Development of Male and Female Reproductive System

Learning Objectives

- To learn the development and congenital abnormalities of testes and the ovaries
- To learn the sex determination
- To learn the development and congenital abnormalities of genital ducts
- To learn the development and congenital abnormalities of external genitalia

Development of genital system

- The sex of the fetus is established at fertilization by the genotype of sperm that fertilizes the ovum
- The gonads begin to attain sexual characteristics from the 7th week.
- Early genital systems in the two sexes are similar; this initial period is called the indifferent stage of sexual development

Development of Gonads

Gonads are derived from three sources

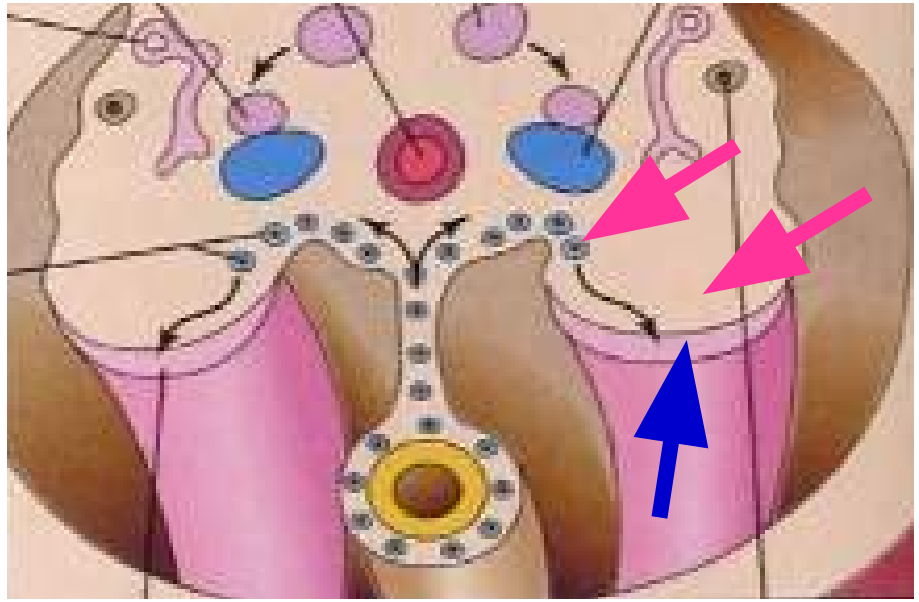
- **The mesothelium:**

  (mesodermal epithelium) lining the posterior abdominal wall

- **The underlying mesenchyme:**

  (embryonic connective tissue)

- **The primordial germ cells:**



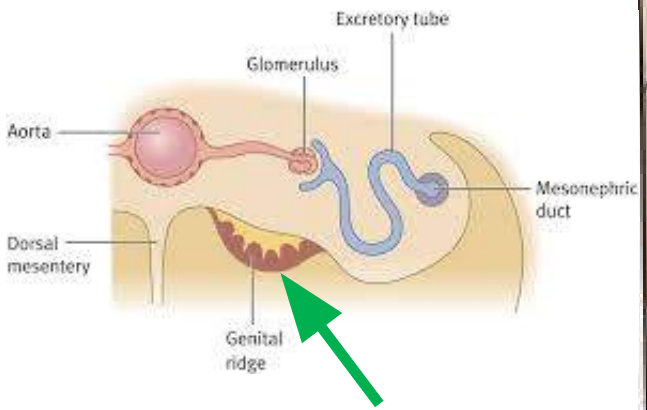
Indifferent gonads

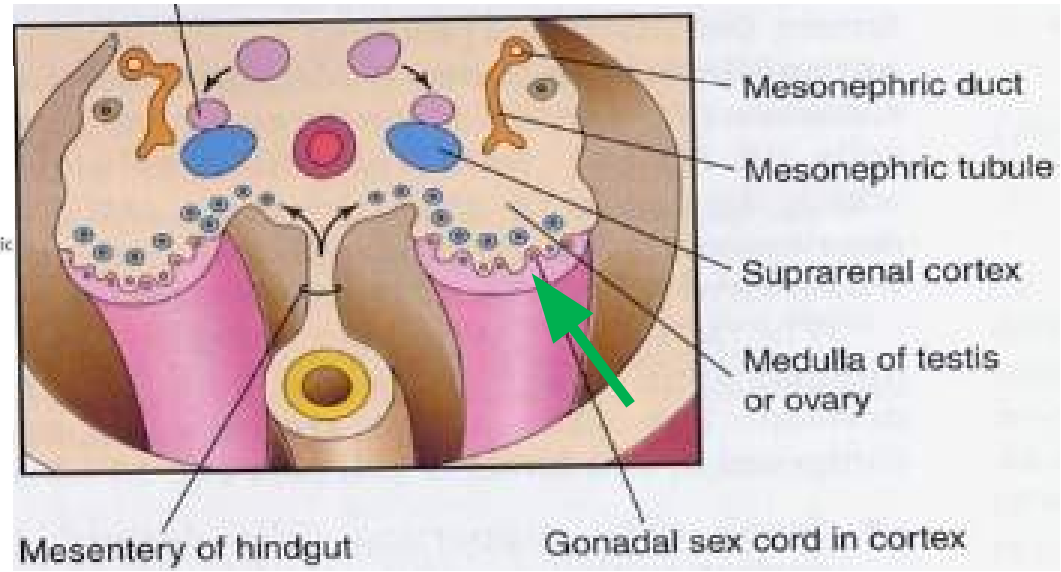
Gonadal (genital) ridges

- During the 5th week, a thickened area of mesothelium develops on the medial side of the mesonephros due to the proliferation of mesothelium and underlying mesenchyme

Gonadal cords

- Finger-like epithelial cords (Gonadal cords) grow into the underlying mesenchyme





Indifferent gonads Cont.,

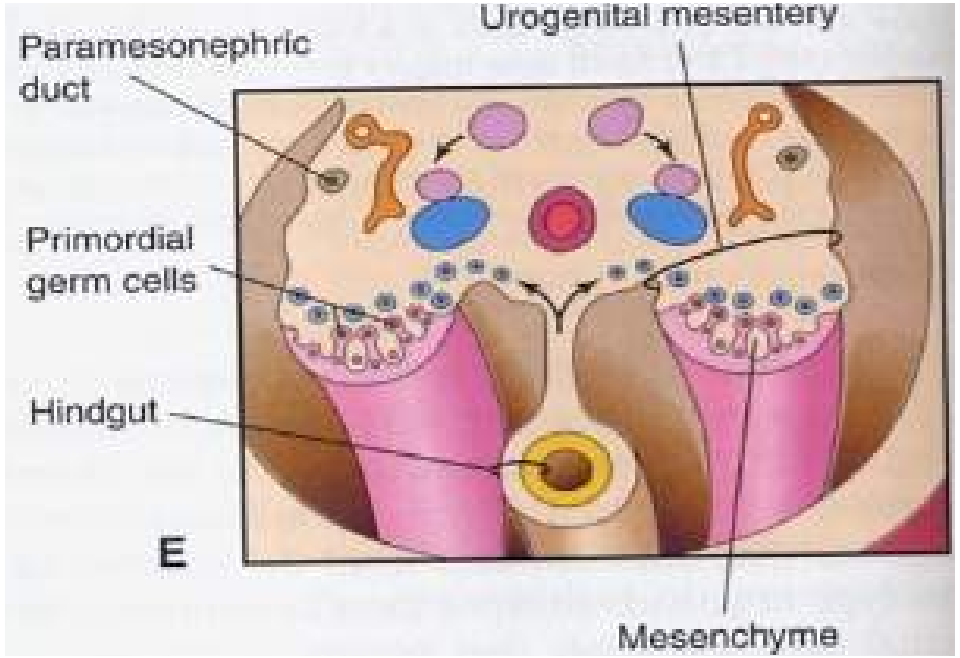
- The indifferent gonad now consists of an external cortex and an internal medulla.
- If the embryo is XX (Female):

  cortex will differentiate into an ovary, and the medulla will regress
- If the embryo is XY (Male):

  medulla differentiates into a testis, and

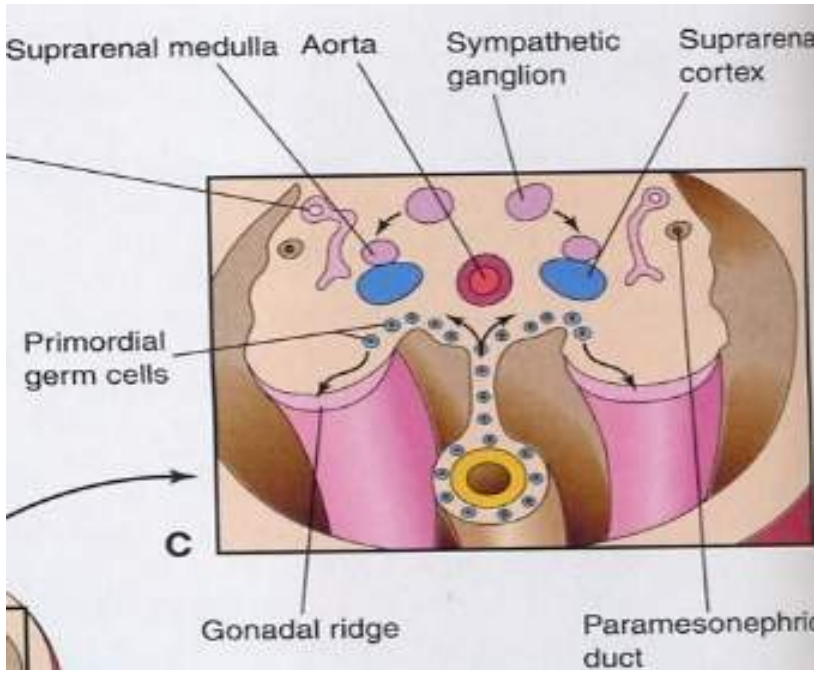
  the cortex will regress except for

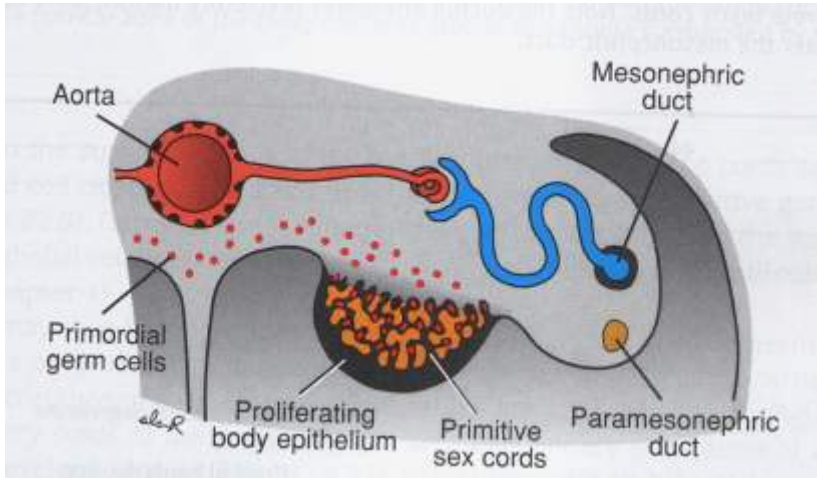
  vestigial remnants



Primordial germ cells

- Primordial germ cells originate in the wall of the yolk sac
- The sex cells are visible early in the 4th week among the endodermal cells of the yolk sac
- The primordial germ cells migrate along the dorsal mesentery of the hindgut to the gonadal ridges
- During 6th week primordial germ cells enter the underlying mesenchyme and are incorporated in the gonadal cords.
- Eventually, they differentiate into oocytes and sperms





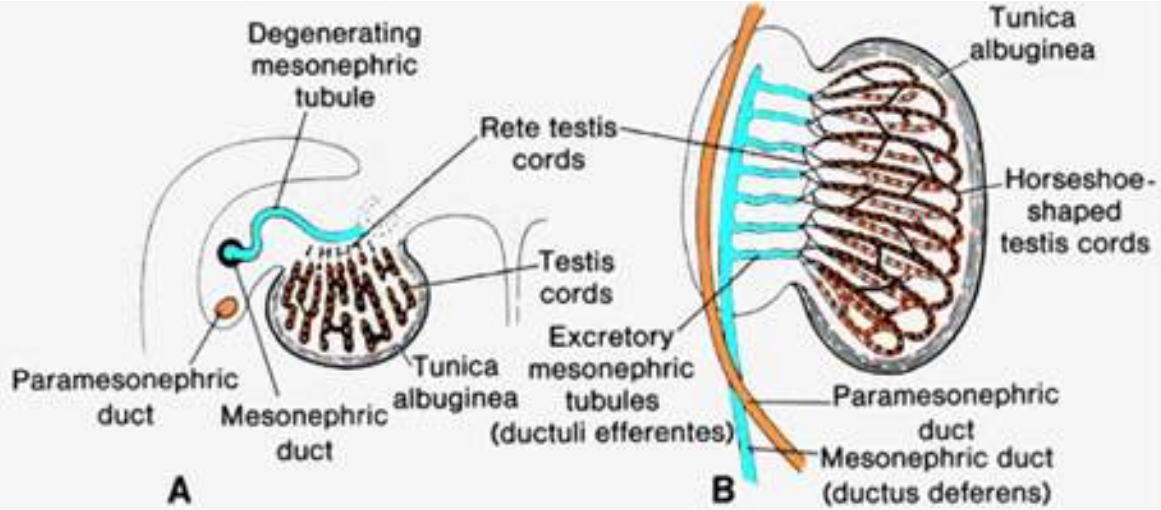
Sex determination

- Chromosomal and genetic sex is established at fertilization and it depends on the type of sperm (X,Y) that fertilizes the X-bearing Oocyte
- The type of gonads that develop is determined by the sex chromosome complex of the embryo (XX or XY)
- Before 7th week gonads of both sexes are identical (indifferent gonads)
- Male phenotype requires Y- chromosome, while female phenotype requires two X chromosomes
- SRY-gene on the short arm of the Y chromosome is needed for the expression of the Testis Determining Factor (TDF).

