in wall of yolk sac close to attachment of allantois
- ▶ 3-6w: PGCs migrate by amoeboid motion along wall of hindgut and **dorsal mesentery** into **genital ridges**
  - **Genital ridges:** a pair of longitudinal ridges developing from mesenchymal cells on the medial side of caudal part of mesonephros at 5<sup>th</sup> week
  - PGCs have inductive influence on gonadal development
  - Failure of PGC migration → gonads do not develop
- ▶ Shortly before and during PGC arrival, genital ridge epithelium proliferates and penetrates underlying mesenchyme → forms **primitive sex (gonadal) cords**
- ▶ **Indifferent gonads:** not possible to differentiate between male and female gonads up to 7 weeks of development

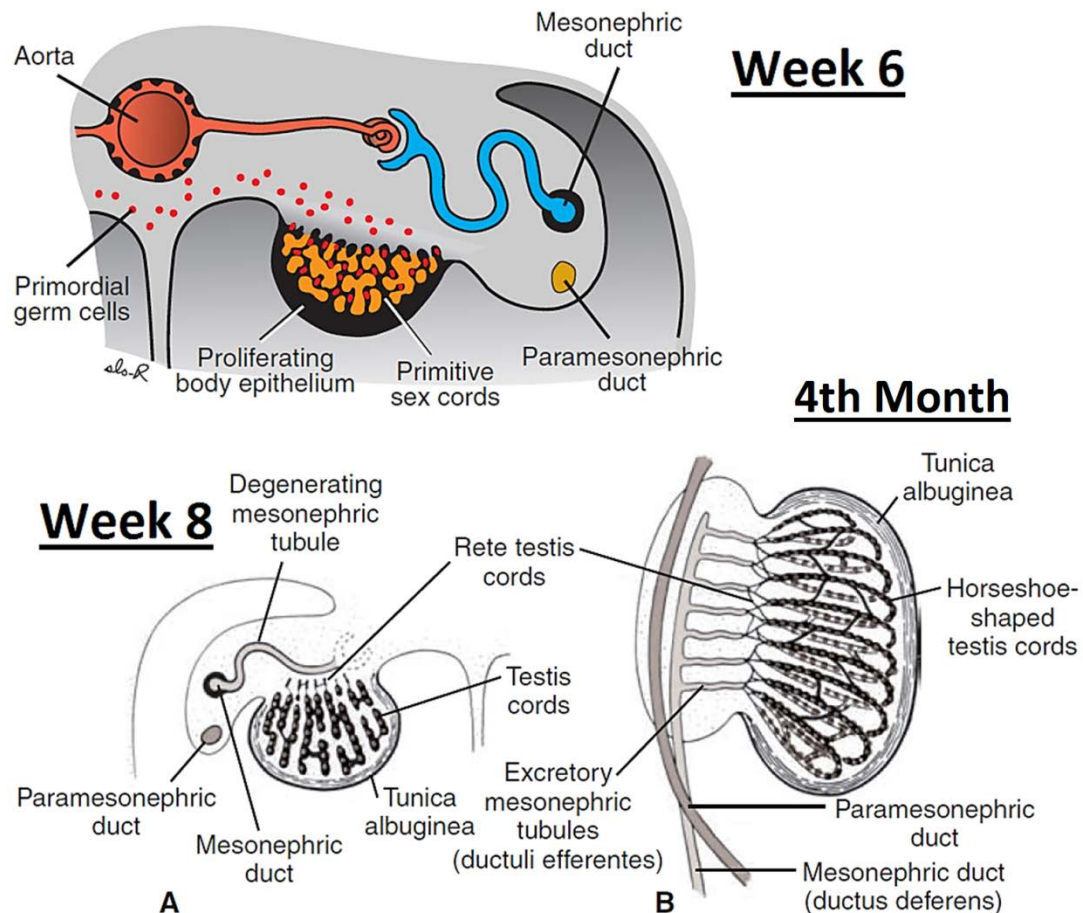


## C. Gonadal Differentiation (8-12w)

- ▶ Fetus has bipotential sexual development for first 3 months
- ▶ Phenotype determination depends on:
  - Presence of sex chromosomes (eg. SRY gene)
  - Prevailing biochemical environment (eg. **Müllerian inhibitory factor**)
  - Prevailing hormonal environment (eg. androgen)
- ▶ **Gonadal differentiation** largely influenced by **SRY gene** on Y chromosome
- ▶ SRY codes for production of **testis-determining factor (TDF)**
  - TDF (male) induces **gonadal cords** to condense and extend into medulla

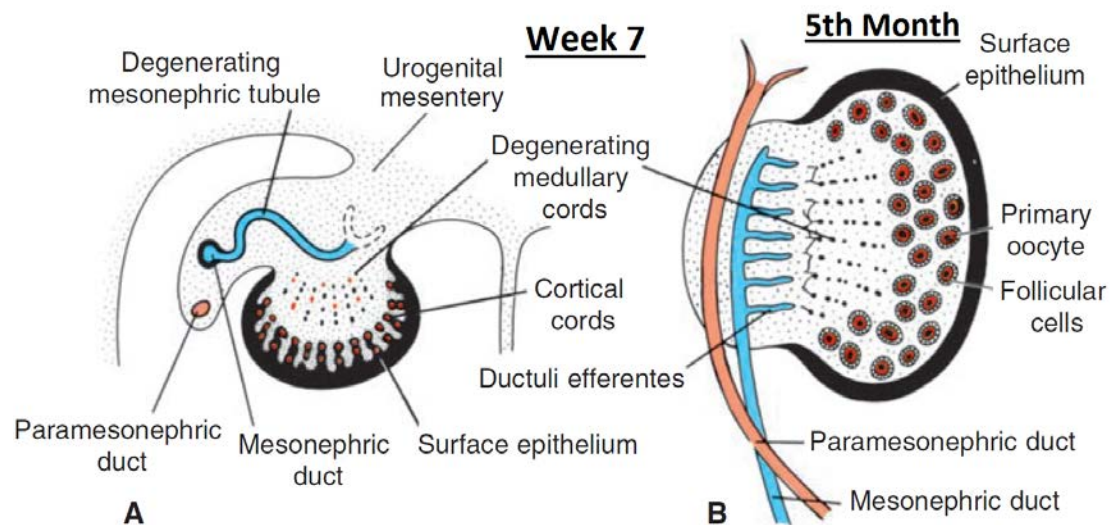


# 1. Gonadal Differentiation in Male (6-12w)



- ▶ Male gonad development involves mitosis during 3-8w
- ▶ 6w: **SRY gene** stimulates **primitive sex cords** to continue to proliferate and penetrate into medulla → forms **medullary cords**
- ▶ Near hilum, **medullary cords** break up and coalesce into a network of tiny cell strands that later gives rise to tubules of **retes testis**
- ▶ **Tunica albuginea** (a dense layer of fibrous c.t.) develops and separates testis cords from surface epithelium
- ▶ 4m: testis cords become horseshoe-shaped with ends connected to **rete testis**
- ▶ Content of testis:
  - Testis cords:
    - **Primitive germ cells** → meiosis (in puberty) to give gametes
    - **Sertoli cells**, from surface epithelium of gonad
  - **Interstitial cells of Leydig**, from original mesenchyme of genital ridge
- ▶ **Testis cords** remain solid until canalization in puberty → **seminiferous tubules**
- ▶ Remnant of collecting tubules of mesonephros form **ductuli efferentes**
  - connect **rete testis** to the **ductus deferens** (derived from **mesonephric duct**)

