Development and anomalies of the female genital system

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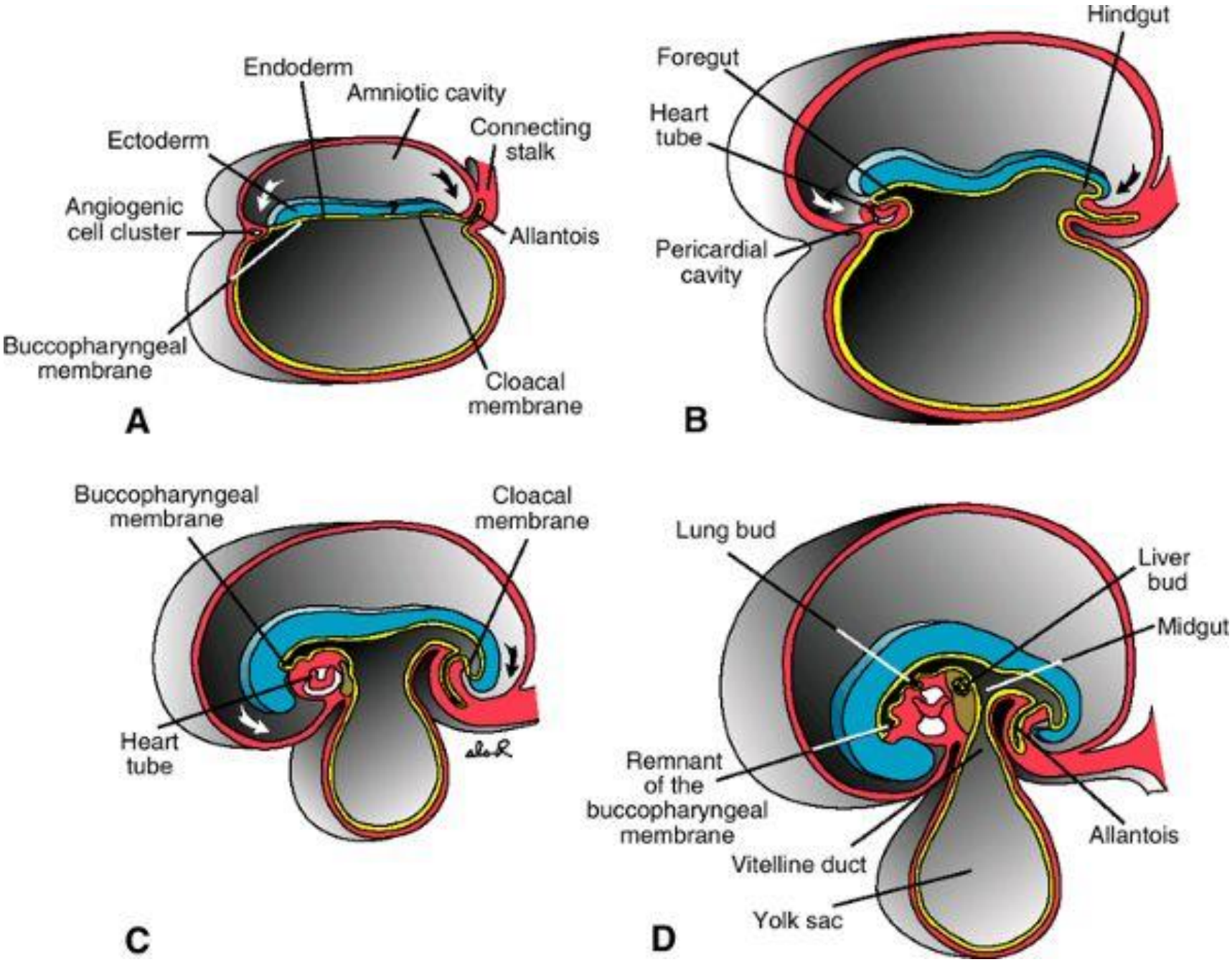
Aim of the lecture

1. Review the basis of development of:
    1. The Gonads.
    2. Uterus and Fallopian tubes.
    3. External genitalia.
2. Discuss the different types of anomalies and their management.