Sex determination Cont.,

- The Y chromosome has a testis determining effect on the medulla of indifferent cords . TDF (regulated by Y chromosome) differentiate the gonadal cords into seminiferous cords
- Absence of a Y chromosome (XX sex chromosome) results in the formation of the ovary
- Types of present gonads determine the type of sexual differentiation of the genital ducts and external genitalia.
- Testosterone produced by the fetal testes determines maleness.
- Primary female sexual differentiation does not depend on hormones; occurs even if the ovaries are absent (depending possibly on an autosomal gene)

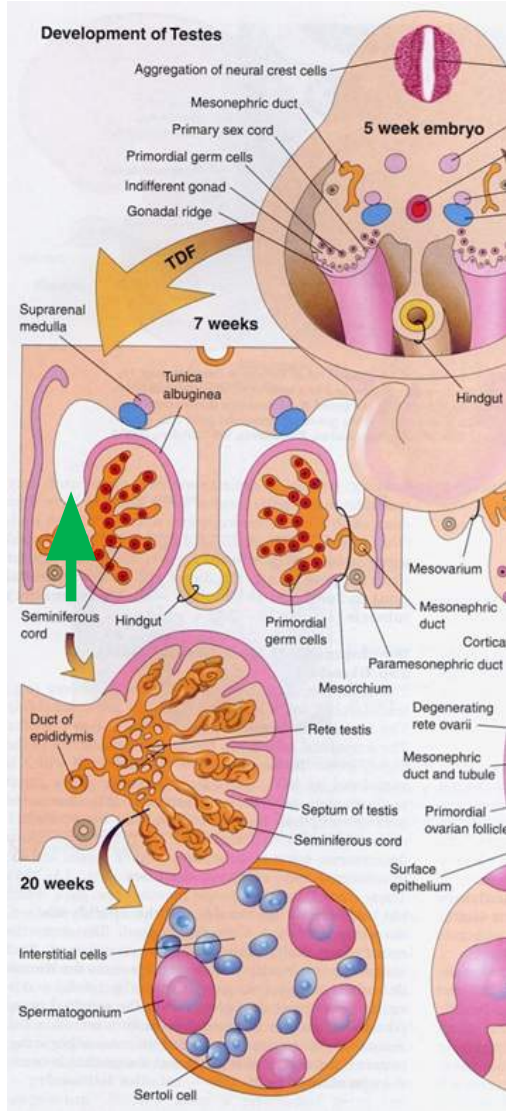
Development of testis



- SRY gene on the short arm of Y-chromosome influences the expression of Testis Determining Factor (TDF).
- TDF induces the gonadal cords (seminiferous cords) to condense and extend into the medulla of the indifferent gonad; where they branch and anastamose to form the rete testis.
- A dense layer of fibrous CT (tunica albuginea) separates the testis cords from the surface epithelium
- Mesenchyme between seminiferous tubules gives rise to interstitial cells of Leydig

Development of testis Cont.,

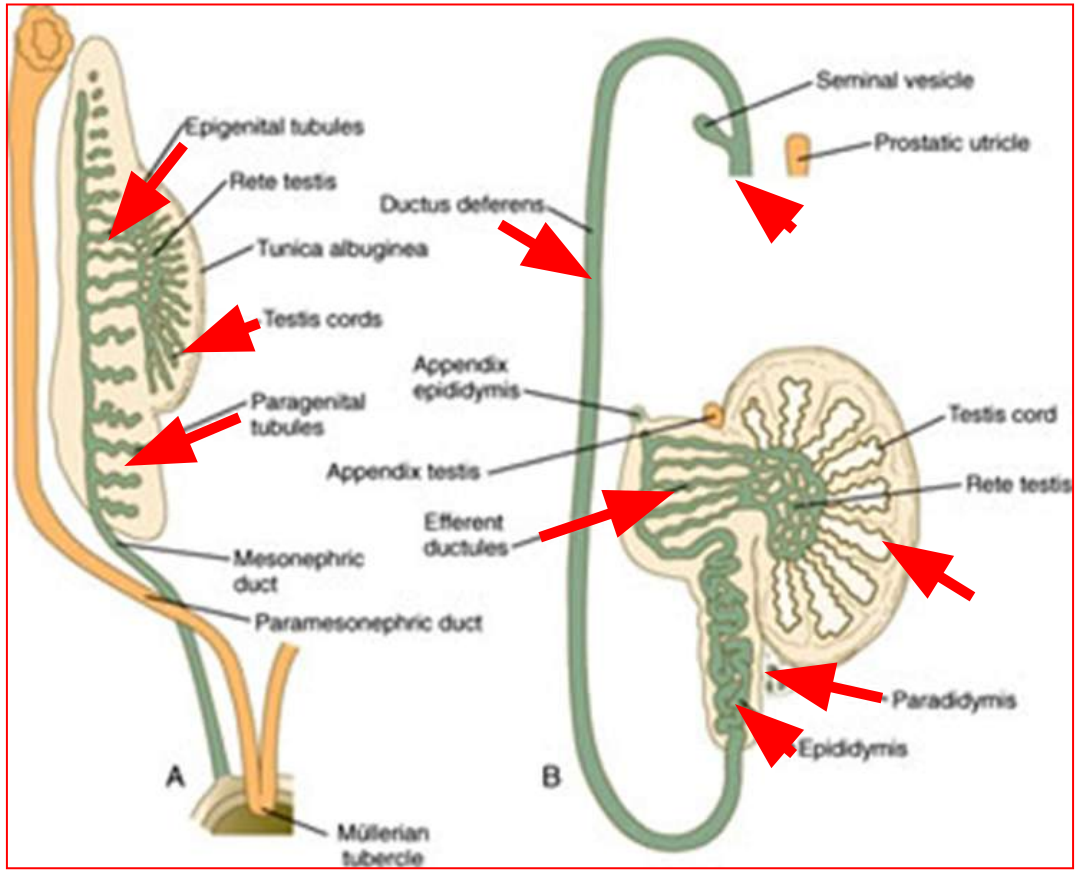
- Gradually the testis separates from degenerating mesonephros and becomes suspended by its mesentery (Mesorchium).
- Testis cords are now composed of primitive germ cells and Sertoli derived from the surface epithelium of the gonad
- By the 8th week, interstitial cells of Leydig secrete androgenic hormones under the effect of human chorionic gonadotropin which induces masculine differentiation of mesonephric ducts and external genitalia
- Anti-Mullerian hormone by Sertoli cell inhibits differentiation of paramesonephric duct into uterus and uterine tubes



Development of Male Genital Ducts

In the fetal testis:

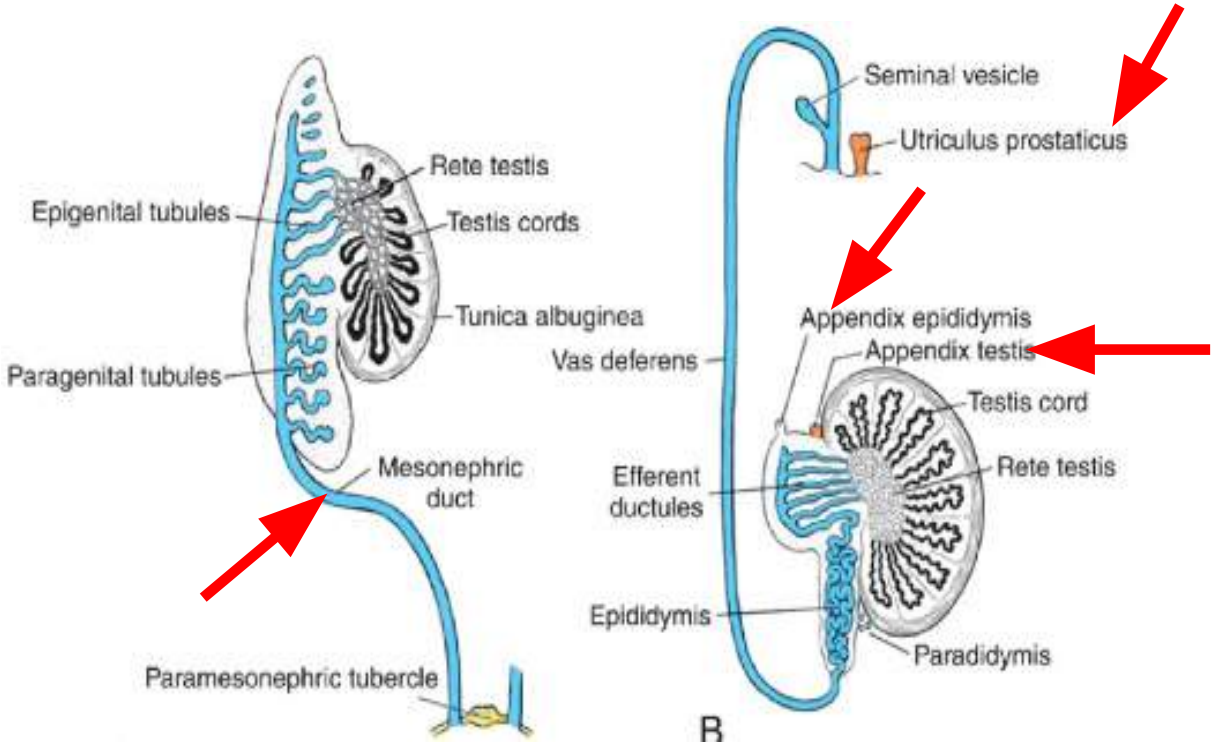
- **Testis cords** remain solid until **puberty**; when they become canalized forming seminiferous tubules
- **Sertoli cells** form most of the seminiferous tubules before puberty
- **Rete testes** become continuous with 15-20 mesonephric tubule (**Epigenital tubules**) that become **efferent tubules**



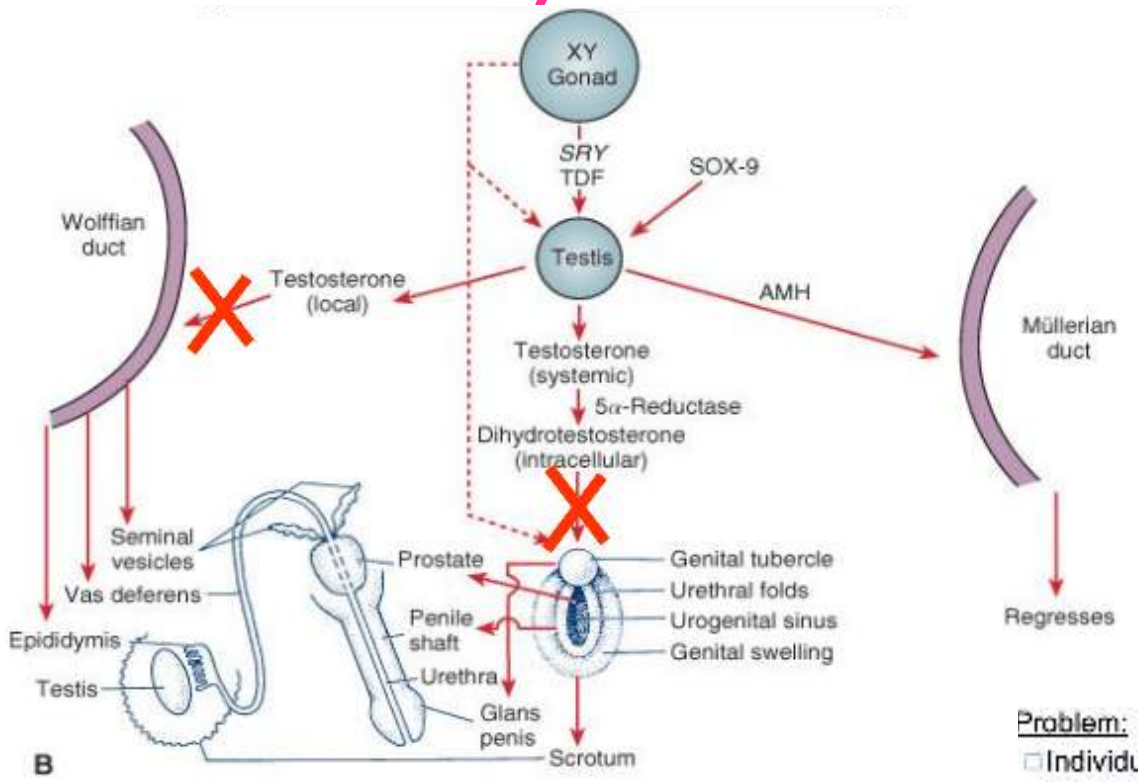
- The mesonephric duct becomes the **ductus epididymis** and **ductus deferens**
- The region of the ducts beyond the seminal vesicles is the **ejaculatory duct**.
- Caudal excretory (**para genital tubules**) do not join the cords of the rete testis; their remnants become **paradidymis**.

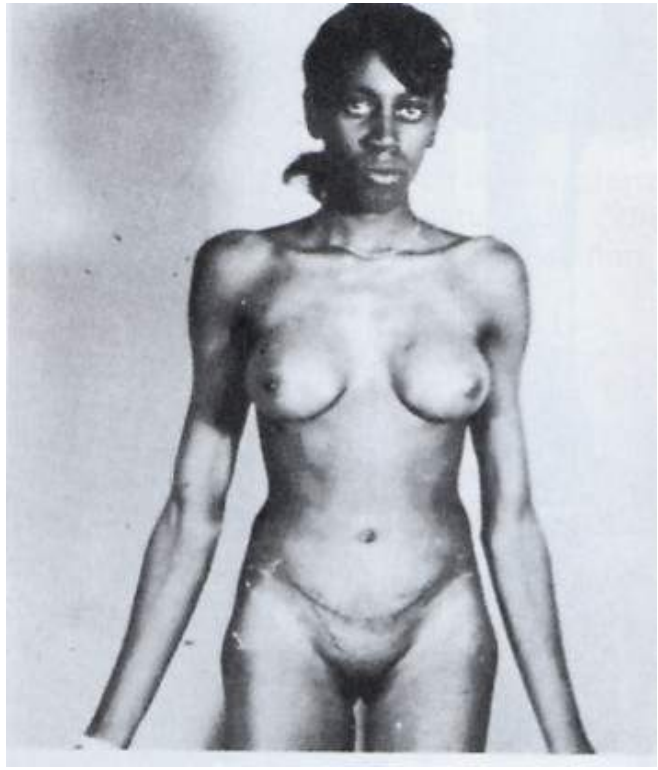
Genital duct development in male

- Remnant of mesonephric duct gives appendix of epididymis
- Remnant of paramesonephric duct gives appendix of testis cranially, and prostatic utricle, caudally.