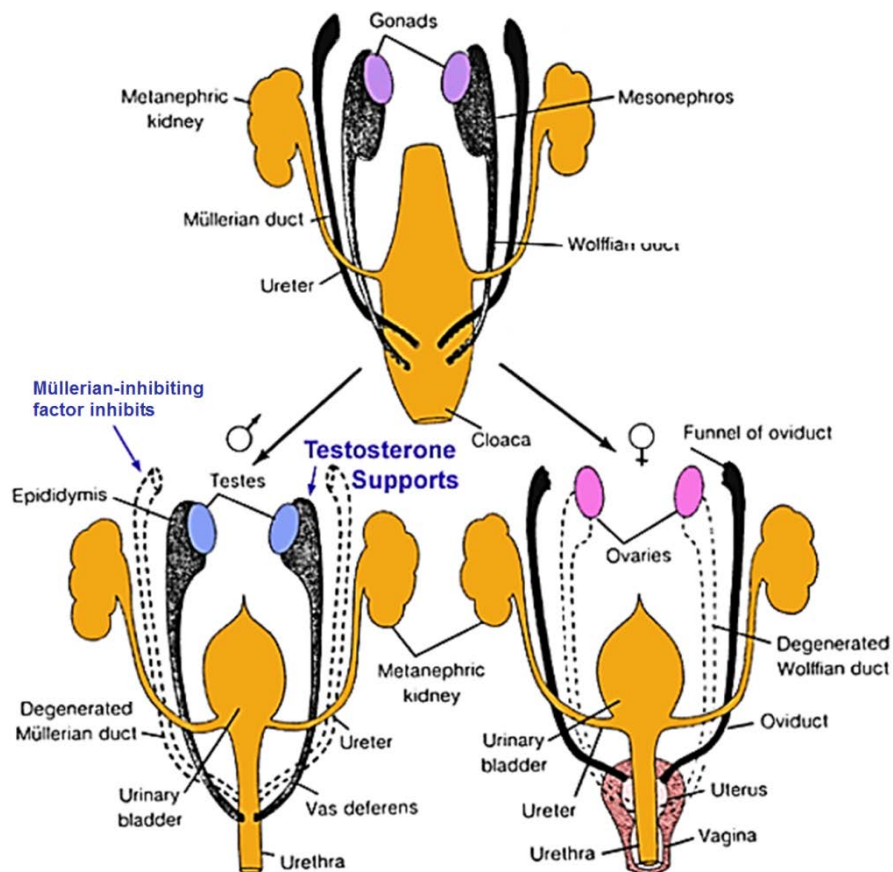
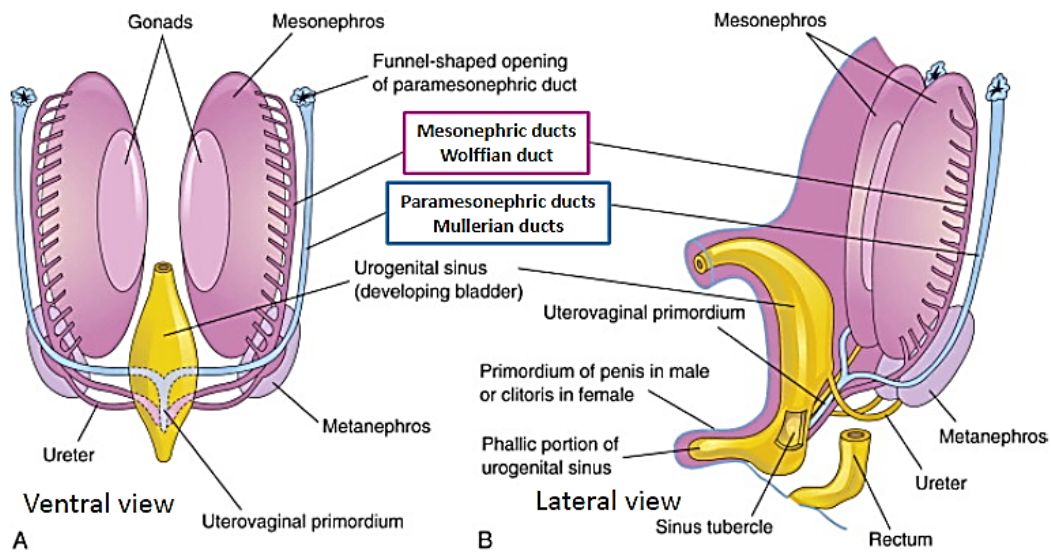
## 2. Gonadal Differentiation in Females (7-12w)



- ▶ Ovaries developed via:
  - Mitosis in 3<sup>rd</sup> – 8<sup>th</sup> week
  - Meiosis in 8<sup>th</sup> week – 4<sup>th</sup> month
- ▶ Without **SRY gene**, **primitive sex cords** dissociate into irregular cell clusters (containing PGCs) and later disappear at medulla of gonad
- ▶ Degenerated **medullary cords** replaced by a vascular stroma forming **ovarian medulla**
- ▶ 7w: surface epithelium continues to proliferate → **cortical cords**
  - Different from **primitive sex cords** which has already disappeared in medulla
- ▶ **Cortical cords** penetrate underlying mesenchyme but remains close to surface
- ▶ 3m: **cortical cords** break up into isolated cell clusters and proliferate to surround each oogonium with a layer of epithelial **follicular cells** → **primordial follicles**