1- Development of the Gonads


Endoderm
Amniotic cavity
Ectoderm
Connecting stalk
Angiogenic cell cluster
Allantois
Buccopharyngeal membrane
Cloacal membrane
A
Hindgut
Foregut
Heart tube
Pericardial cavity
B
Buccopharyngeal membrane
Cloacal membrane
Heart tube
C
Lung bud
Liver bud
Midgut
Remnant of the buccopharyngeal membrane
Allantois
Vitelline duct
Yolk sac
D

Development of the Gonads

- Gonads appear initially as a pair of longitudinal ridges, the genital or gonadal ridges. They are formed by proliferation of the epithelium and a condensation of underlying mesenchyme. Germ cells do not appear in the genital ridges until the sixth week of development.

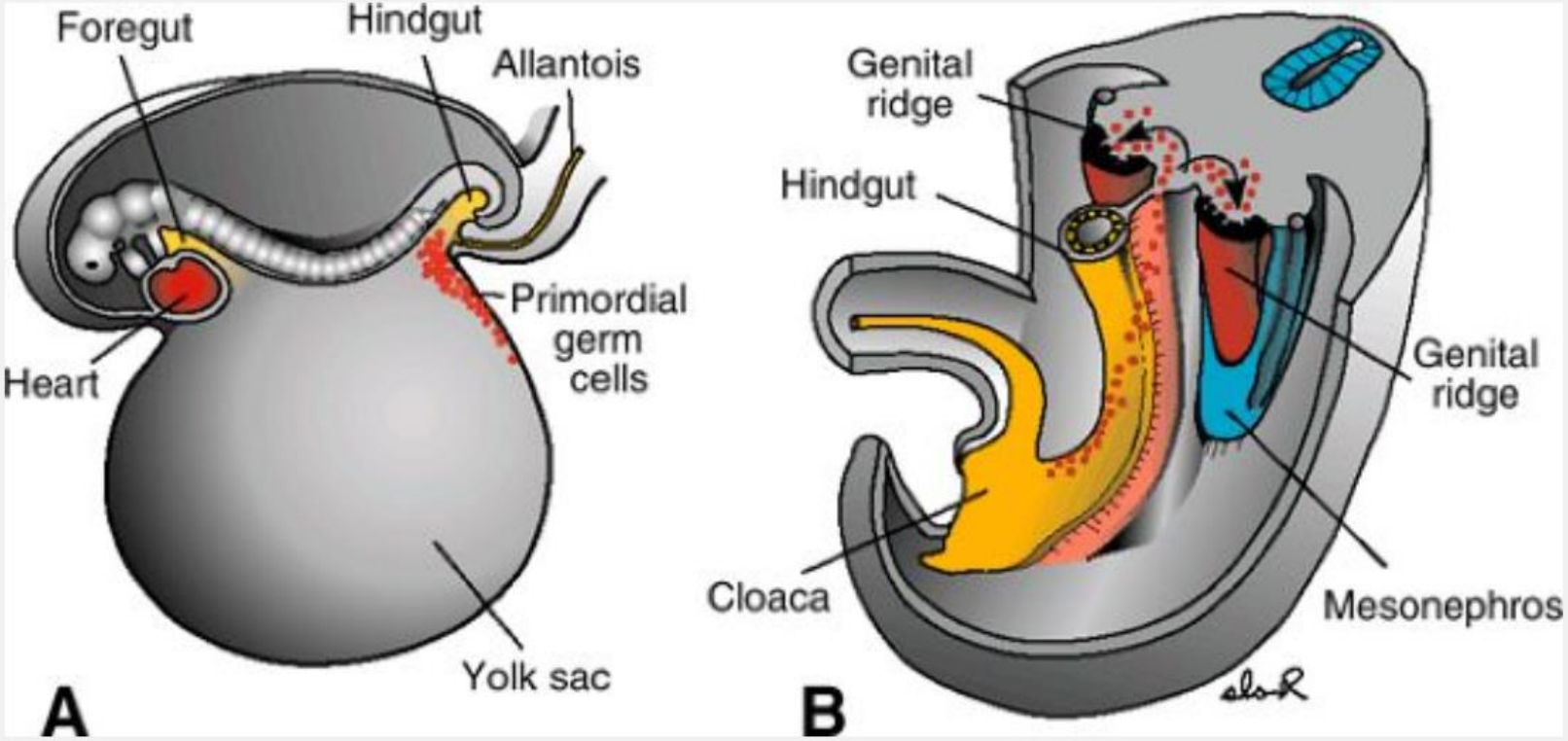


Figure 15.18 A. A 3-week embryo showing the primordial germ cells in the wall of the yolk sac close to the attachment of the allantois. **B.** Migrational path of the primordial germ cells along the wall of the hindgut and the dorsal mesentery into the genital ridge.

Development of the Gonads

- Primordial germ cells first appear at an early stage of development among endoderm cells in the wall of the yolk sac close to the allantois. They migrate by ameboid movement along the dorsal mesentery of the hindgut, arriving at the primitive gonads at the beginning of the fifth week and invading the genital ridges in the sixth week.