Androgen Insensitivity Syndrome (testicular feminization):46XY



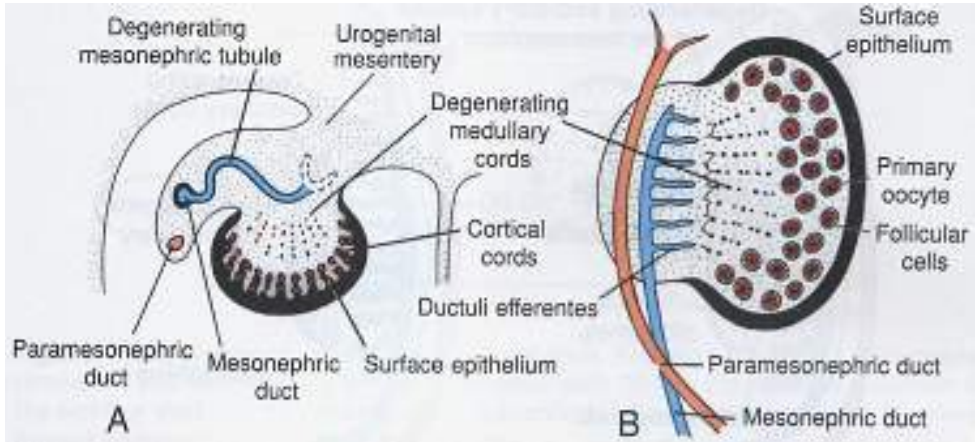


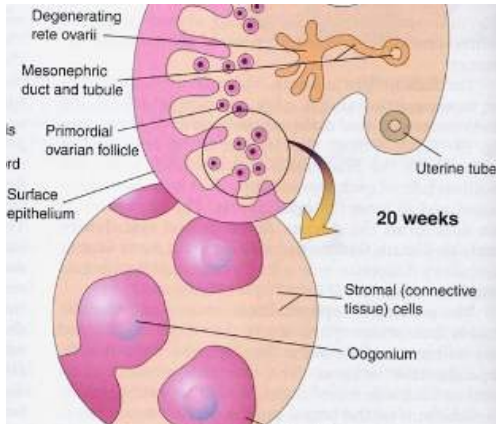
Problem: No functional androgen receptor

- Individuals are XY
- Testes develop
  - Secrete AMH & testosterone
  - Both Wolffian and Müllerian ducts regress
- Female external genitalia develop, but have blind-ended vagina
- Infertile
- Classified as a girl at birth
- Diagnosed at puberty because of primary amenorrhea

Development of the Ovary

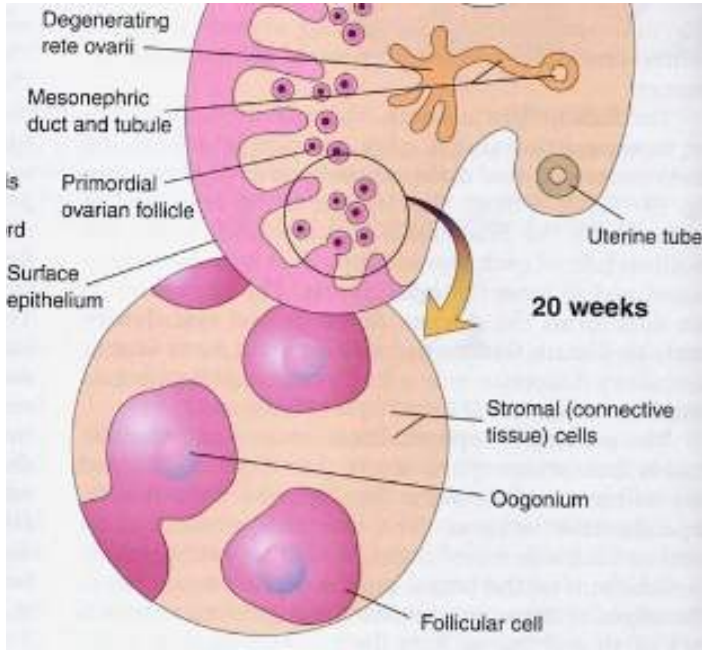
- Genes in X chromosome and some autosomal genes play a role in ovarian development
- Gonadal cords extend into the medulla of the ovary to form a rudimentary rete ovarii that degenerate and are replaced by a vascular stroma that forms the ovarian medulla
- Gonadal cords in the cortex extend from surface epithelium underlying mesenchyme of developing ovary
- As cortical cords increase in size, primordial germ cells are incorporated into them.





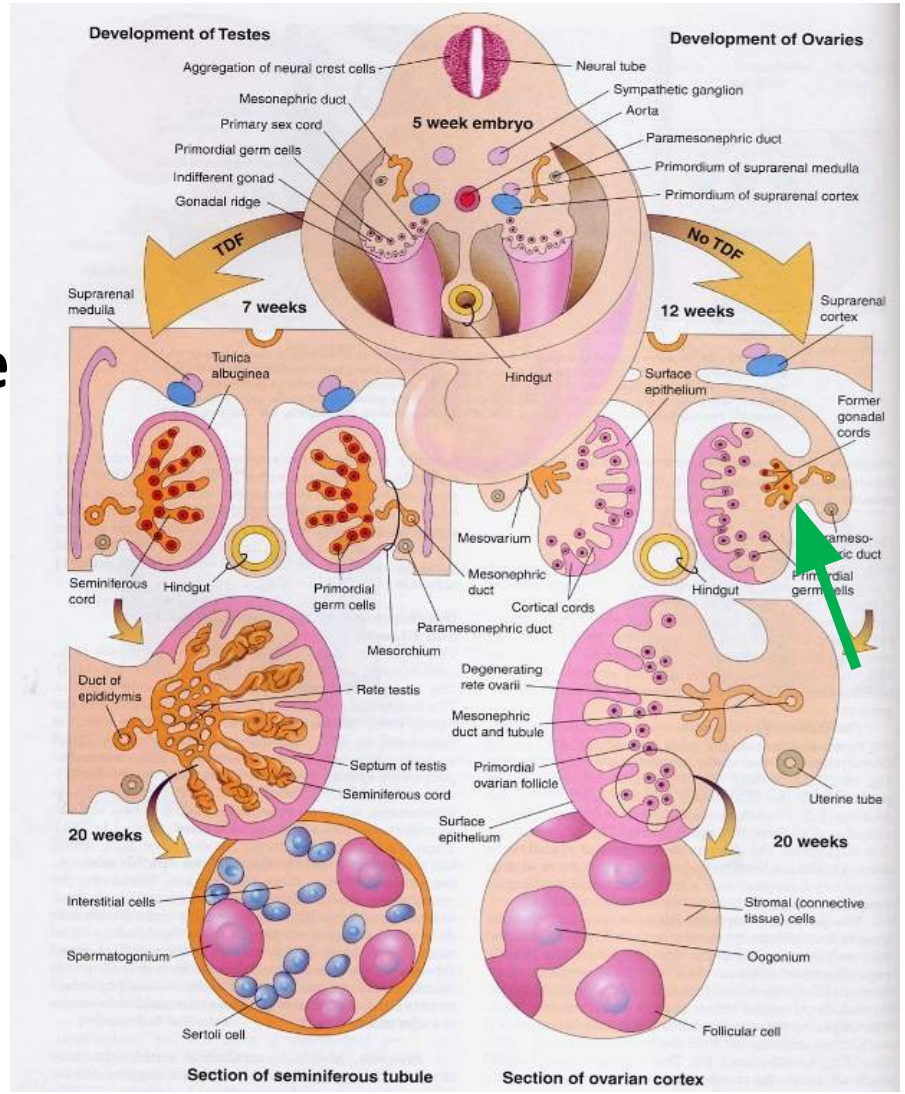
Development of the Ovary Cont.,

- At the 16th week, cortical cords break up into isolated cell clusters (Primordial follicles).
- Each follicle consists of Oogonium surrounded by a single layer of flattened follicular cells derived from surface epithelium



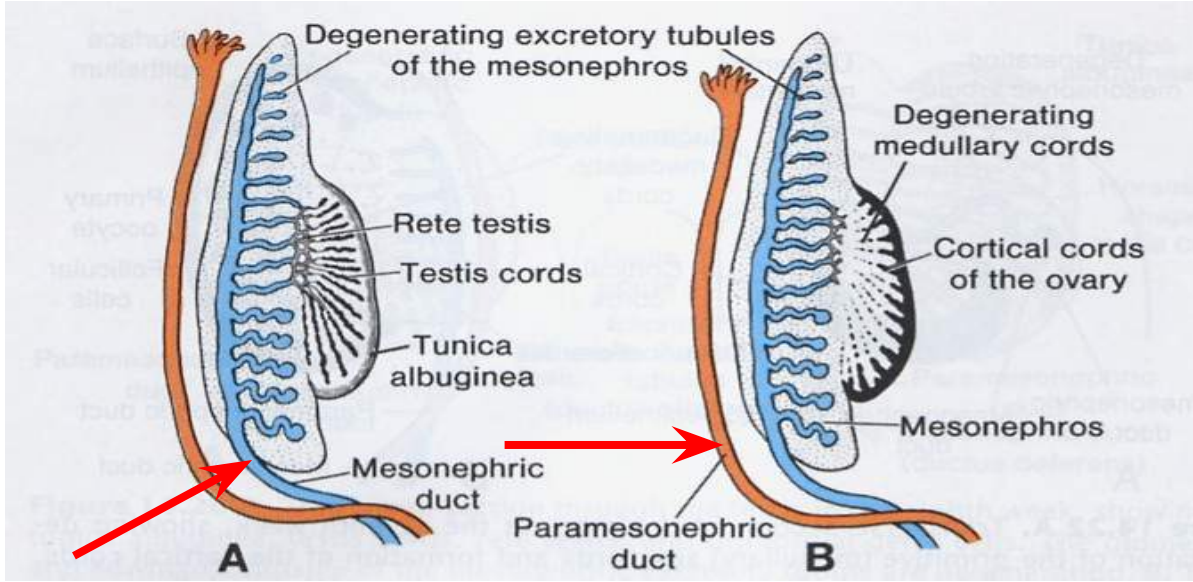
Development of Ovary

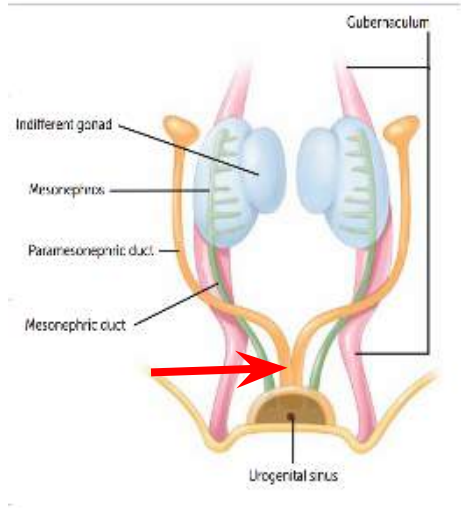
- After birth, the surface epithelium covering the ovary becomes flattened to a single layer continuous with the peritoneal covering of the posterior abdominal wall (germinal epithelium)
- Surface epithelium becomes separated from the follicles by a thin fibrous capsule (Tunica Albugenia)
- Ovary become suspended by mesentery (mesovarium) after separation from regressing mesonephros



Development of Female Genital ducts

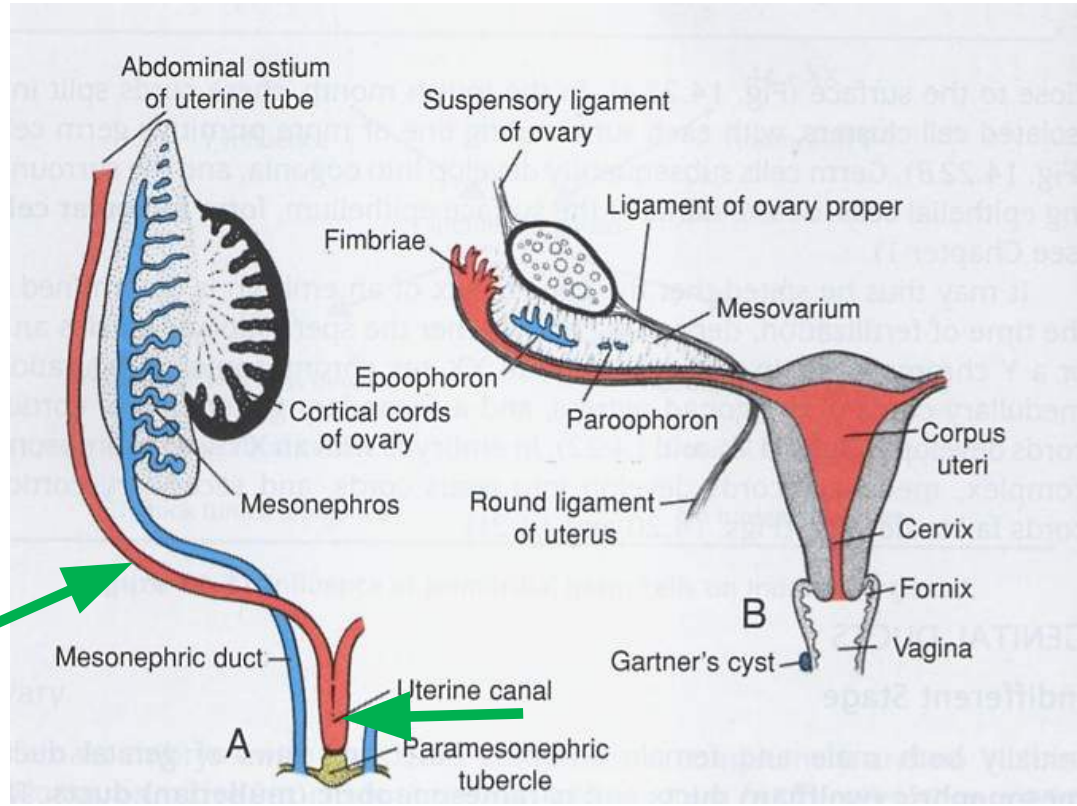
- At the beginning, both male and female embryos have 2 pairs of genital ducts:
  - Mesonephric (Wolffian) ducts
  - Paramesonephric (müllerian) ducts
- The caudal tip of the combined ducts projects into the posterior wall of the urogenital sinus causing a swelling (paramesonephric/müllerian tubercle)
- The mesonephric ducts open into the urogenital sinus on either side of the müllerian tubercle





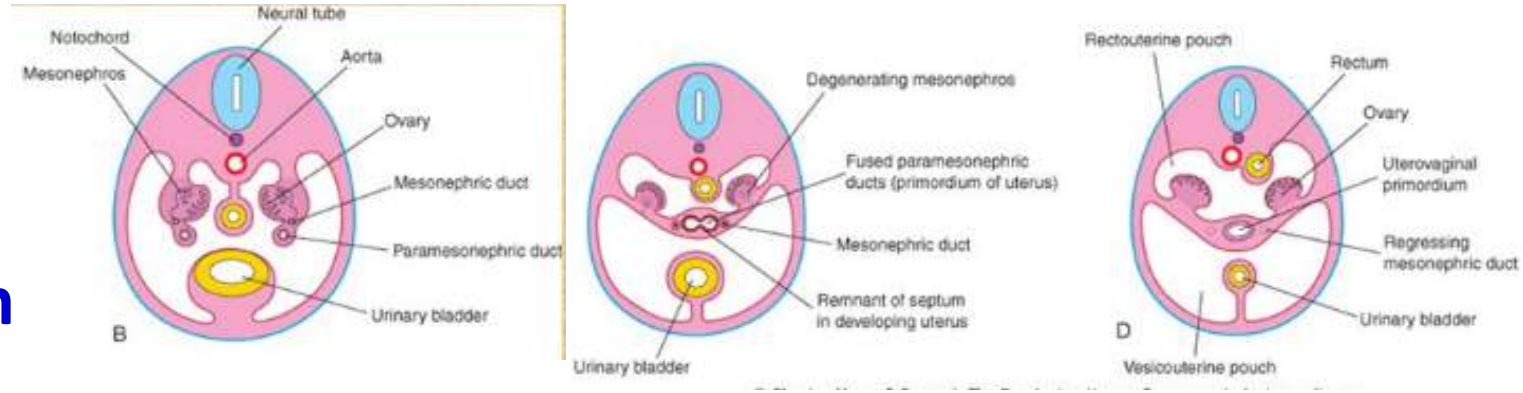
Genital duct development in female

- **Paramesonephric ducts** develop into the main genital ducts
- Initially, 3 parts can be recognized in each duct:
- The cranial vertical portion that opens into the abdominal cavity develops into the lateral part of the uterine tube
- The horizontal part that crosses the mesonephric duct develops to the medial part uterine tube
- The caudal vertical part that fuses with its partner from the opposite side to form a uterine canal