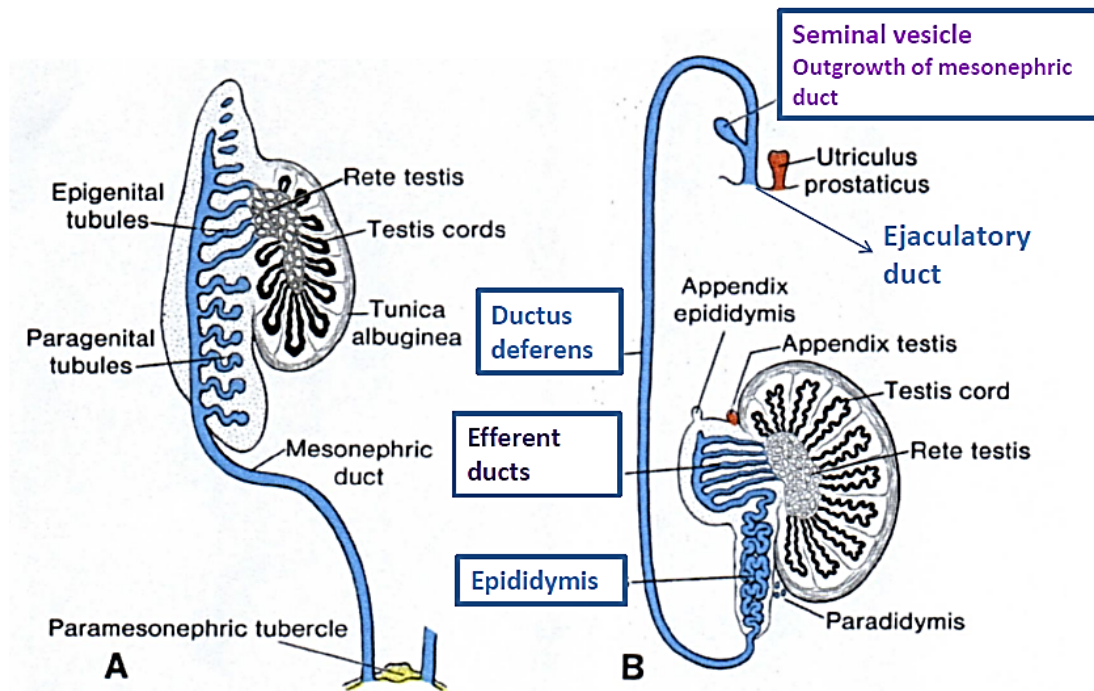
## D. Development of Genital Ducts

### 1. Indifferent Genital Ducts



- ▶ Genital duct derived from **mesonephric** and **paramesonephric ducts**
- ▶ **Mesonephric duct** → male genital tract
- ▶ **Paramesonephric duct** → female genital tract

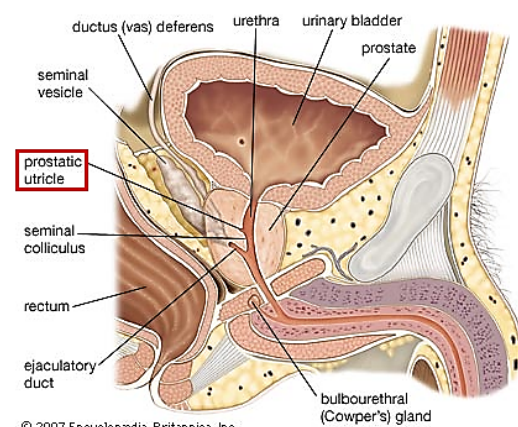
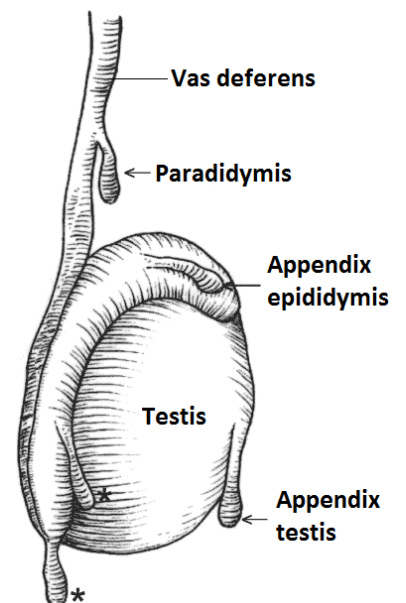
## 2. Development of Male Genital Ducts



- Fetal testes produce:
  - **Testosterone (T)** (from **Leydig cells**) to stimulate **mesonephric ducts**
    - **male genital tract**
  - **Müllerian-inhibitory factor (MIF)** (from **Sertoli cells**) to cause **paramesonephric ducts** to regress
- **Mesonephric tubules:**
  - Cranial-most → **appendix epididymis** (vestigial)
  - Cranial → **efferent ducts**
  - Caudal → **paradiidymis** (vestigial)
- **Mesonephric duct:**
  - Cranial-most → **appendix epididymis** (vestigial)
  - Cranial → **epididymis**
  - Middle → **ductus deferens + ejaculatory duct**
  - Caudal → **trigone of bladder**
- Outgrowth of **mesonephric ducts** → **seminal vesicles**
- **Paramesonephric ducts**
  - **appendix testis + prostatic utricle** (vestigial)

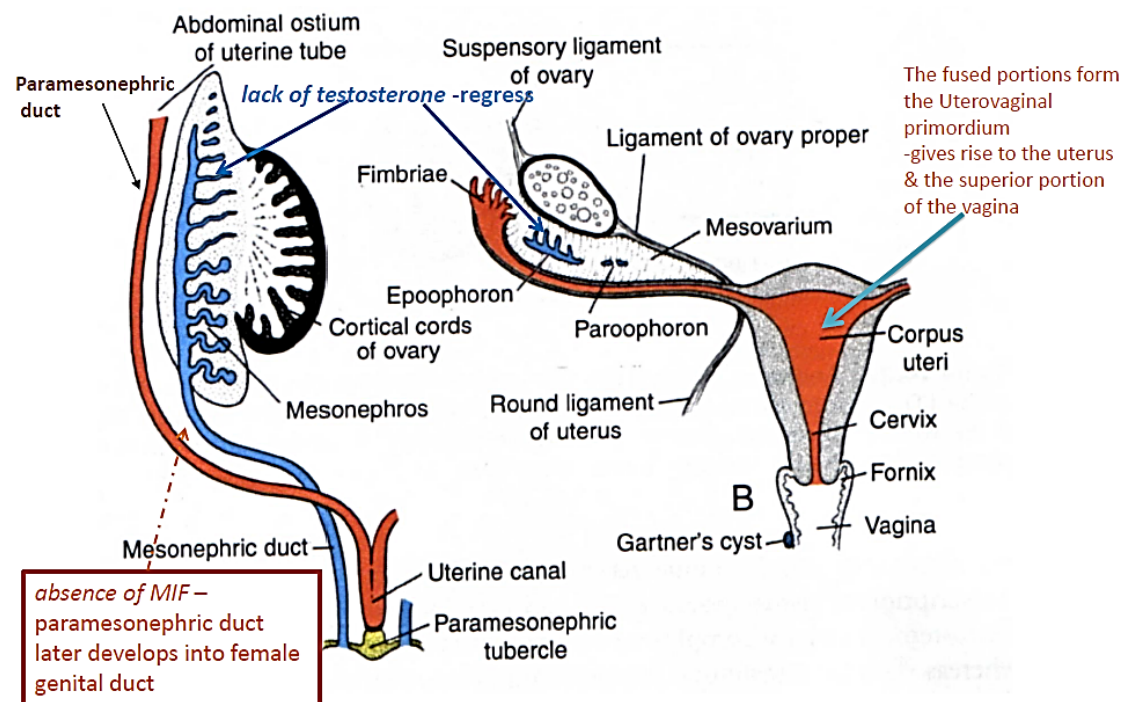
**\*Prostatic utricle:** small indentation in prostatic urethra