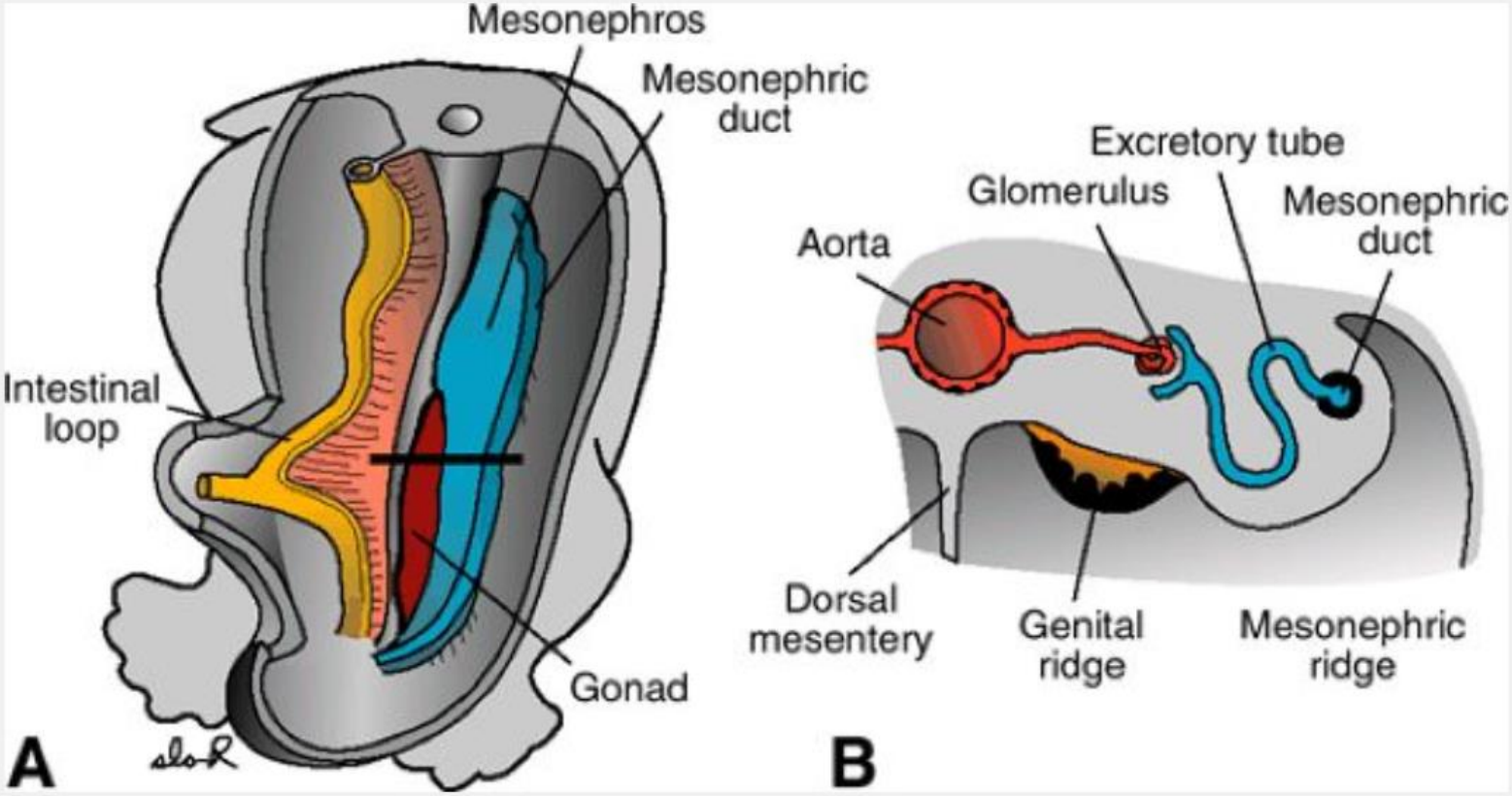


Figure 15.17 A. Relation of the genital ridge and the mesonephros showing location of the mesonephric duct. **B.** Transverse section through the mesonephros and genital ridge at the level indicated in **A.**

Development of the Gonads

- If they fail to reach the ridges, the gonads do not develop. Hence, the primordial germ cells have an inductive influence on development of the gonad into ovary or testis.

Development of the Gonads

- Shortly before and during arrival of primordial germ cells, the epithelium of the genital ridge proliferates, and epithelial cells penetrate the underlying mesenchyme. Here they form a number of irregularly shaped cords, the primitive sex cords

Development of the Gonads

- In both male and female embryos, these cords are connected to surface epithelium, and it is impossible to differentiate between the male and female gonad. Hence, the gonad is known as the indifferent gonad.