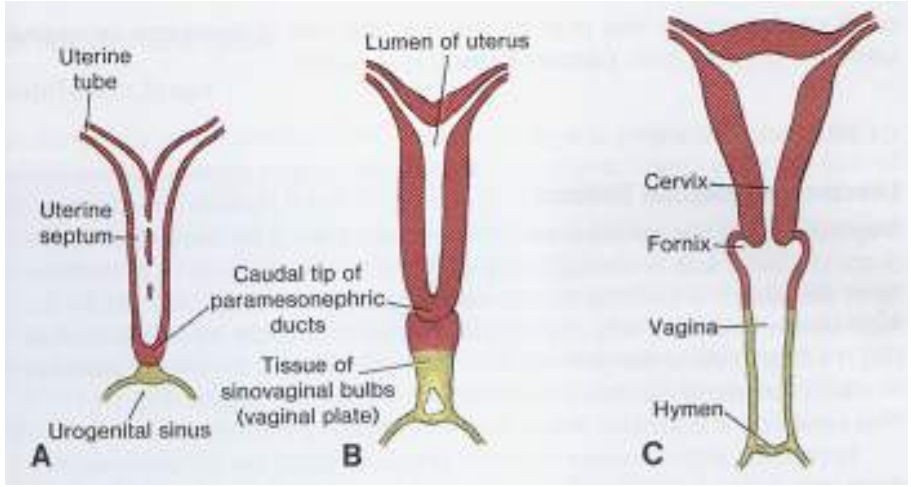
Genital duct development in female

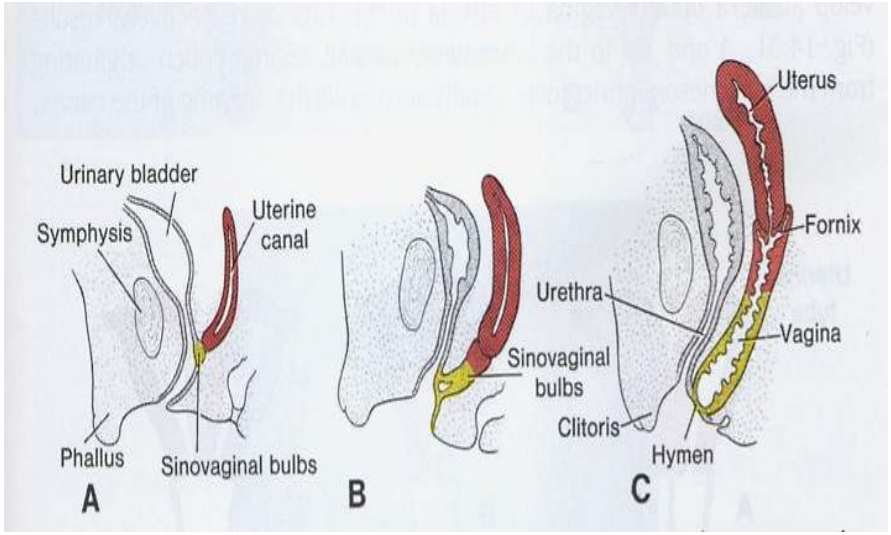
- The second part of the paramesonephric ducts move medio-caudally; from urogenital ridges gradually come to lie in a transverse plane
- As the ducts fuse in the midline; a broad transverse pelvic fold (broad ligament of the uterus) is established. The uterine tube lies in its upper border and the ovary lies on its posterior surface
- The uterus and broad ligament divide the pelvic cavity into uterorectal and ureterovesical pouches
- Fused paramesonephric ducts differentiate into the corpus and cervix of the uterus.
- They are surrounded by a layer of mesenchyme that forms the myometrium and the perimetrium



Development of vagina

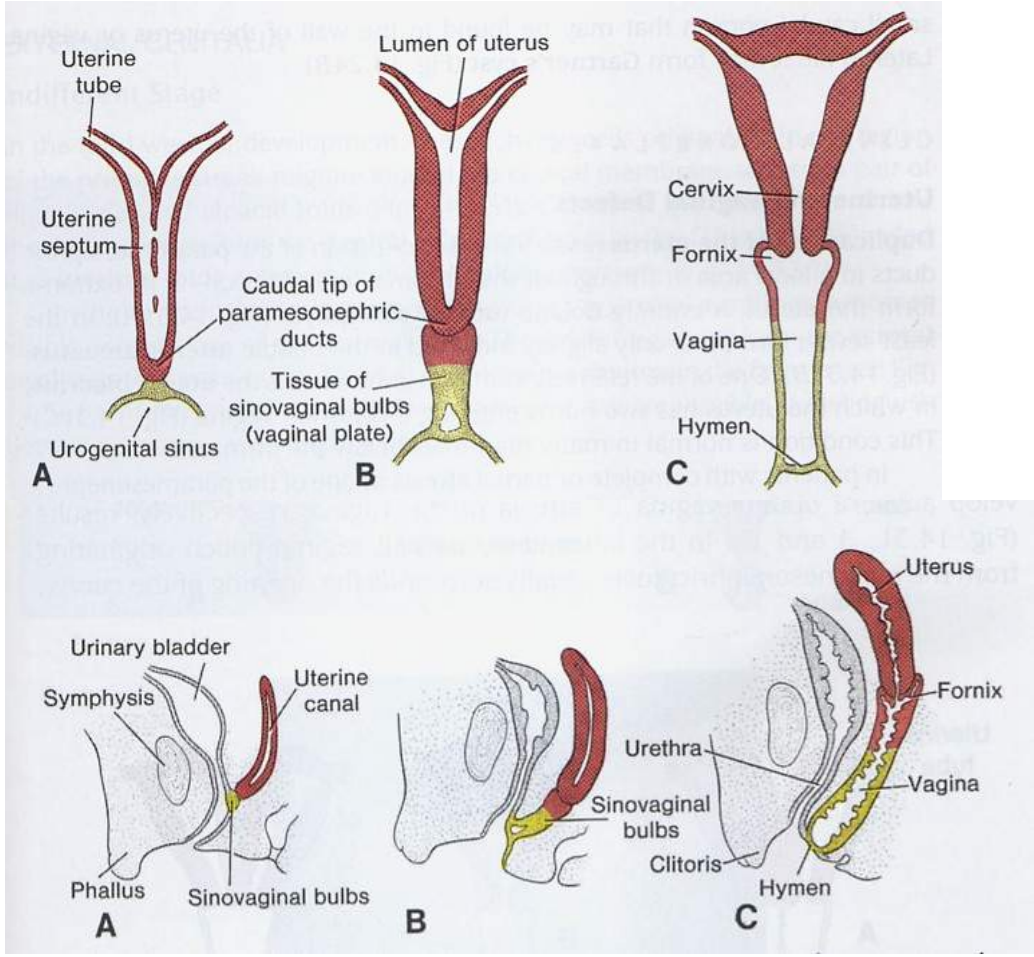
- After the solid tip of the mesonephric ducts reaches the urogenital sinus; two solid evaginations (sinovaginal bulbs) grow out from the pelvic part of the sinus.
- Sinovaginal bulbs proliferate and form a solid vaginal plate.
- Proliferation continues at the cranial end of the plate; increasing the distance between the uterus and the urogenital sinus.
- By the 5th month vaginal outgrowth is entirely canalized. Vaginal fornices (wing-like expansions of the vagina around the end of uterus) are of paramesonephric origin





Development of vagina

- **The vagina has two origins:**
  - **upper portion derived from the uterine canal**
  - **lower portion derived from the urogenital sinus**
- **Lumen of the vagina remains separated from that of the urogenital sinus by a thin tissue plate; the hymen**
- **Hymen consists of the epithelial lining of the sinus and a thin layer of vaginal cells. It usually develops an opening during perinatal life**

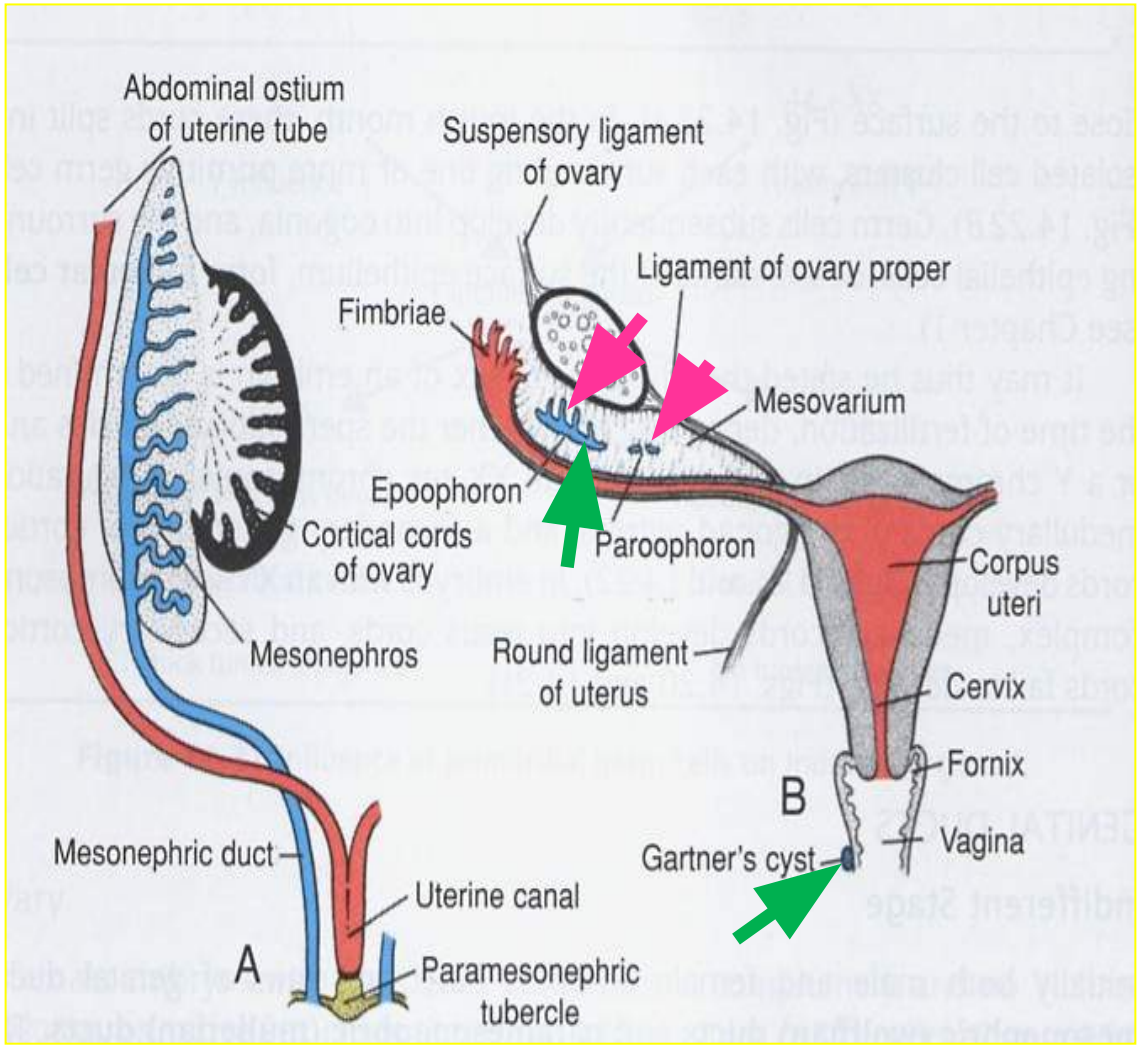


Remnants of the ducts in female

- Remnants of the cranial and caudal excretory mesonephric tubules in the mesovarium disappear except for small portions that remain as epoophoron

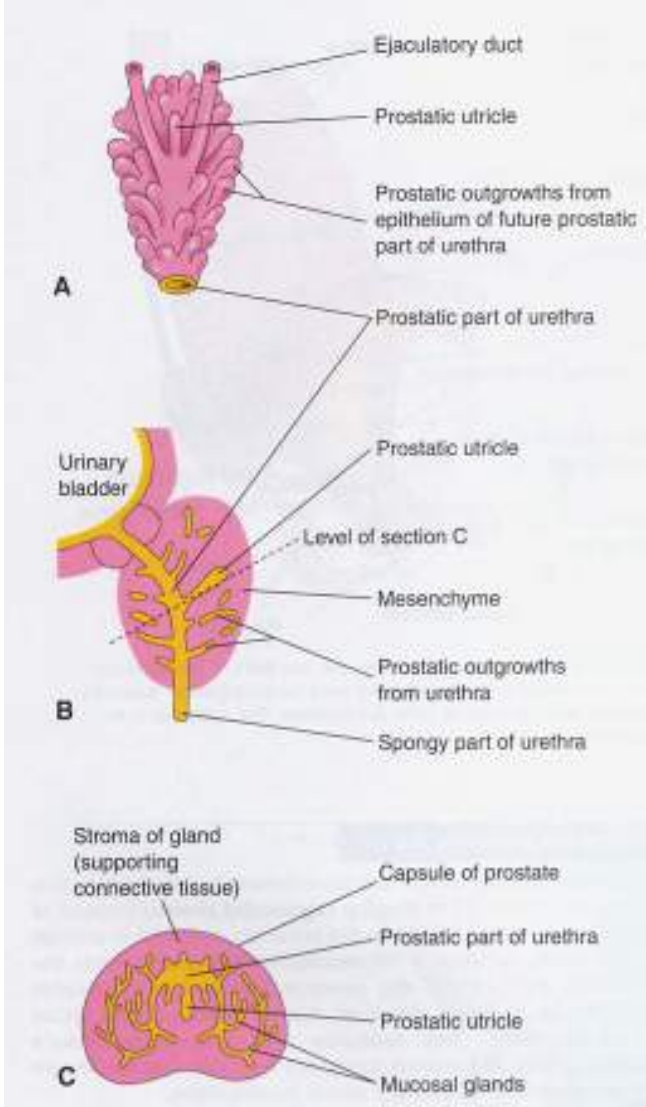
  and paroophoron respectively.

- Mesonephric duct disappears except for a small cranial portion found in epoophoron and a small caudal portion in the wall of the uterus or vagina (Gartner's cyst).



Development of male genital glands

- A lateral outgrowth from the caudal end of each mesonephric duct gives rise to seminal vesicle/gland
- Multiple endodermal outgrowths arising from the prostatic part of the urethra grow into the surrounding mesenchyme and differentiate into prostate glandular epithelium; mesenchyme differentiates into prostatic stroma
- Bulbourethral glands develop from paired outgrowths from the spongy part of the urethra



Congenital anomalies of vagina

- **Absence of vagina:**

  Results from the failure of sinovaginal bulbs to develop.