**\*\*Vestigial:** evolutionally retained embryonic remnant with no apparent function



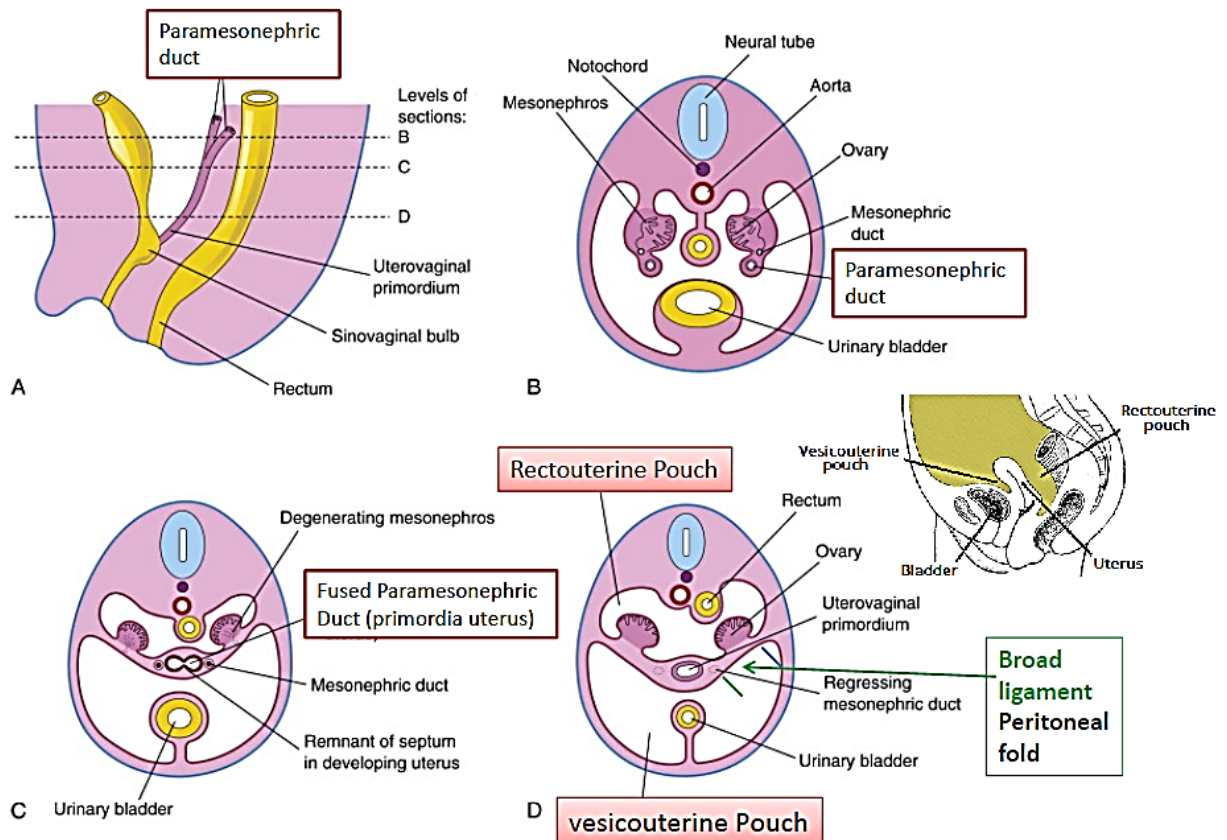
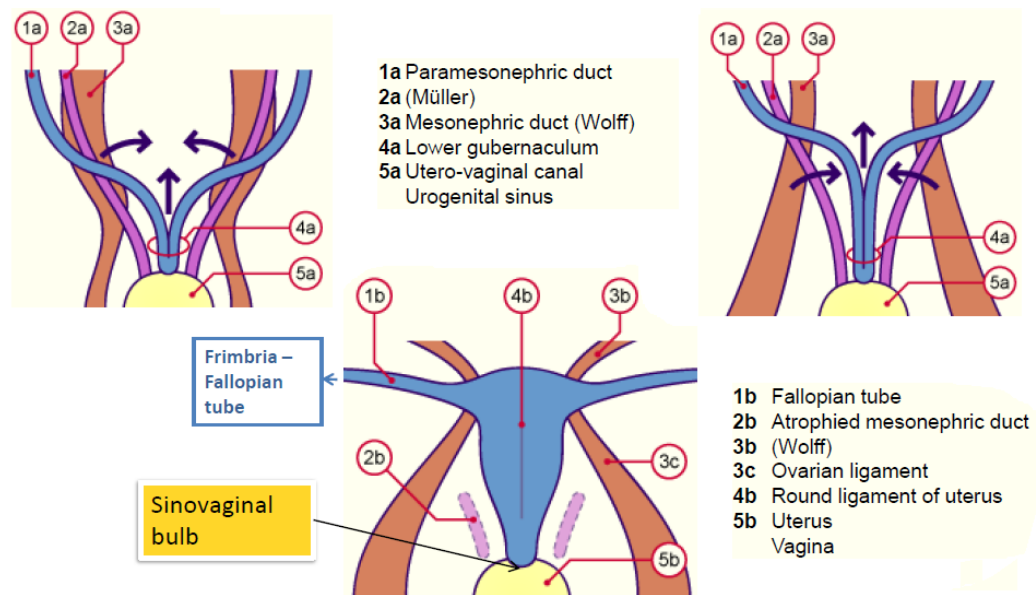
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### 3. Development of Female Genital Ducts



- ▶ Absence of **testosterone** → regression of **mesonephric ducts**
- ▶ Absence of **MIF** → **paramesonephric duct** develops into female genital tract
- ▶ **Paramesonephric duct** develops into:
  - Cranial: forms **oviducts**
  - Caudal: bilateral ducts fuse to form **uterovaginal primordium**
- ▶ **Mesonephric duct and tubules** develop into:
  - Cranial-most: **epoophoron**
  - Cranial: **paroophoron**
  - Caudal: **Gartner's duct (cyst)**