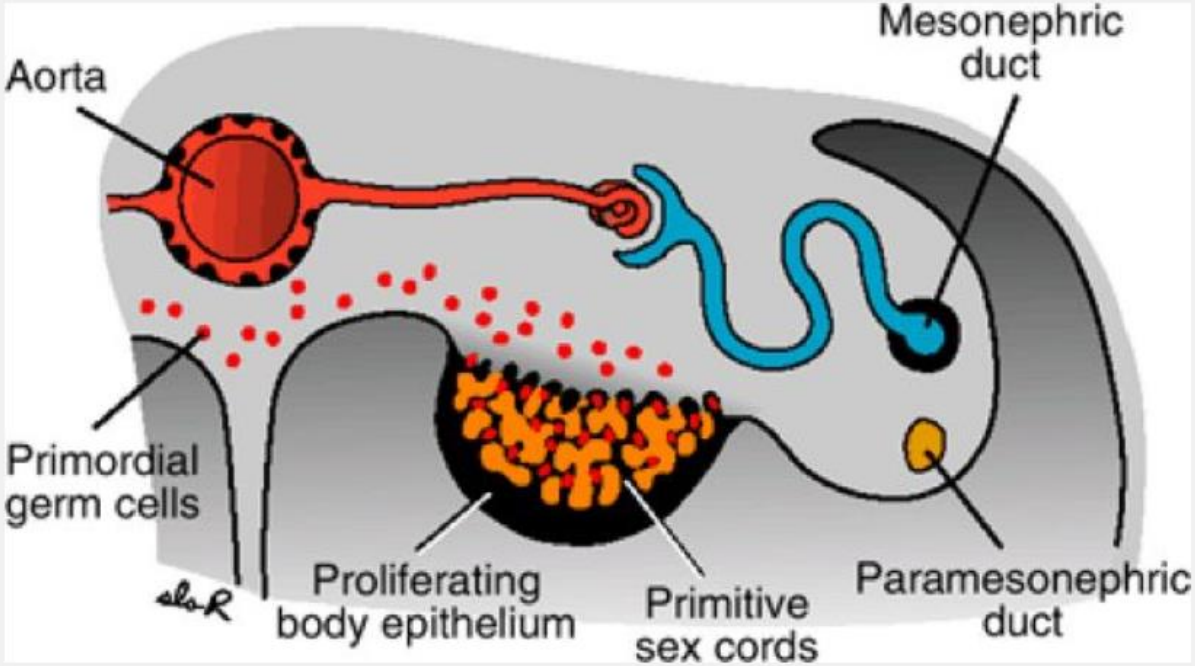


Figure 15.19 Transverse section through the lumbar region of a 6-week embryo showing the indifferent gonad with the primitive sex cords. Some of the primordial germ cells are surrounded by cells of the primitive sex cords.

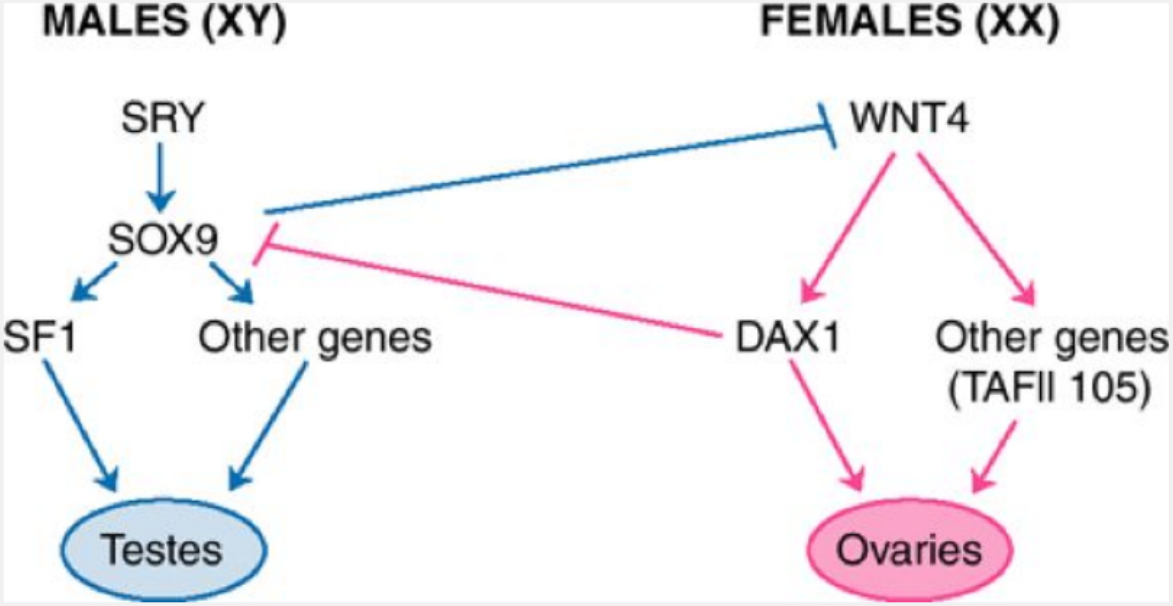


Figure 15.25 Schematic showing genes responsible for differentiation of the testes and ovaries. In both males and females, *SOX9* and *WNT4* are expressed in the gonadal ridges. In males, the expression of *SRY* upregulates *SOX9*, which in turn activates expression of *steroidogenesis factor 1 (SF1)* and other genes responsible for testes differentiation, while inhibiting expression of *WNT4*. In females, the uninhibited expression of *WNT4* upregulates *DAX1* that in turn inhibits *SOX9* expression. Then under the continued influence of *WNT4*, other downstream target genes (perhaps *TAFII105*) induce ovarian differentiation.