- **Vaginal atresia:**

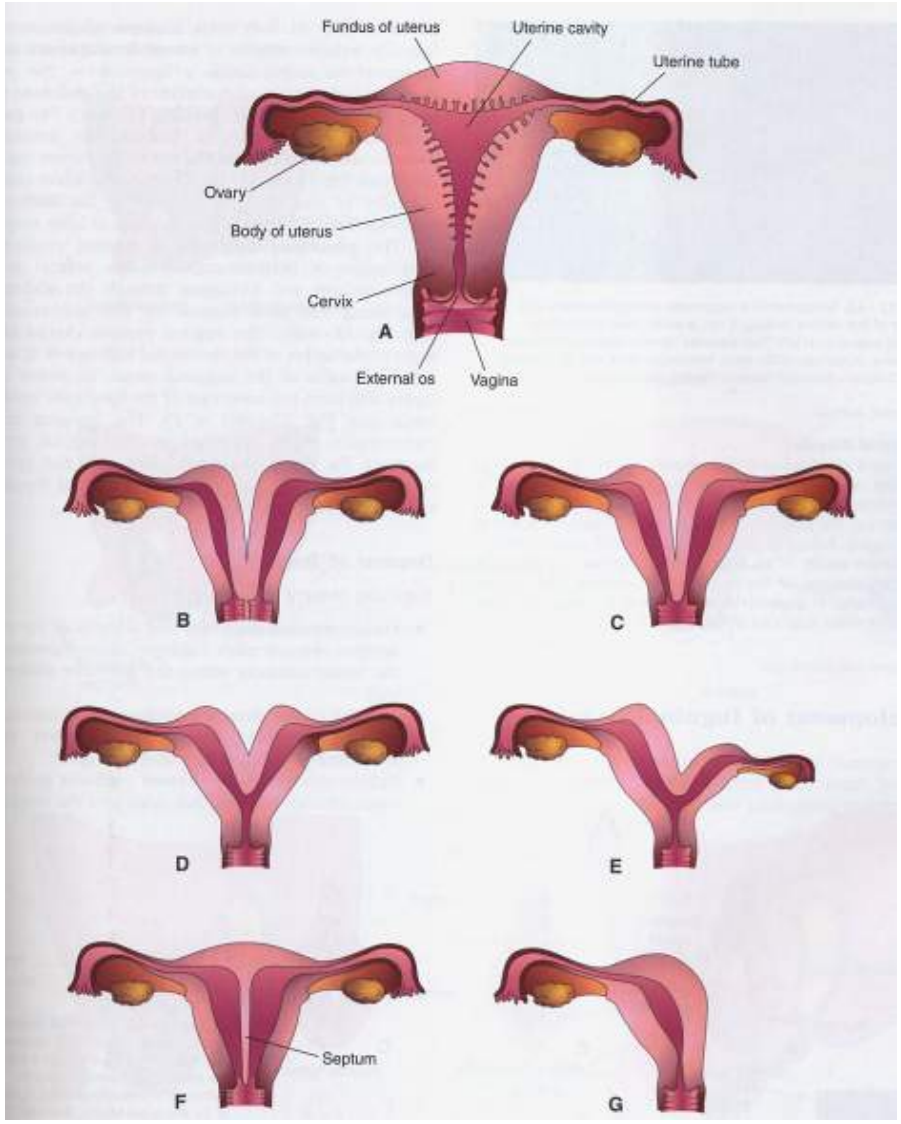
  Failure of the recanalization of the vaginal plate.

- **Imperforate hymen:**

  Failure of perforation of the inferior end of the vaginal plate

Uterine anomalies

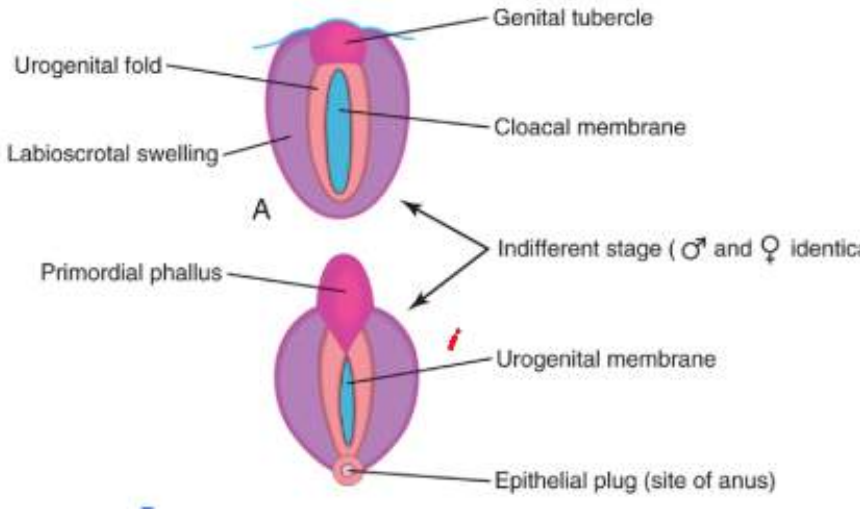
A. Normal uterus and vagina
B. Double uterus
C. Double uterus with single vagina
D. Bicornuate uterus
E. Bicornuate uterus with a rudimentary left horn
F. Septate uterus
G. Unicornuate uterus



Development of External Eenitalia

Indifferent Stage

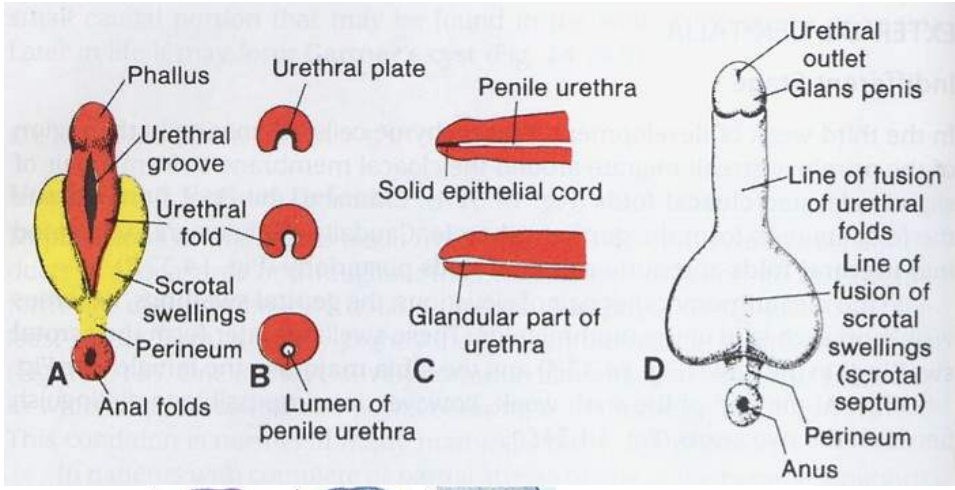
- In the 3rd week, mesenchyme cells originating in the region of the primitive streak migrate around the cloacal membrane to make a pair of slightly elevated urogenital folds.
- Cranial to the cloacal membrane, the folds unite to form the genital tubercle
- Caudally, the folds are subdivided into urogenital folds anteriorly and anal folds posteriorly

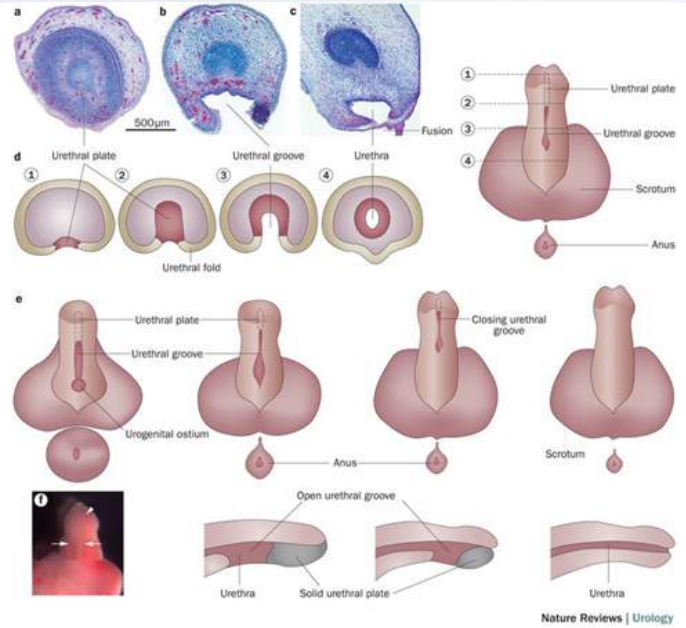


- Another pair of elevations (Labioscrotal folds) becomes visible on each side of the urogenital folds
- Later these swellings from the scrotal swellings in males, labia majora in females

Development of external genitalia in male

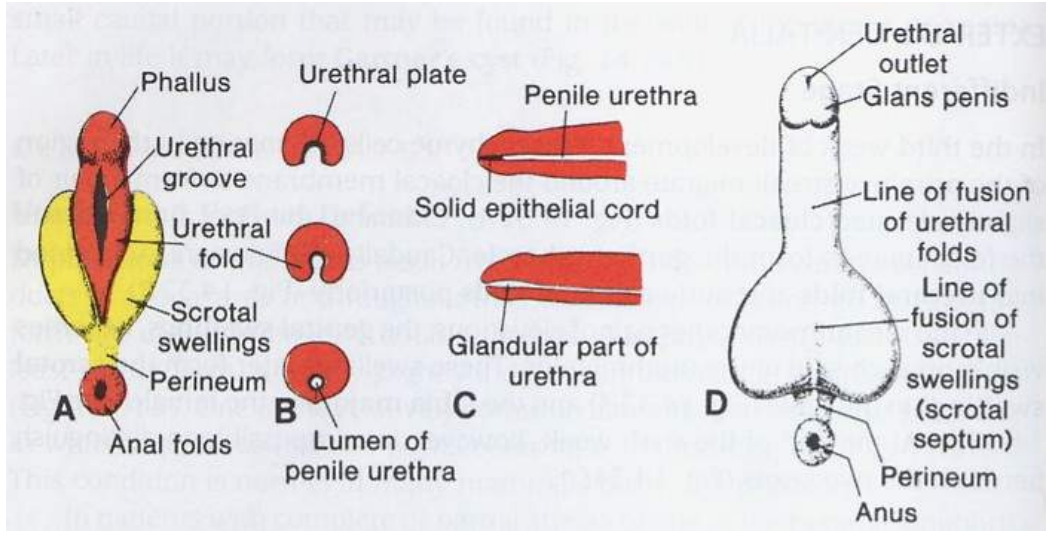
- Is under the influence of androgens from the fetal testes
- Characterized by rapid elongation of the genital tubercle (phallus); during which the phallus pulls the urethral folds forward so that they form the lateral walls of the urethral groove
- The urethral groove does not reach the most distal part (glans)
- The epithelial lining of the groove which originates from the endoderm, proliferates to form the urethral plate

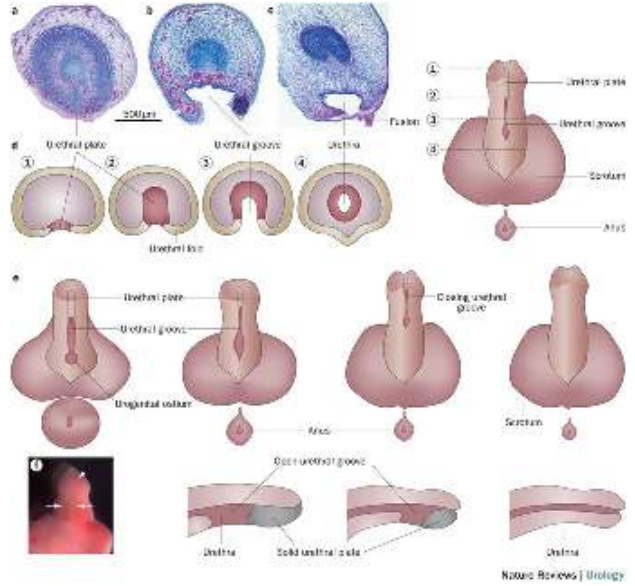




Development of external genitalia in male

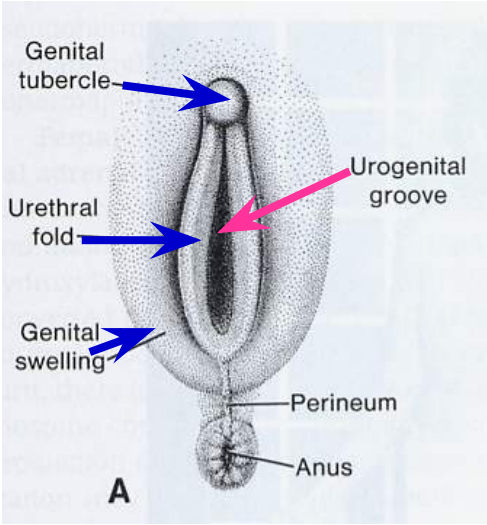
- At the end of third month the two urethral folds close over the urethral plate; forming the penile urethra
- This canal does not extend to the tip of the phallus
- The most distal urethra is formed during 4th month when ectodermal cells from the tip of the glans penetrate inward and form an epithelial cord.
- Recanalization of epithelial cord forms the external urethral meatus
- The genital/scrotal swellings arise in the inguinal region; move caudally and each one makes up half of the scrotum, separated by scrotal septum.

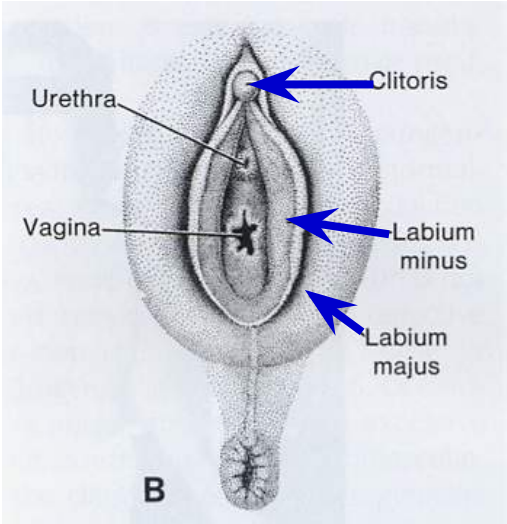




Development of external genitalia in female

- Under the effect of estrogens, the genital tubercle elongates only slightly forming the clitoris
- Urethral folds do not fuse; develop into labia minora
- Genital swellings enlarge and form the labia majora
- The urogenital groove is open and forms the vestibule
- Although the genital tubercle does not elongate extensively in females, it is larger than in males during the early stages; resulting in mistakes in identification of the sex by US examination.