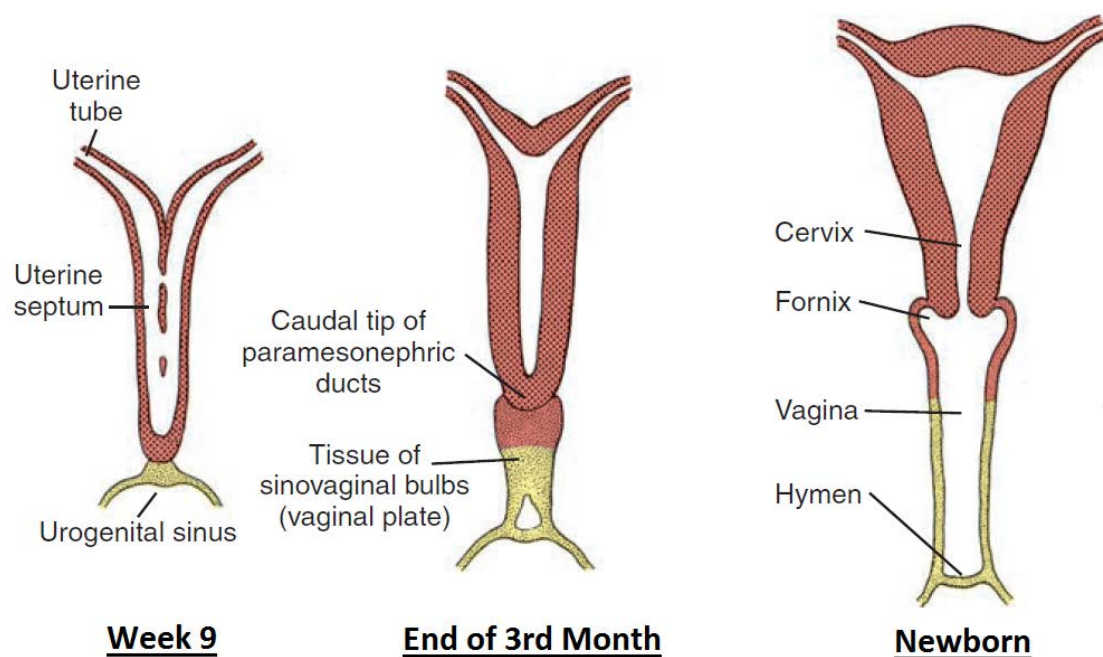
## a. Formation of Uterus



- ▶ **Peritoneal folds** on each side move medially and carry bilateral **paramesonephric ducts** towards midline
- ▶ Caudal part of **paramesonephric ducts** fuse to form **uterovaginal primordium**
- ▶ **Peritoneal folds** on each side form the **broad ligament of uterus**

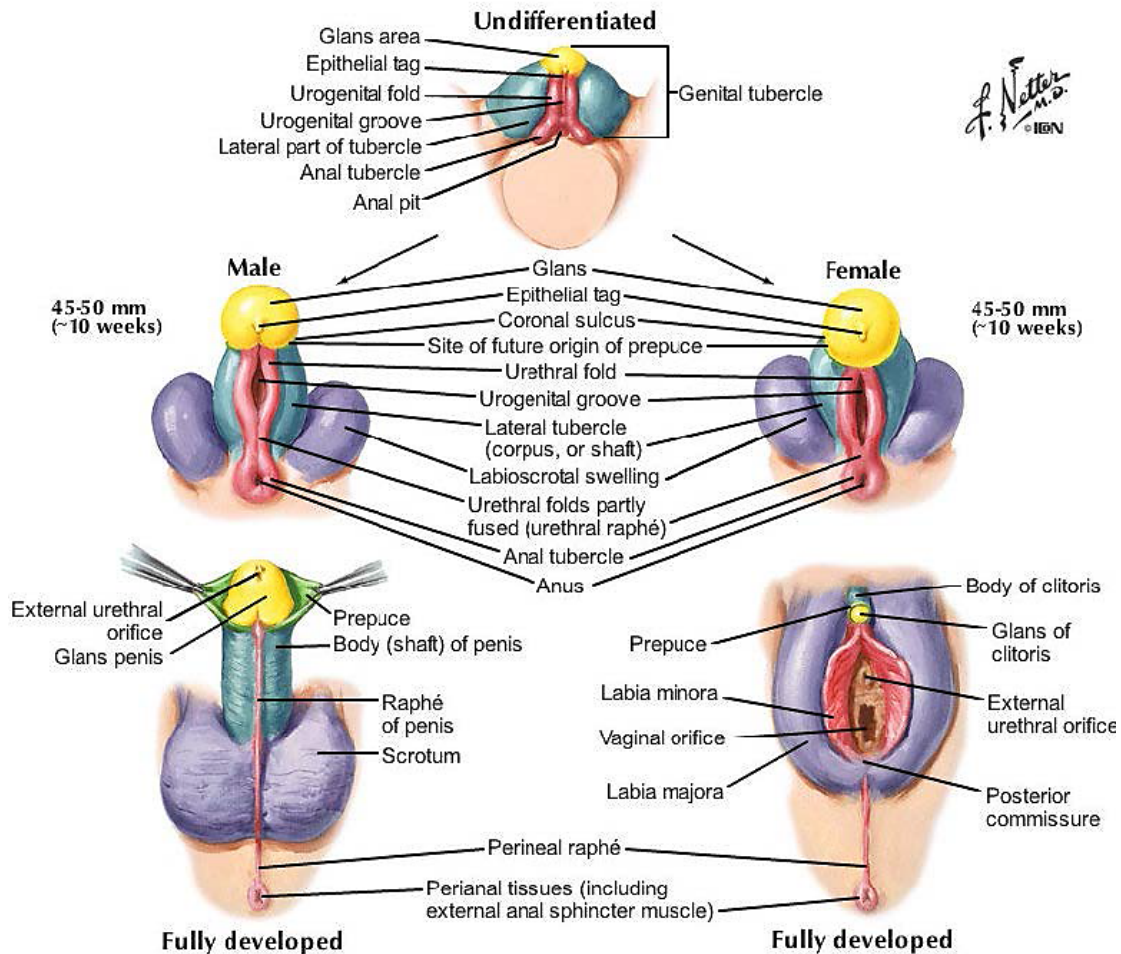
*\*Gubernaculum: undifferentiated mesenchyme attaching to caudal ends of gonads  
→ scrotal ligament (M) and ovarian ligament + round ligament of uterus (F)*