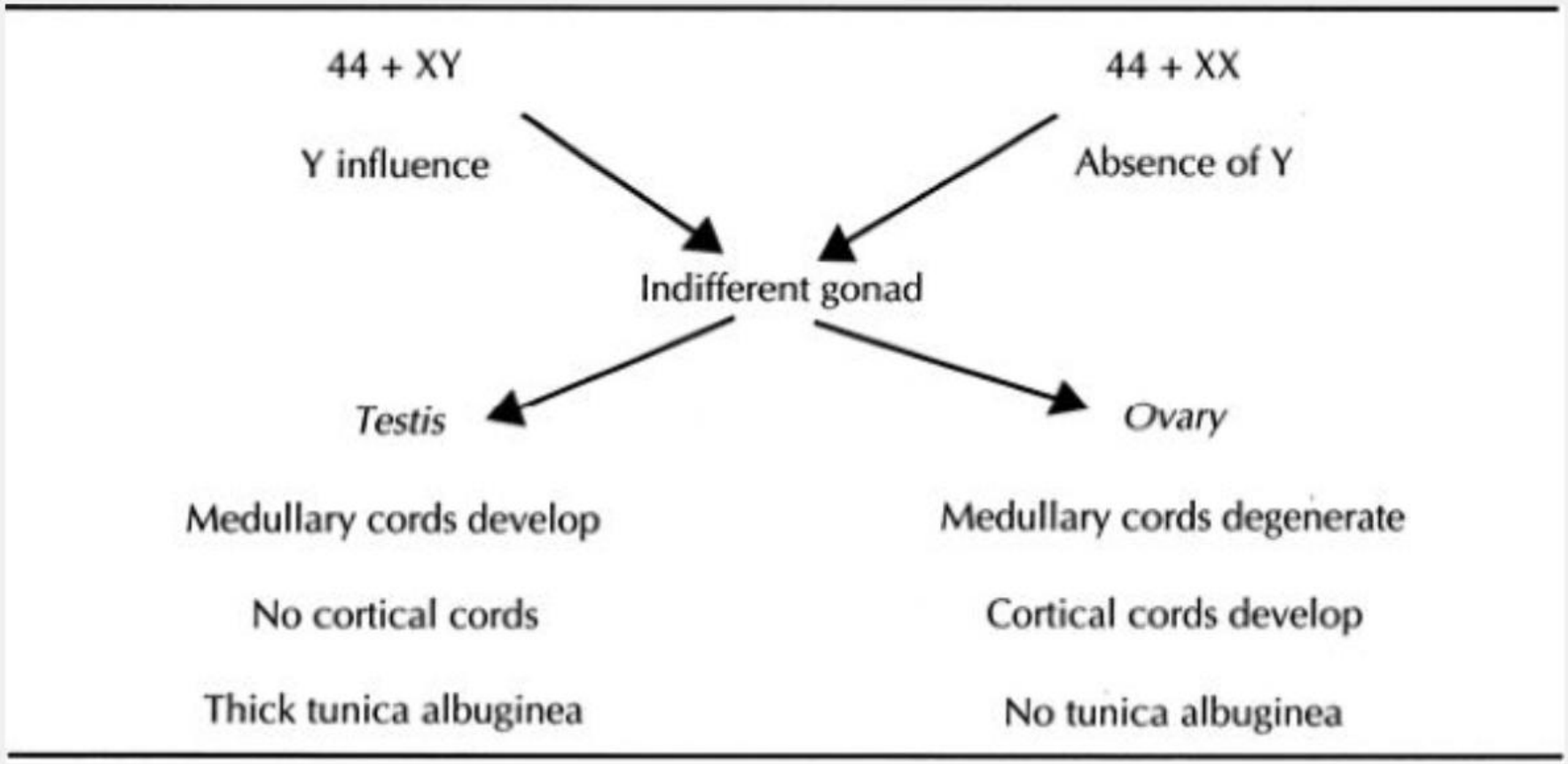


Figure 15.21 Influence of primordial germ cells on indifferent gonad.