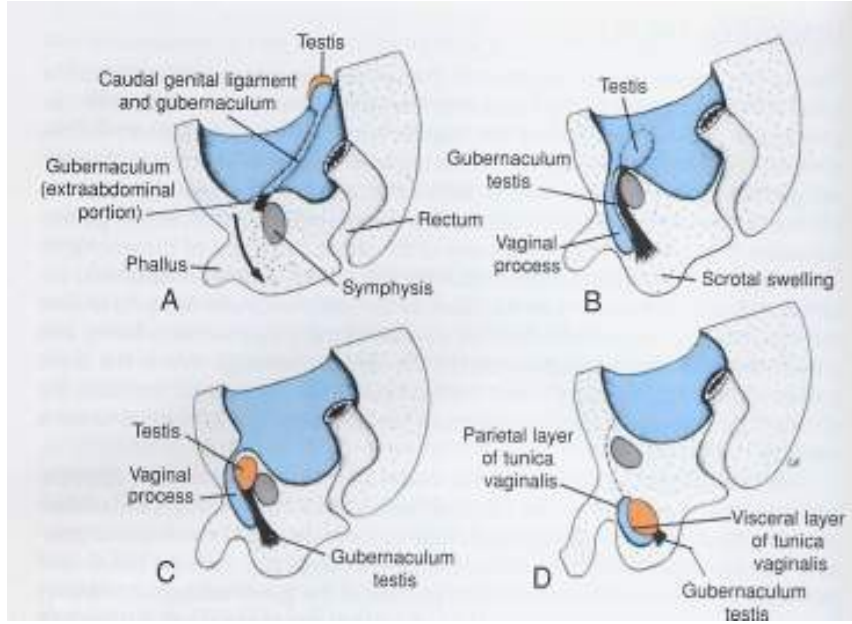


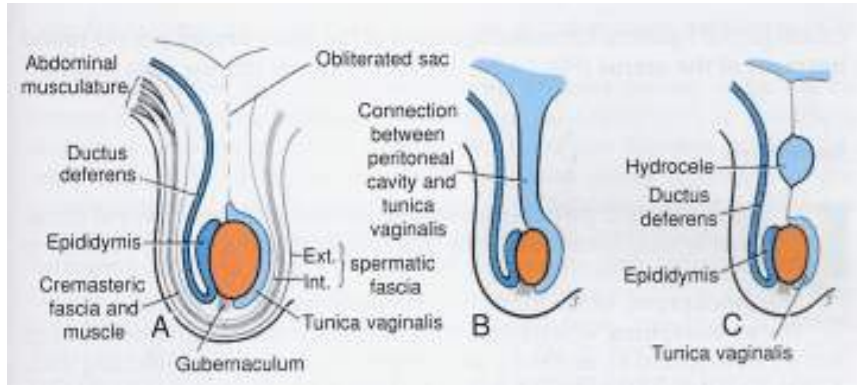
Congenital anomalies of penis

- **Hypospadias:** most common anomaly of the penis. The external urethral orifice is on the ventral surface of the glans penis (penile hypospadias). Resulting from inadequate production of androgens by the fetal testes/ or inadequate receptor sites for the hormone
- **Epispadias:** The urethra opens on the dorsal surface of the penis; often associated with exstrophy of the bladder; resulting from inadequate ectodermal-mesodermal interactions during the development of genital tubercle
- **Agenesis of external genitalia:** Absence of penis or clitoris; resulting from the failure of development of genital tubercle.
- **Bifid penis and double penis:** vary rare, often associated with exstrophy of the bladder or urinary anomalies; results when two genital tubercles develop.
- **Micropenis:** The penis is so small that it is almost hidden by the suprapubic pad of fat. It results from a fetal testicular failure.

Descent of the testes

- By 26 weeks have descended retroperitoneally from the posterior abdominal wall to the deep inguinal rings
- Androgens, gubernaculum (a mesenchymal condensation) may guide the descent
- Descent may take 2-3 days and the inguinal canal contracts after they enter the scrotum
- As the testis and the ductus deferens descend, they are ensheathed by the facial extensions of the abdominal wall



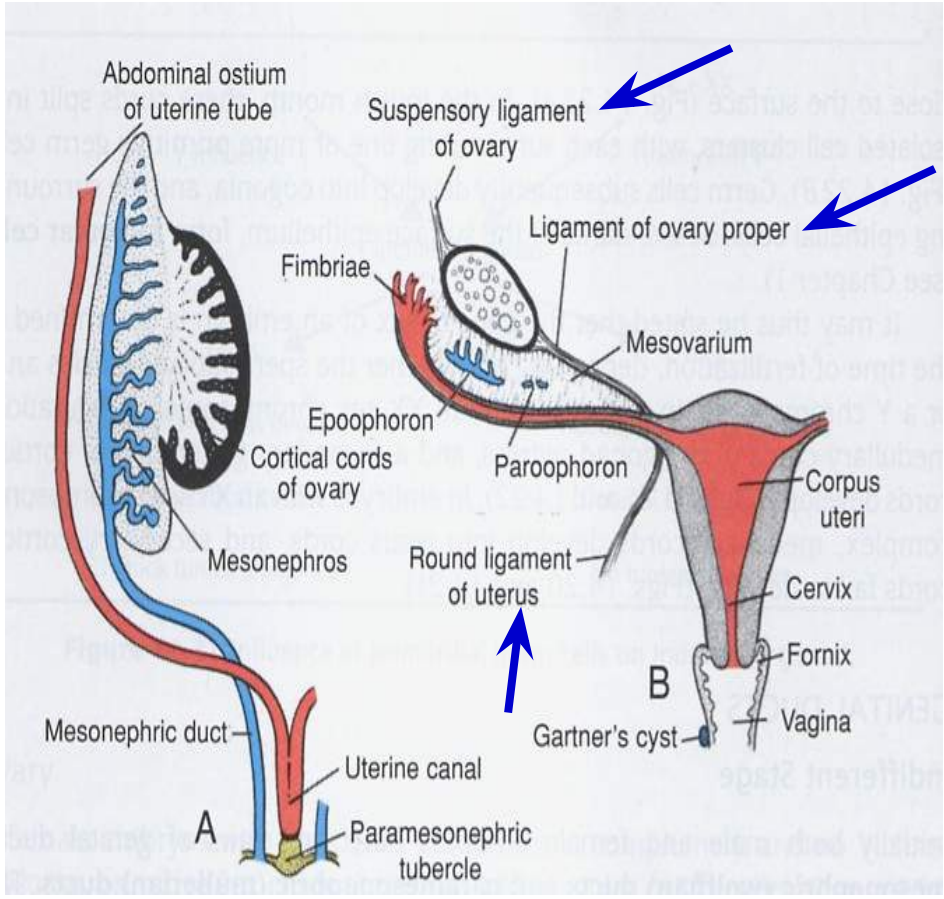


Congenital anomalies of descent of the testes

- **Cryptorchidism or undescended testis:** occurs in 30 % of premature, 3-4% of full-term males. It may be uni or bilateral. Failure of descent in the first year causes atrophy of the testes. It may be in the abdominal cavity or anywhere along the descent path, usually in the inguinal canal. It may be caused by the deficiency of androgen production in the testes.
- **Ectopic testes:** After traversing the inguinal canal, the testis may deviate from its usual path of descent and lodge in various abnormal locations.

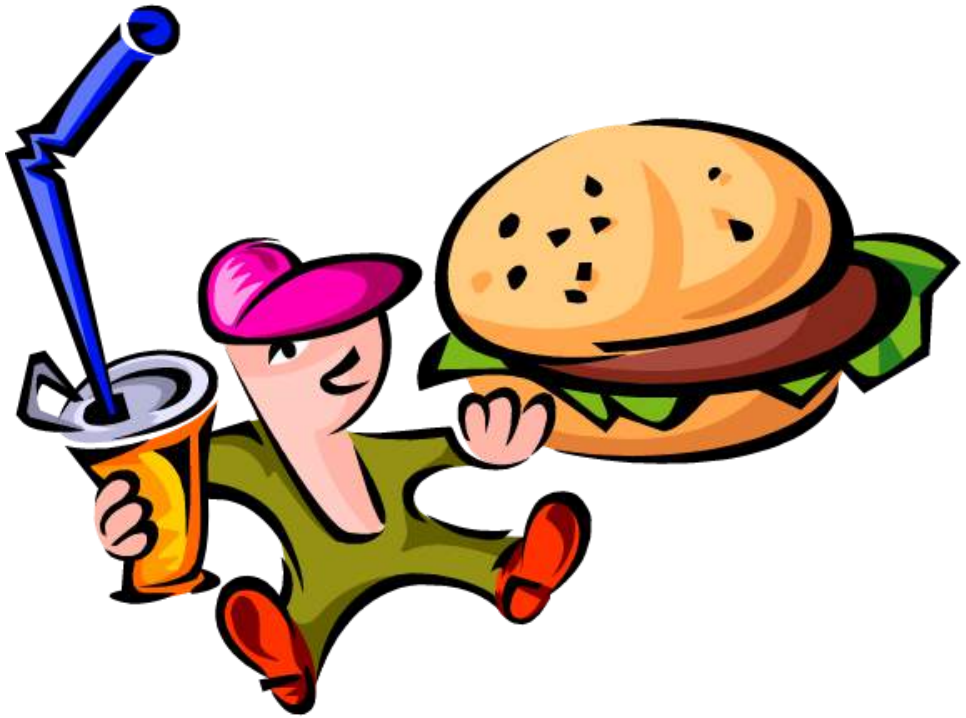
Descent of the ovaries

- Descent is considerably less in female
- The ovaries settle below the rim of the true pelvis
- The cranial genital ligament forms the suspensory ligament of the ovary
- The caudal genital ligament forms the ligament of the ovary proper and the round ligament of the uterus



MALE	EMBRYONIC STRUCTURE	FEMALE
Testis	Indifferent gonad	Ovary
Seminiferous tubules	Cortex	*Ovarian follicles*
Rete testis	Medulla	*Rete ovarii*
Gubernaculum testis	Gubernaculum	*Ovarian ligament*
		Round ligament of uterus
Efferent ductules of testis	Mesonephric tubules	Epoophoron
Paradidymis		Paroophoron
Appendix of epididymis	Mesonephric duct	Appendix vesiculosa
Duct of epididymis		Duct of epoophoron
Ductus deferens		Longitudinal duct; Gartner duct
Ureter, pelvis, calices, and collecting tubules		*Ureter, pelvis, calices, and collecting tubules*
Ejaculatory duct and seminal gland		
Appendix of testis	Paramesonephric duct	Hydatid (of Morgagni)
		Uterine tube
		Uterus
Urinary bladder	Urogenital sinus	*Urinary bladder*
Urethra (except navicular fossa)		*Urethra*
Prostatic utricle		*Vagina*
Prostate gland		*Urethral and paraurethral glands*
Bulbourethral glands		*Greater vestibular glands*
Seminal colliculus	Sinus tubercle	Hymen
Penis	Phallus	*Clitoris*
Glans penis		*Glans of clitoris*
Corpora cavernosa of penis		*Corpora cavernosa of clitoris*
Corpus spongiosum of penis		*Bulb of vestibule*
Ventral aspect of penis	Urogenital folds	*Labia minora*
Scrotum	Labioscrotal swellings	*Labia majora*

Your comments???