## b. Formation of Vagina



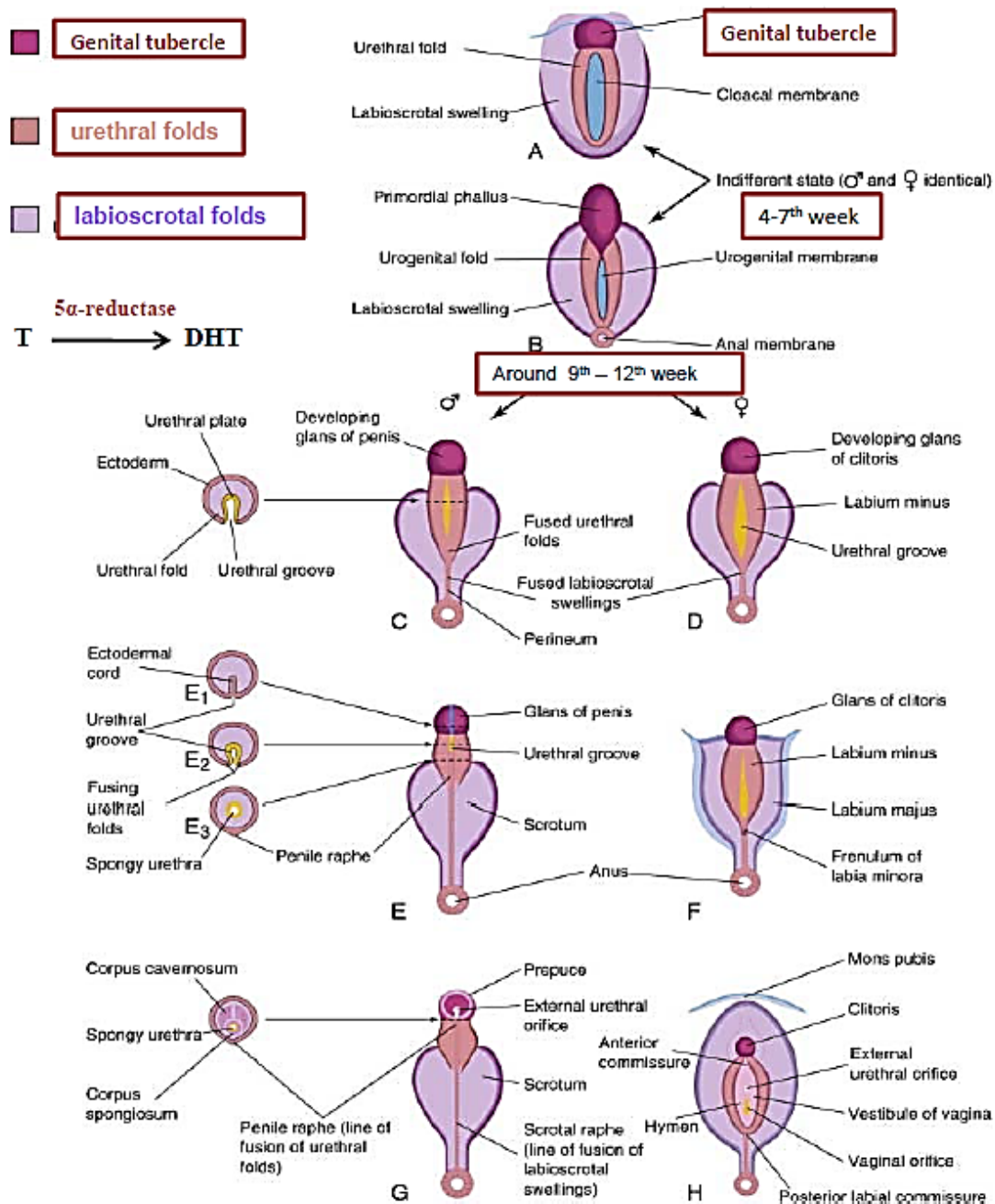
- ▶ Solid caudal end of **uterovaginal primordium** grows downward and reaches **urogenital sinus**
- ▶ Shortly afterwards, two **sinovaginal bulbs** (solid evaginations) grow out of pelvic **urogenital sinus** → proliferate to form a solid **vaginal plate**
- ▶ Continual proliferation at cranial side of **vaginal plate**
- ▶ 5m: canalization of entire vaginal outgrowth
- ▶ **Dual origin:** both paramesonephric duct and sinovaginal bulb contributes to vagina formation
  - Upper vagina (including fornices) derived from paramesonephric duct
  - Lower vagina derived from urogenital sinus
- ▶ Lumen of vagina remains separated from urogenital sinus by **hymen** (thin tissue plate)
  - Consists of epithelial lining of sinus + a thin layer of vaginal cells
  - Usually develops a small opening during perinatal life

## E. Development of External Genitalia



- ▶ Male genitalia formation induced by **dihydrotestosterone (DHT)**
  - Conversion of testosterone into DHT catalyzed by **5 $\alpha$ -reductase**
  - Lack of **5 $\alpha$ -reductase** → phenotypical female
- ▶ Formed from three structures near cloacal opening:
  - **Genital tubercle** → penis (male) or clitoris (female)
  - **Cloacal (urogenital, urethral, genital) folds** → penile urethra (male) or labia minora (female)
  - **Genital swelling (labioscrotal fold)** → scrotum (male) or labia majora (female)

Female	Male
<b>From the Genital Tubercle/Phallus</b>	
Clitoris: Glans clitoridis Corpora cavernosa clitoridis Bulb of the vestibule	Penis: Glans penis (and navicular fossa) Corpora cavernosum penis Corpus spongiosum penis
<b>From the Urogenital Folds</b>	
Labia minora Perineal raphe Perianal tissue (and external anal sphincter)	Ventral aspect of penis Most of the penile urethra Perineal raphe Perianal tissue (and external sphincter)
<b>From the Labioscrotal Folds</b>	
Labia majora	Scrotum
<b>From the Indifferent Gonad</b>	
Ovary: follicles from secondary sex cords in cortex	Testis: seminiferous tubules from primary sex cords
Vestigial: rete ovarii in medulla	Rete testis in medulla
<b>From the Gubernaculum</b>	
Ovarian ligament Round ligament of the uterus	Gubernaculum testis