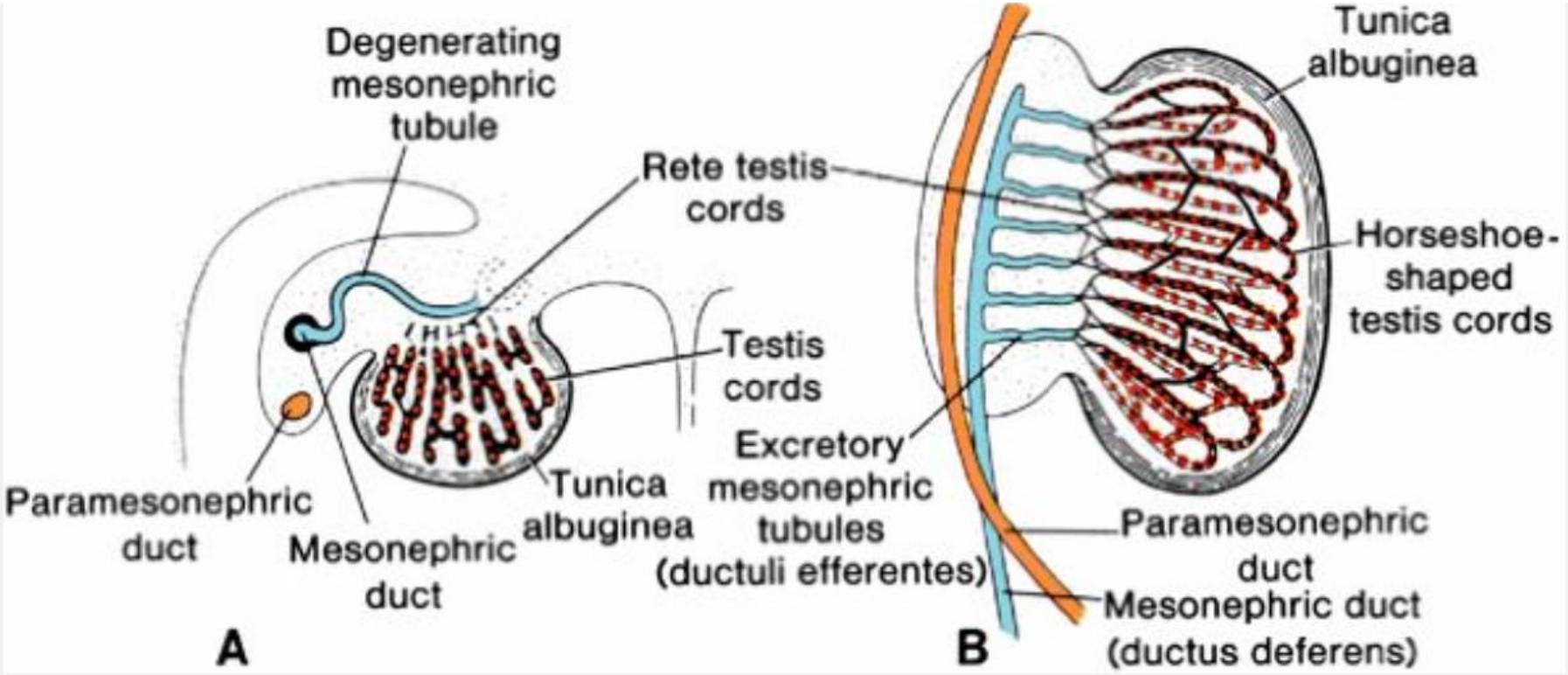


Figure 15.20 A. Transverse section through the testis in the eighth week, showing the tunica albuginea, testis cords, rete testis, and primordial germ cells. The glomerulus and Bowman's capsule of the mesonephric excretory tubule are degenerating. **B.** Testis and genital duct in the fourth month. The horseshoe-shaped testis cords are continuous with the rete testis cords. Note the ductuli efferentes (excretory mesonephric tubules), which enter the mesonephric duct.

Development of the Gonads

- In female embryos with an XX sex chromosome complement and no Y chromosome, primitive sex cords dissociate into irregular cell clusters. These clusters, containing groups of primitive germ cells, occupy the medullary part of the ovary. Later, they disappear and are replaced by a vascular stroma that forms the ovarian medulla.

Development of the Gonads

- The surface epithelium of the female gonad, unlike that of the male, continues to proliferate. In the seventh week, it gives rise to a second generation of cords, cortical cords, which penetrate the underlying mesenchyme but remain close to the surface.