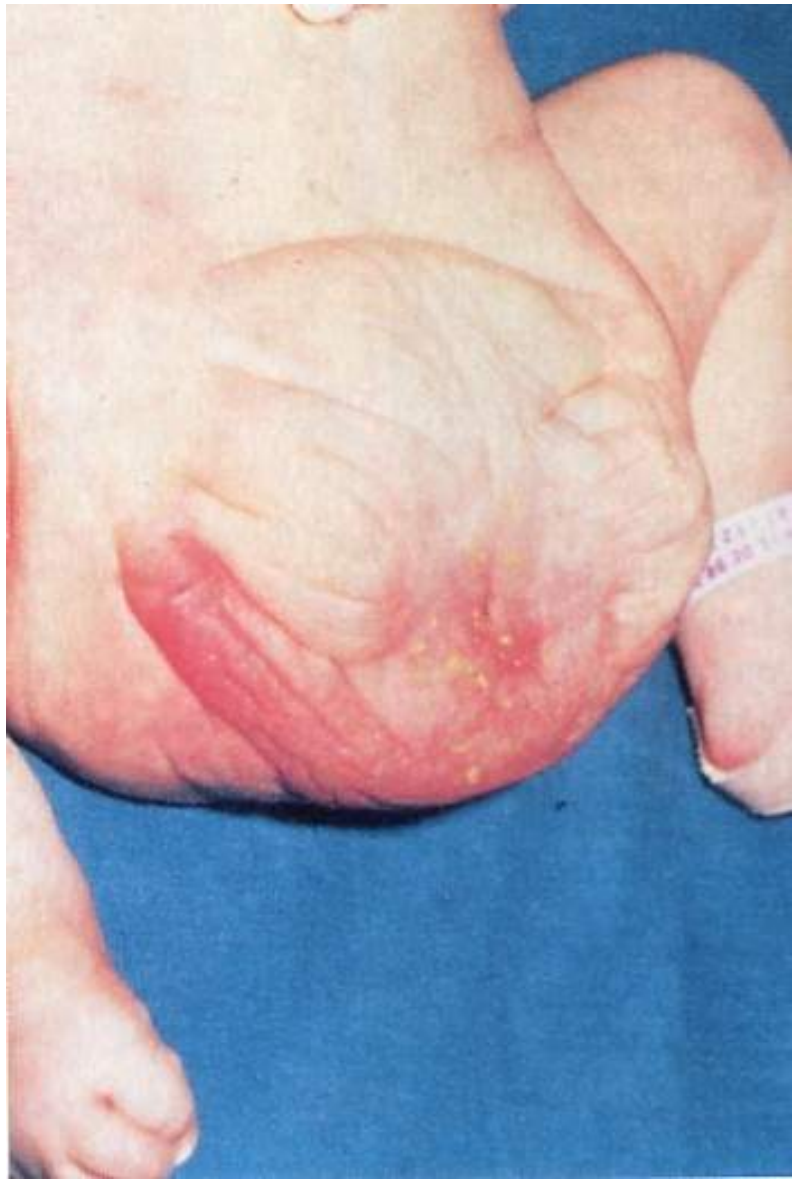


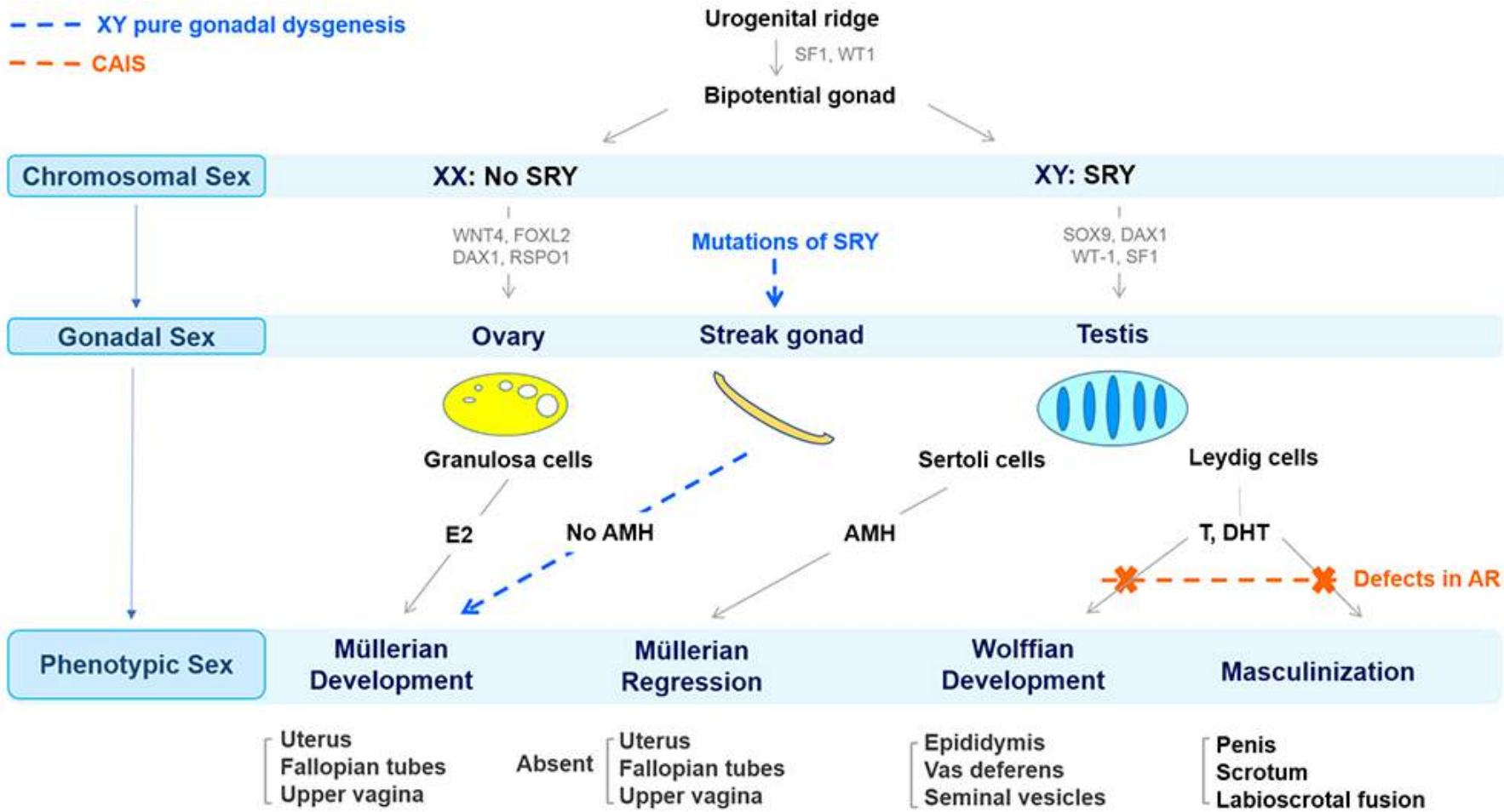
Thank You

Abnormal sex chromosome complexes

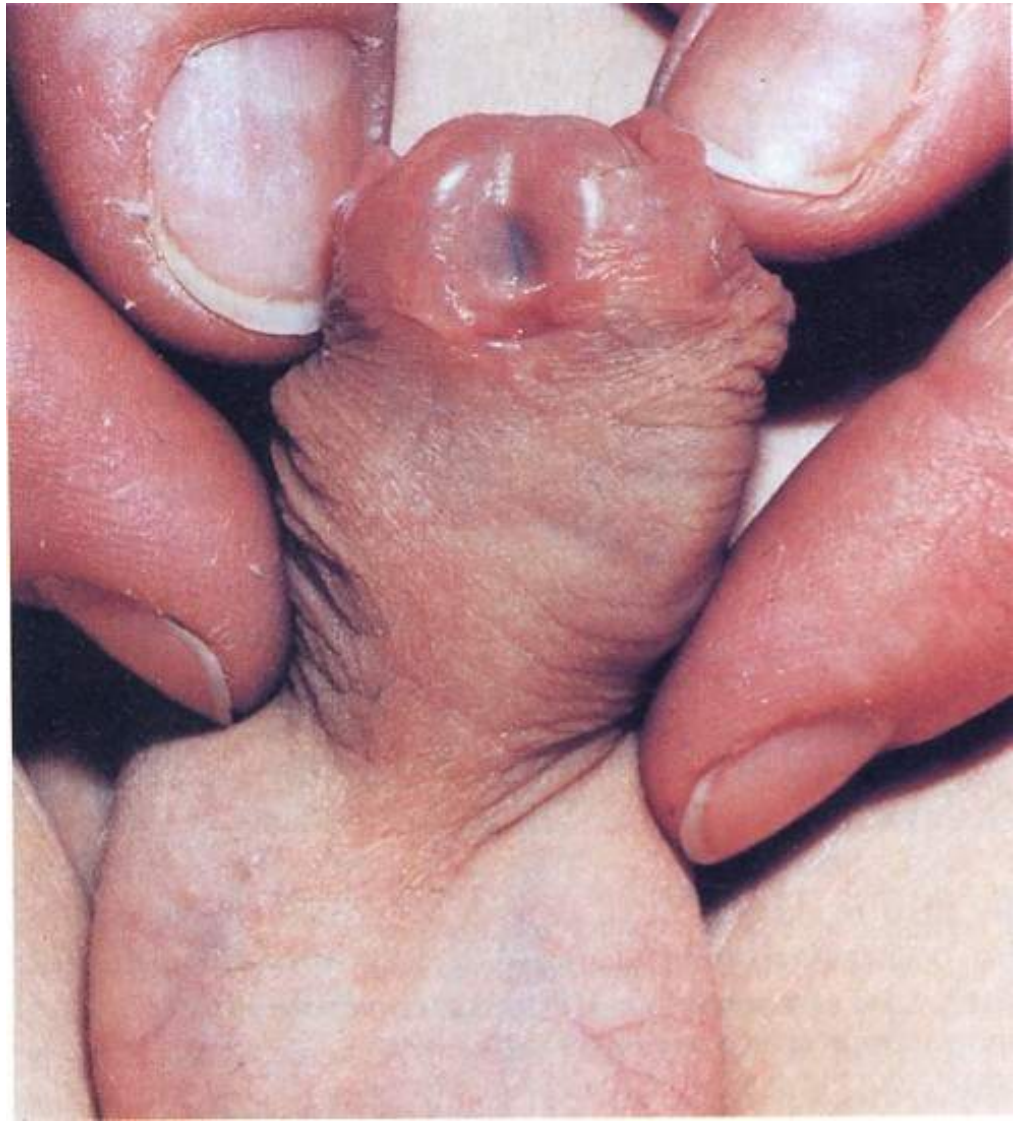
- **XXX, XXY**
- **The number of X chromosomes appears to be unimportant in sex determination**
- **If a normal Y chromosome is present the embryo develops as a male. If the Y chromosome or its testis-determining region is absent female development occurs**

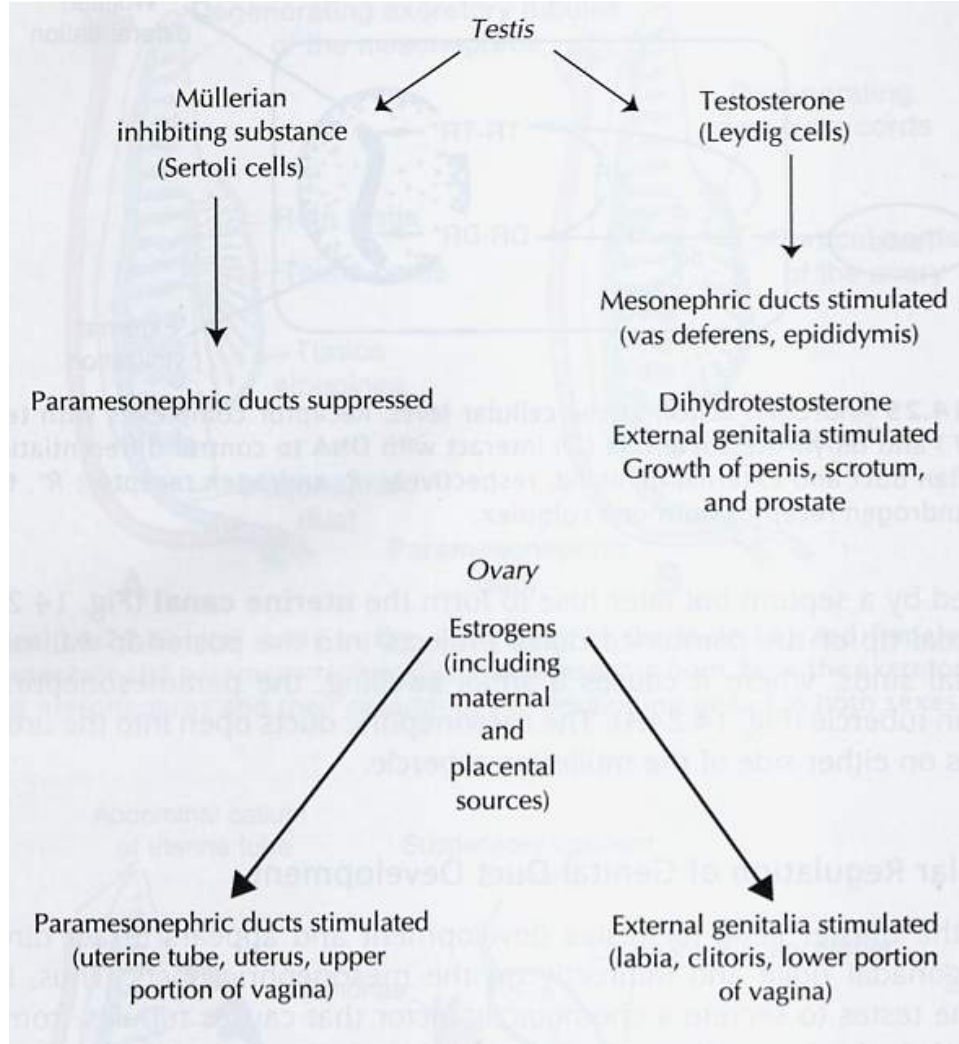
Agenesis of external genitalia



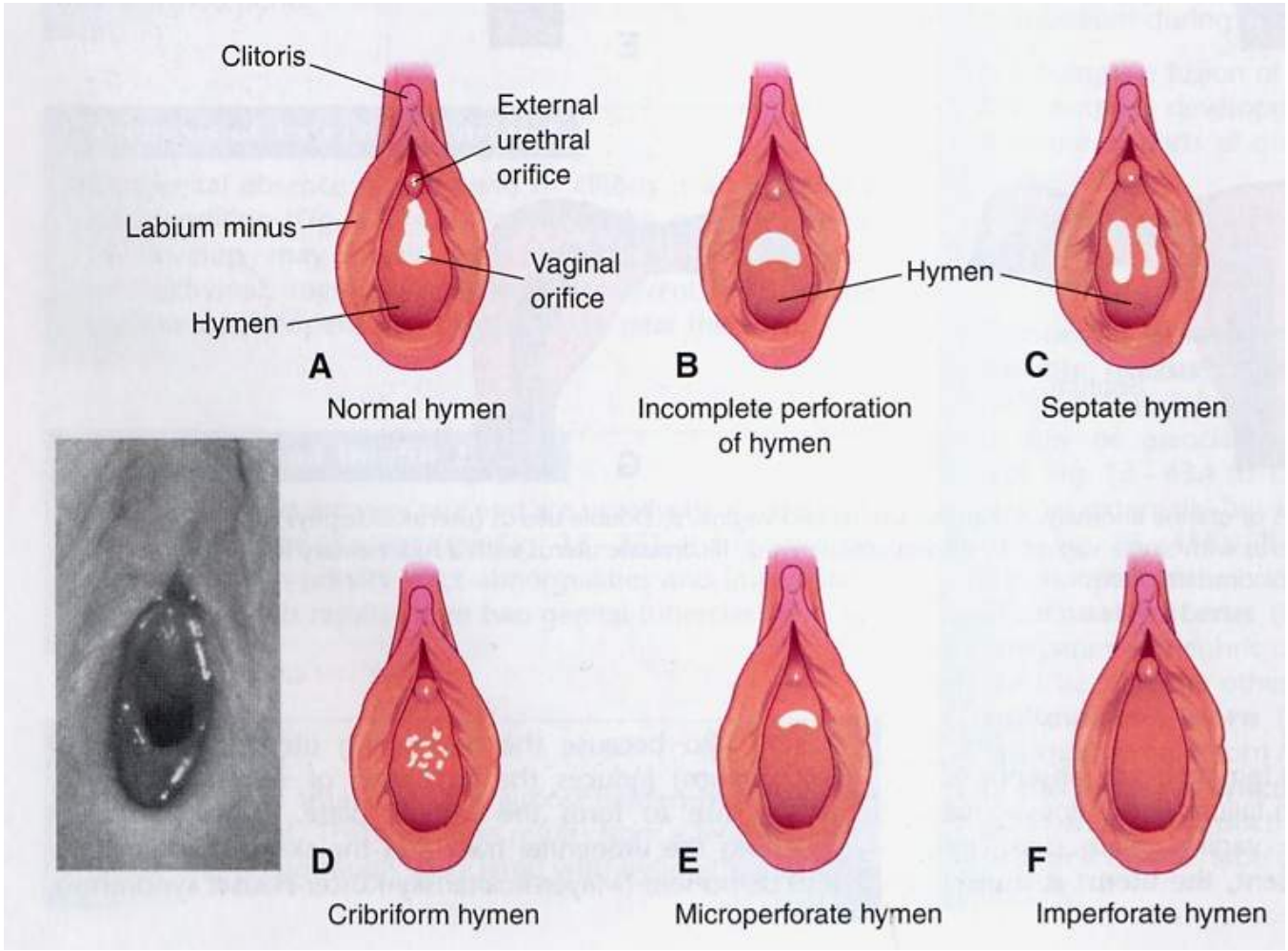

XY pure gonadal dysgenesis
CAIS
Urogenital ridge
SF1, WT1
Bipotential gonad
Chromosomal Sex
XX: No SRY
XY: SRY
WNT4, FOXL2
DAX1, RSPO1
Mutations of SRY
SOX9, DAX1
WT-1, SF1
Gonadal Sex
Ovary
Streak gonad
Testis
Granulosa cells
Sertoli cells
Leydig cells
E2
No AMH
AMH
T, DHT
Defects in AR
Phenotypic Sex
Müllerian Development
Müllerian Regression
Wolffian Development
Masculinization
Uterus
Fallopian tubes
Upper vagina
Absent
Uterus
Fallopian tubes
Upper vagina
Epididymis
Vas deferens
Seminal vesicles
Penis
Scrotum
Labioscrotal fusion

Hypospadias

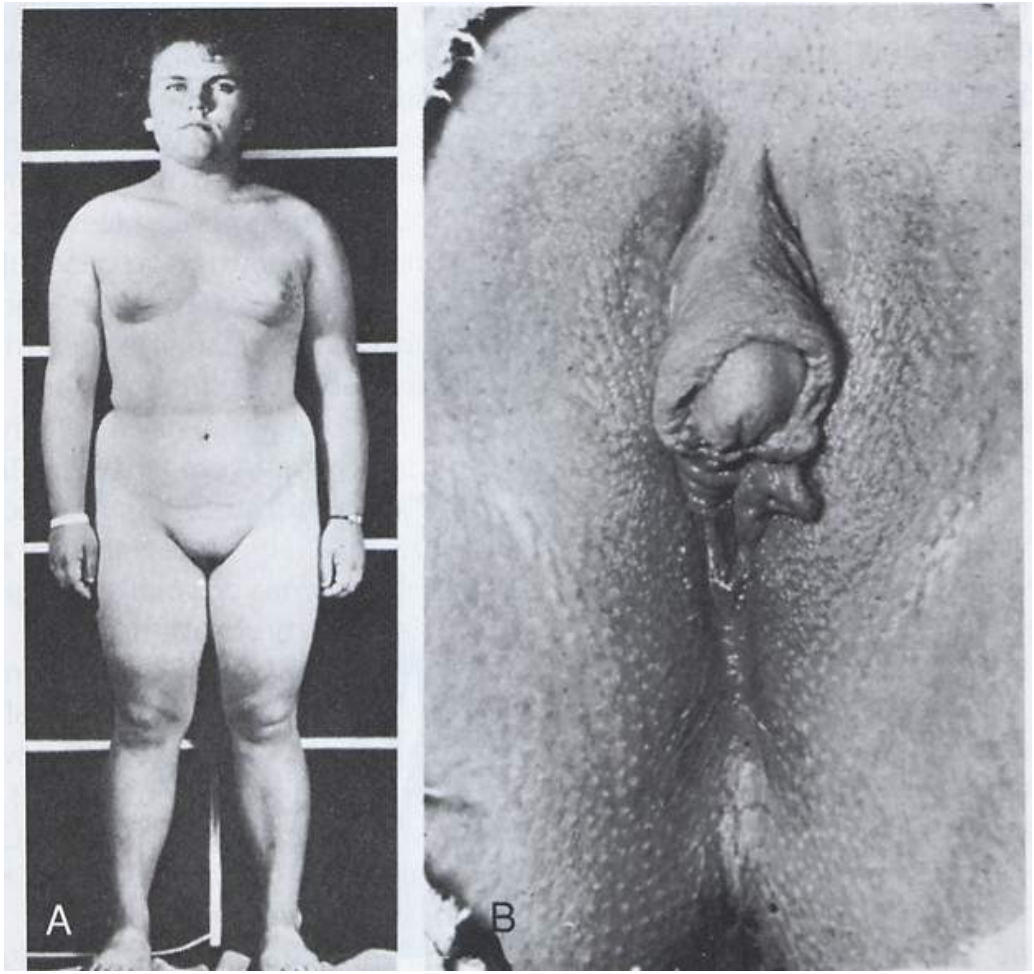



Testis
Müllerian inhibiting substance (Sertoli cells)
Testosterone (Leydig cells)
Mesonephric ducts stimulated (vas deferens, epididymis)
Paramesonephric ducts suppressed
Dihydrotestosterone
External genitalia stimulated
Growth of penis, scrotum, and prostate
Ovary
Estrogens (including maternal and placental sources)
Paramesonephric ducts stimulated (uterine tube, uterus, upper portion of vagina)
External genitalia stimulated (labia, clitoris, lower portion of vagina)