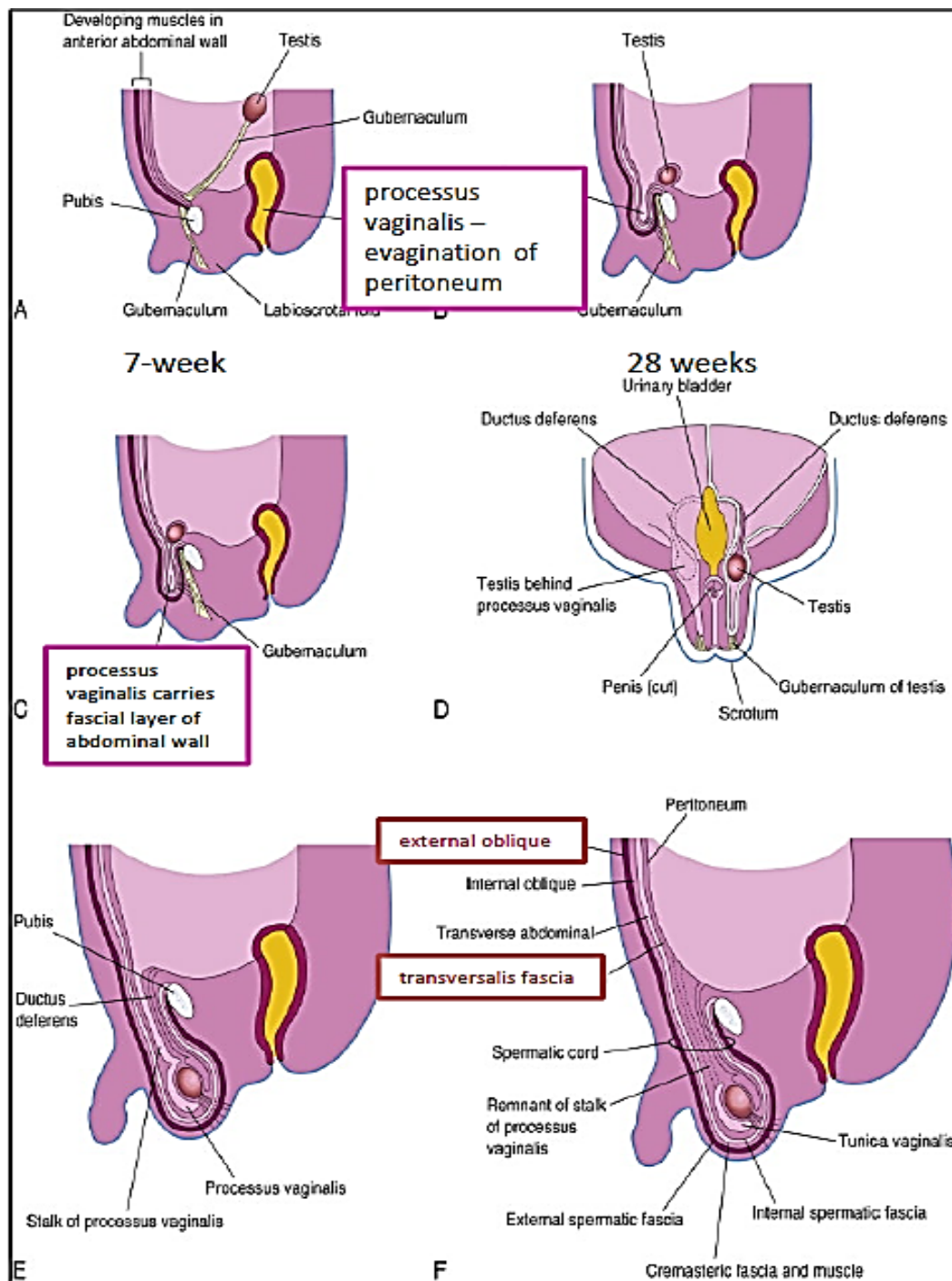
## 1. Development of Female Genitalia

- **Phallus** becomes **clitoris**
- **Urogenital folds** do not fuse and forms **labia minora**
- **Labioscrotal folds** fuse only at ends to form **labia majora**

## 2. Development of Male Genitalia

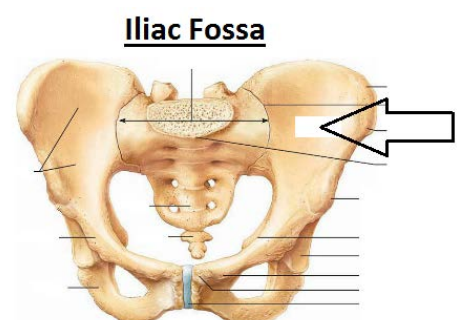
- Development of scrotum and penis induced by **DHT**:
  - 1) **Phallus** elongates to form penis;
  - 2) **Elongation** pulls **urethral folds** together  $\rightarrow$  fuse and enclose urethra;
  - 3) Urethral opening moves progressively towards end of penis;
  - 4) **Labioscrotal swellings** fuse to form **scrotum**.

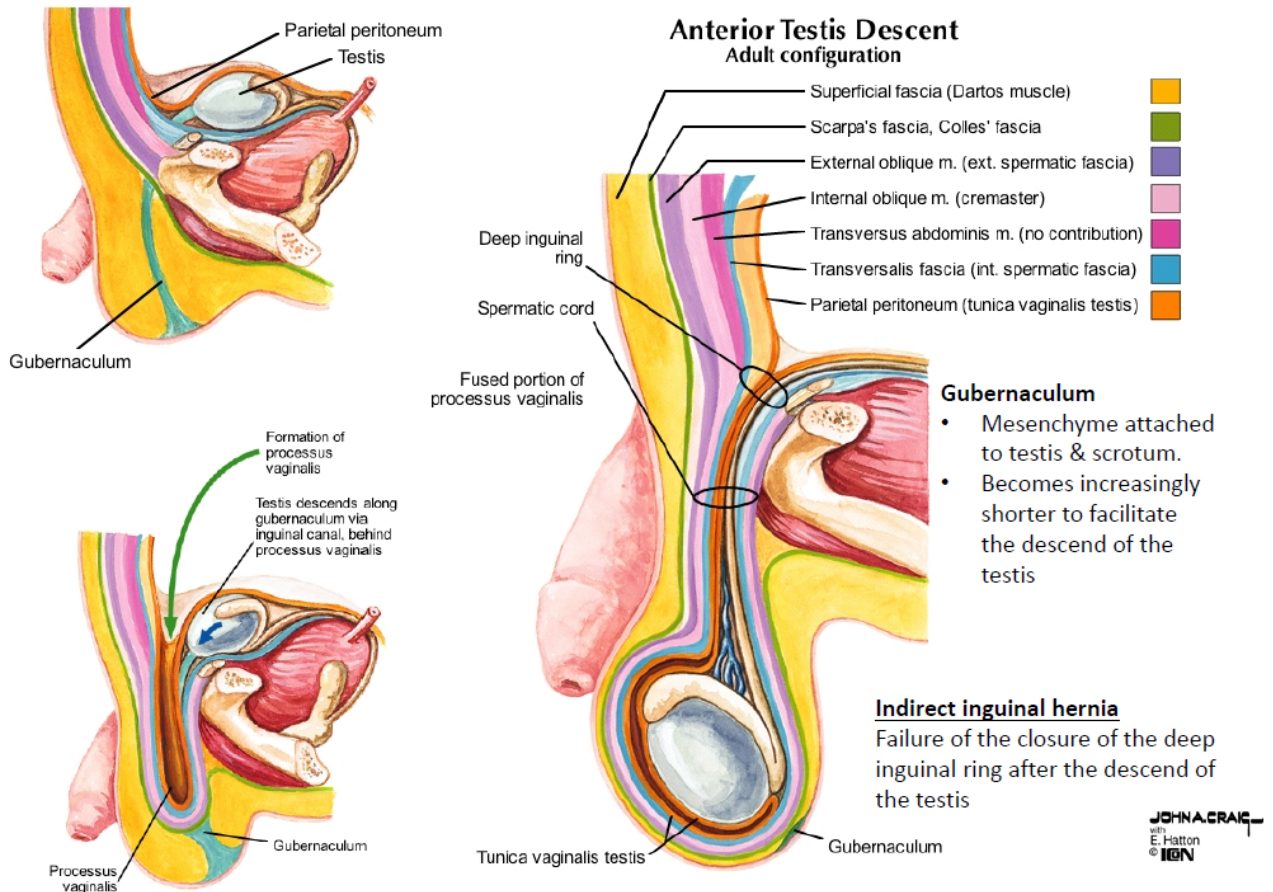
## a. Descent of Testis (3-9m)



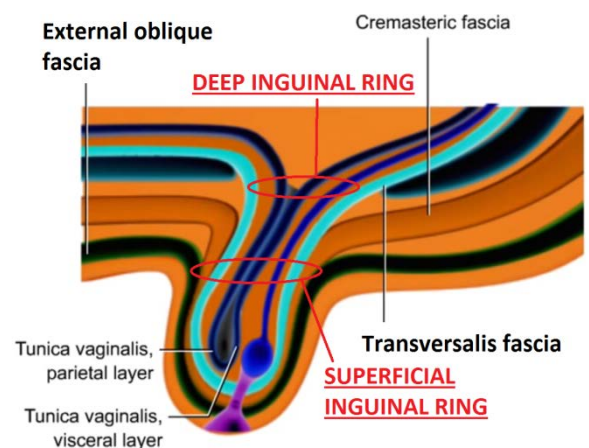
### ► 3-9m: testes descend through the **inguinal canal** into the **scrotum**

- 3m: descent to **iliac fossa**
- 4-7m: **deep inguinal ring**
- 7m: through **inguinal canal**
- 8m: **external inguinal ring**
- 9m: enter **scrotum**





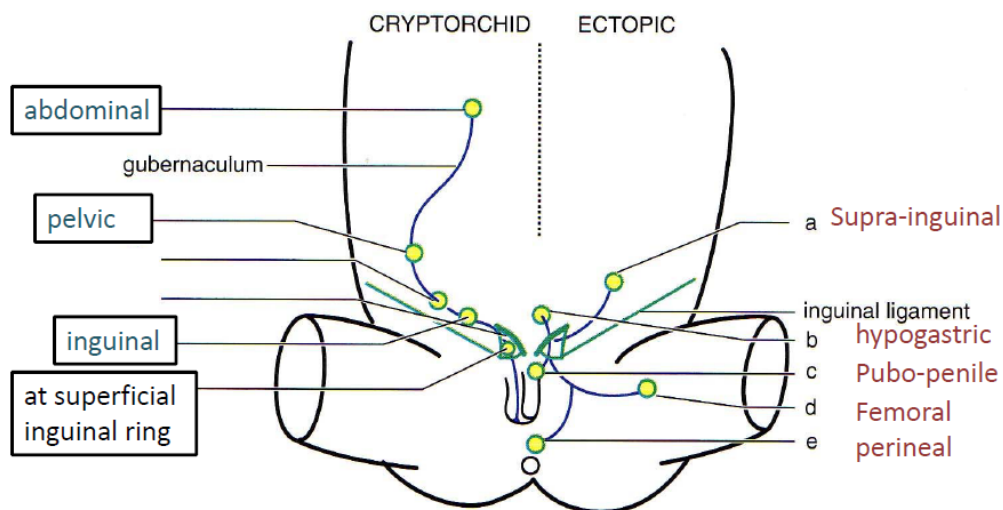
- ▶ Testicular descent occurs in two distinct and sequential phases:
  - **Transabdominal phase:** development and growth of **gubernaculum** pulls testis towards base of abdomen
    - Regulated by **insulin-like factor 3 (INSL3)**
  - **Inguino-scrotal phase:** development of **cranial suspensory ligament** (cranial portion of gubernaculum) blocked → regression of gubernaculum
    - testis go through inguinal canal into scrotum
    - Regulated by **testosterone**
- ▶ **Processus vaginalis:** evagination of peritoneum into the scrotum
  - Descend along with descent of testis
  - Carries extensions of layer of abdominal wall → forms walls of **inguinal canal**, **spermatic cord** and **testis**
- ▶ After descent of testis, abdominal wall closes at **deep** and **superficial inguinal rings** to form **inguinal canal**
  - **Deep inguinal ring** marked by opening in **transversalis fascia**
  - **Superficial inguinal ring** marked by opening in **external oblique aponeurosis**
  - Failure of closure → **indirect inguinal hernia**



## F. Congenital Anomalies of Genital System

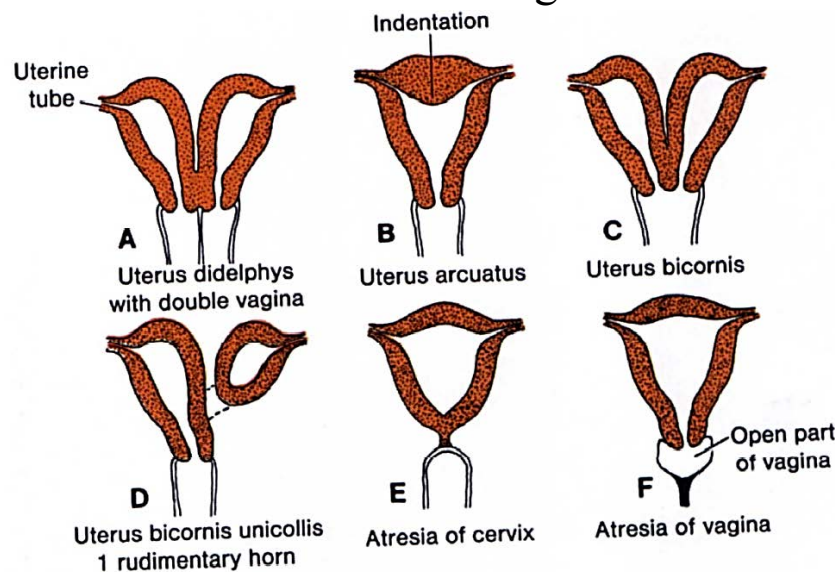
- ▶ Abnormal number of sex chromosome:
  - Eg. **Klinefelter syndrome** (XXY, 47): testicular dysgenesis of seminiferous tubules
  - Eg. **Turner's syndrome** (XO, 45): ovarian dysgenesis
- ▶ Phenotypic defects or **pseudohermaphroditism**:
  - **Hermaphroditism**: genetic intersex (due to mosaic etc.)
  - **Pseudohermaphroditism**: genotypic sex masked by phenotypic appearance that closely resembles the other sex
  - Caused by biochemical lesion
  - Eg. androgen insensitivity → testicular feminization
    - Have normal chromosomes (46, XY)
    - Eg. non-binding of testosterone to androgen receptors
    - Eg. androgens in peripheral tissue converted by aromatase enzymes to oestrogens
- ▶ Developmental arrest in male → external genitalia defect
  - Eg. **epispadia, hypospadias, micropenis**
- ▶ Developmental arrest in female
  - Eg. failure by oviduct openings to develop

### 1. Cryptorchidism and Ectopic Testicles



- ▶ **Cryptorchidism**: hidden testes
- ▶ Both **cryptorchidism** and **ectopic testis** can be caused by abnormal descent of testis
- ▶ Testis can be found along the original position of **gubernaculum** or in nearby areas

## 2. Malformations in Uterus and Vagina



- ▶ **Uterus didelphys**: presence of two uteruses
  - Due to partial failure by paramesonephric ducts to fuse
- ▶ **Uterus arcuatus**: uterine cavity displays a concave contour towards the fundus
  - Due to incomplete resorption of uterine septum
- ▶ **Uterus bicornis**: separation of uterus into two horns by a septum
  - Due to incomplete resorption of uterine septum
- ▶ **Uterus bicornis unicollis**: separation of one uterine horn from the other
  - Due to complete failure by paramesonephric ducts to fuse
- ▶ **Atresia of cervix**: absence of cervical opening
  - Due to failure of canalization between vaginal lumen and uterus
- ▶ **Atresia of vagina**: absence of vaginal opening
  - Due to failure of complete formation of sinovaginal bulbs

## 3. Congenital Adrenal Hyperplasia



Figure 13–17 External genitalia of a newborn female infant with congenital adrenal hyperplasia (CAH). The virilization was caused by excessive androgens produced by the suprarenal glands during the fetal period. Note the enlarged clitoris and fusion of the labia majora to form a scrotum