Congenital anomalies of the hymen



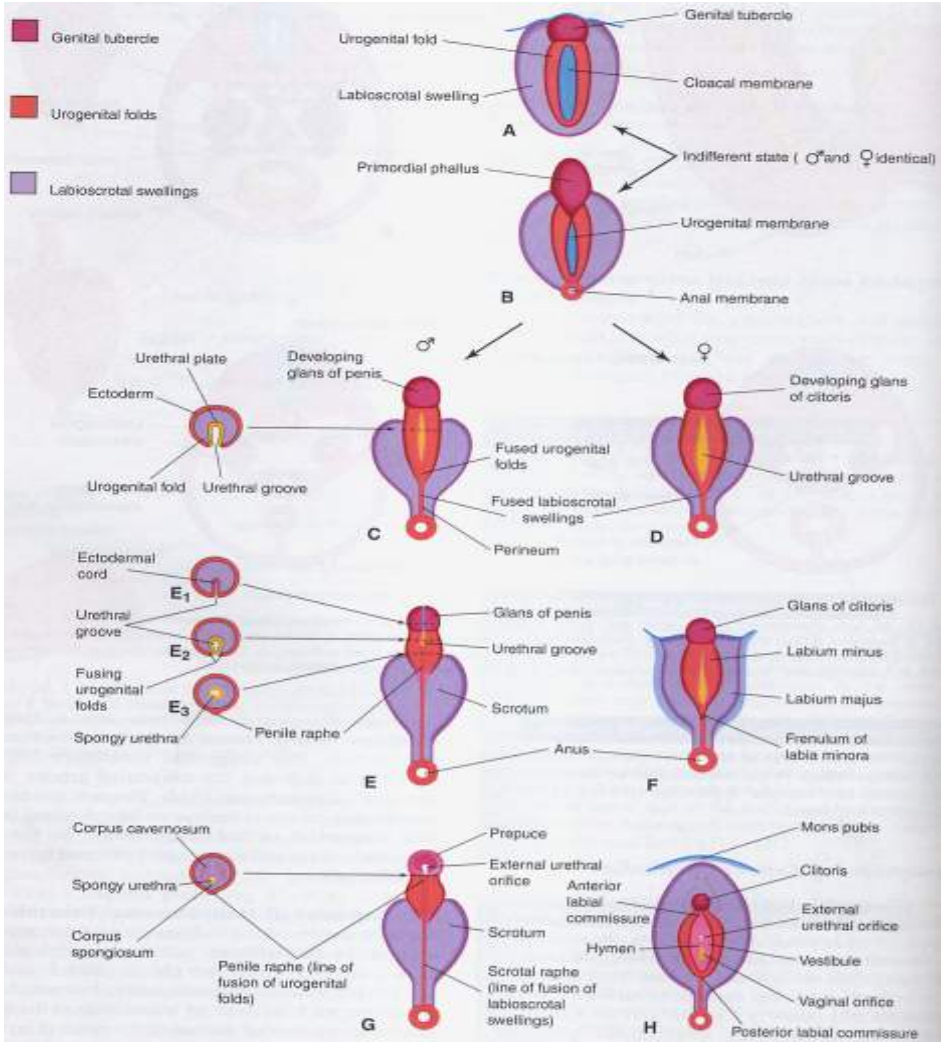
Female pseudohermaphroditism (caused by congenital adrenal hyperplasia)



Female ducts in males

- **If testes fail to develop (agonadal males), similar development of mesonephric ducts occurs in males, because of the absence of MIS**

Development of external genitalia



A-B: 4th-7th week
İndifferent stage

C, D: 9th week
E, F: 11th week
G, H: 12th week

Congenital malformations:Determination of fetal sex

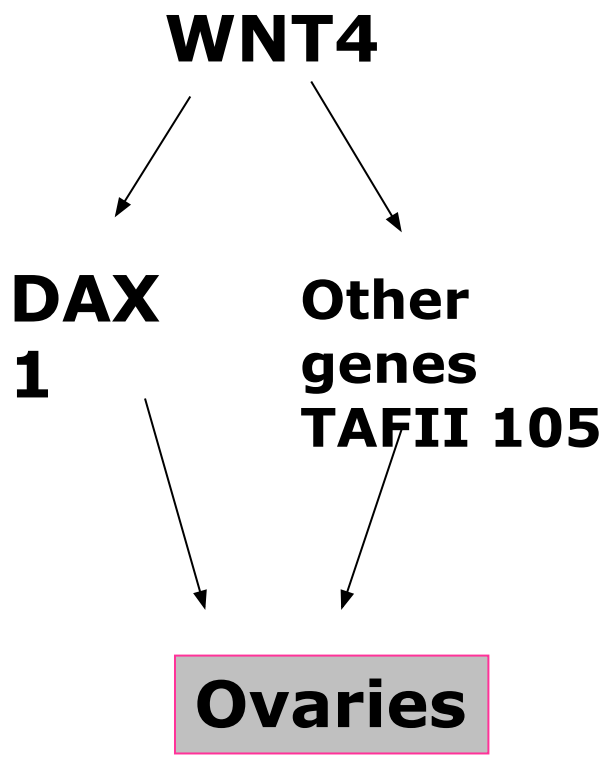
- **Androgen insensitivity syndrome (testicular feminization):** **Normal-appearing females with the presence of testes and 46XY chromosomes. They are medically and legally female. There is resistance to the action of testosterone at the cellular receptor**
- **Mixed gonadal dysgenesis:** **very rare, having chromatin negative nuclei (sex chromatin negative), a testis on one side, an undifferentiated gonad on the other side. The internal genitalia are female but may have male derivatives. The external genitalia may vary from female to male.**

Congenital malformations:Determination of fetal sex

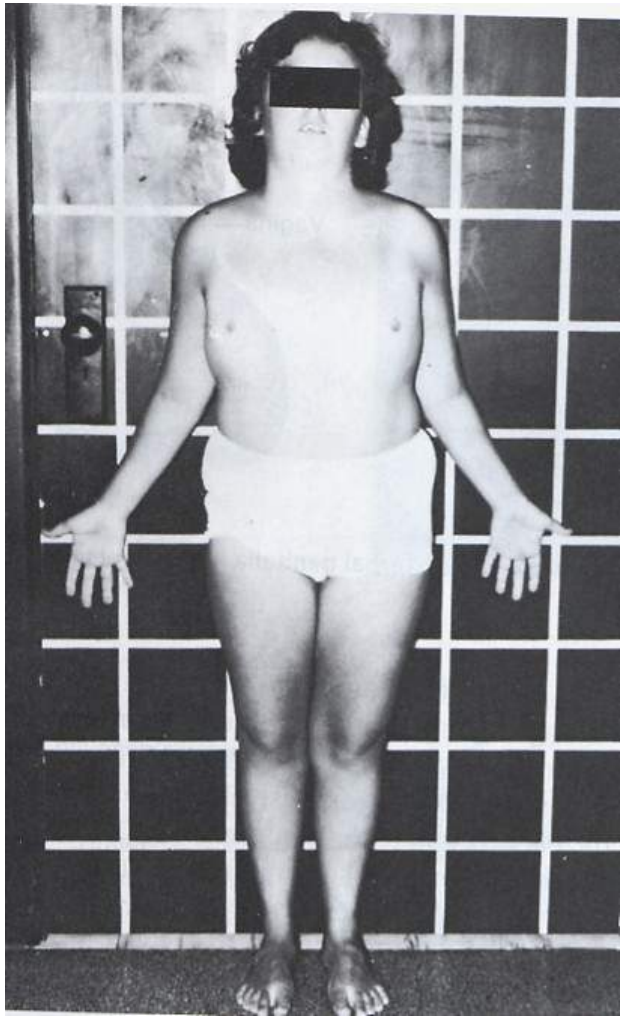
- **Ambiguous genitalia:** if there is normal sexual differentiation, internal and external genitalia are consistent with the chromosome complement
- **True hermaphroditism:** having ovarian and testicular tissue either in the same or opposite gonads (70 % are 46 XX, 20 % 46 XX/46 XY mosaicism, 10 % 46XY)
- **Female pseudohermaphroditism:** 46 XX, having ovaries, resulting from the exposure to excessive androgens of a female fetus. Virilization of external genitalia occurs. A common cause is congenital adrenal hyperplasia, a rare cause may be a maternal masculinizing tumor.
- **Male pseudohermaphroditism:** 46XY having testis, with no sex chromatin. Internal and external genitalia are variable caused by inadequate production of testosterone and MIF by the testes.

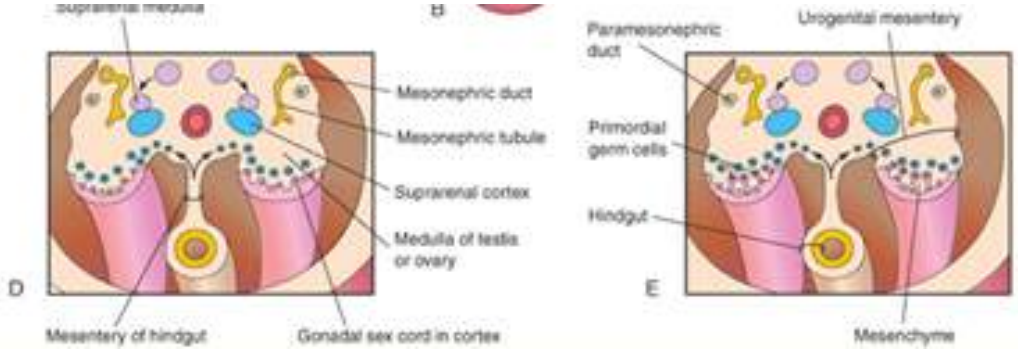
Molecular regulation of female genital duct development

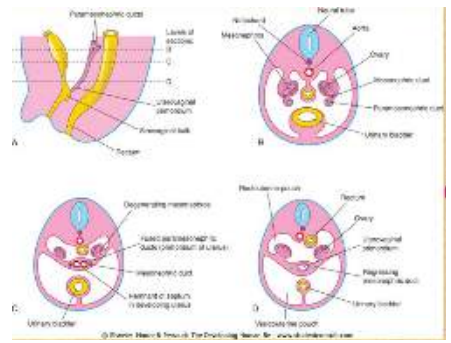
- WNT4 is the ovary determining gene; upregulating DAX1 which is a member of the nuclear hormone receptor family
- DAX1 inhibits the function of SOX9
- WNT regulates expression of other genes (TAFII105....TATA binding protein for RNA polimerase in ovarian follicular cells) responsible for ovarian differentiation
- Mice that do not synthesize that subunit do not form ovaries
- Estrogens are involves in sexual differentiation; under their influence paramesonephric (mullerian) ducts are stimulated to form ext genitalia

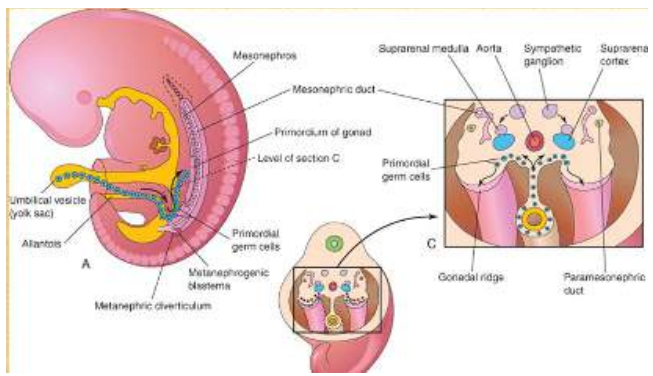


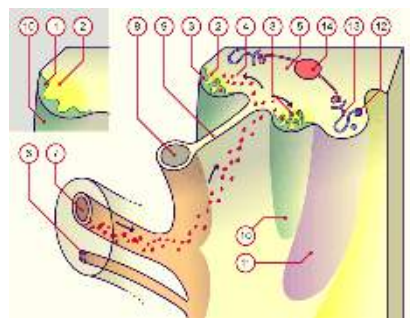
Turner syndrome (45X)




Mesonephric duct
Mesonephric tubule
Suprarenal cortex
Medulla of testis or ovary
D
Mesentery of hindgut
Gonadal sex cord in cortex
Paramesonephric duct
Urogenital mesentery
Primordial germ cells
Hindgut
E
Mesenchyme




Mesonephros
Mesonephric duct
Primordium of gonad
Level of section C
Umbilical vesicle (yolk sac)
Allantois
Primordial germ cells
Metanephrogenic blastema
Metanephric diverticulum
A
Suprarenal medulla
Aorta
Sympathetic ganglion
Suprarena cortex
Primordial germ cells
C
Gonadal ridge
Paramesonephric duct



Molecular regulation of male genital duct development

- SRY is a transcription factor and the master gene for testes development; possibly acting in conjunction with the autosomal gene SOX9 a transcription regulator also inducing testes differentiation
- SOX9 binds the promoter region of the gene for antimullerian hormone/mullerian inhibiting substance (AMH, MIH) regulating this genes expression
- At the begining SRY and/or SOX9 induce the testes to secrete FGF-9 acting as a chemotactic factor that causes tubules from the mesonephric duct to penetrate the gonadal ridge.
- Without penetration by these tubules differentiation of the testes does not continue.
- Next SRY directly or indirectly through SOX9 upregulates production of stetoidogenesis factor-1 (SF-1) that stimulates differention of Sertoli and Leydig cells. SF1 with SOX9 increase AMH leading to regression of the paramesonephric (mullerian)ducts.
- SF1 upregulates the genes for enzymes that synthesize testosterone