Development of the Gonads

- In the fourth month, these cords split into isolated cell clusters, with each surrounding one or more primitive germ cells. Germ cells subsequently develop into oogonia, and the surrounding epithelial cells, descendants of the surface epithelium, form follicular cells.

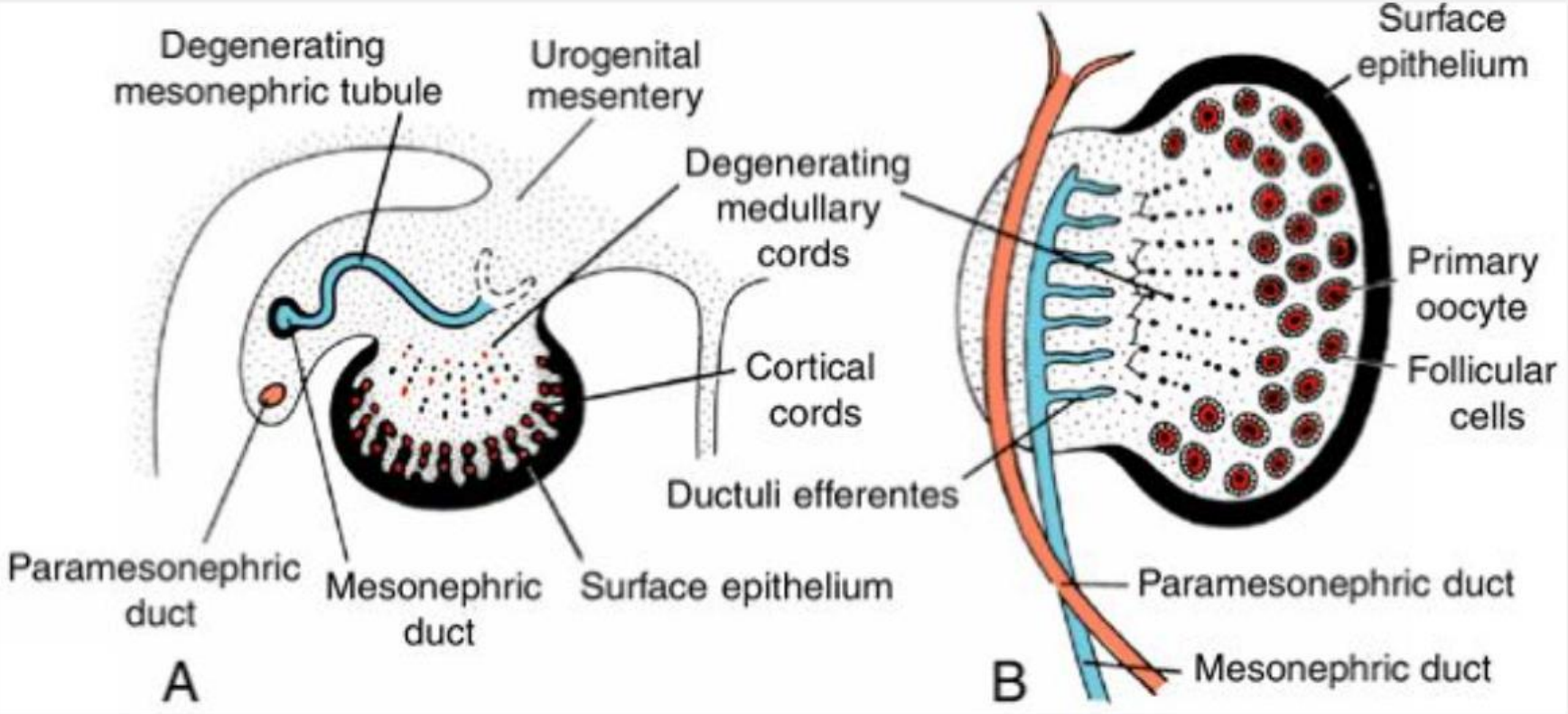
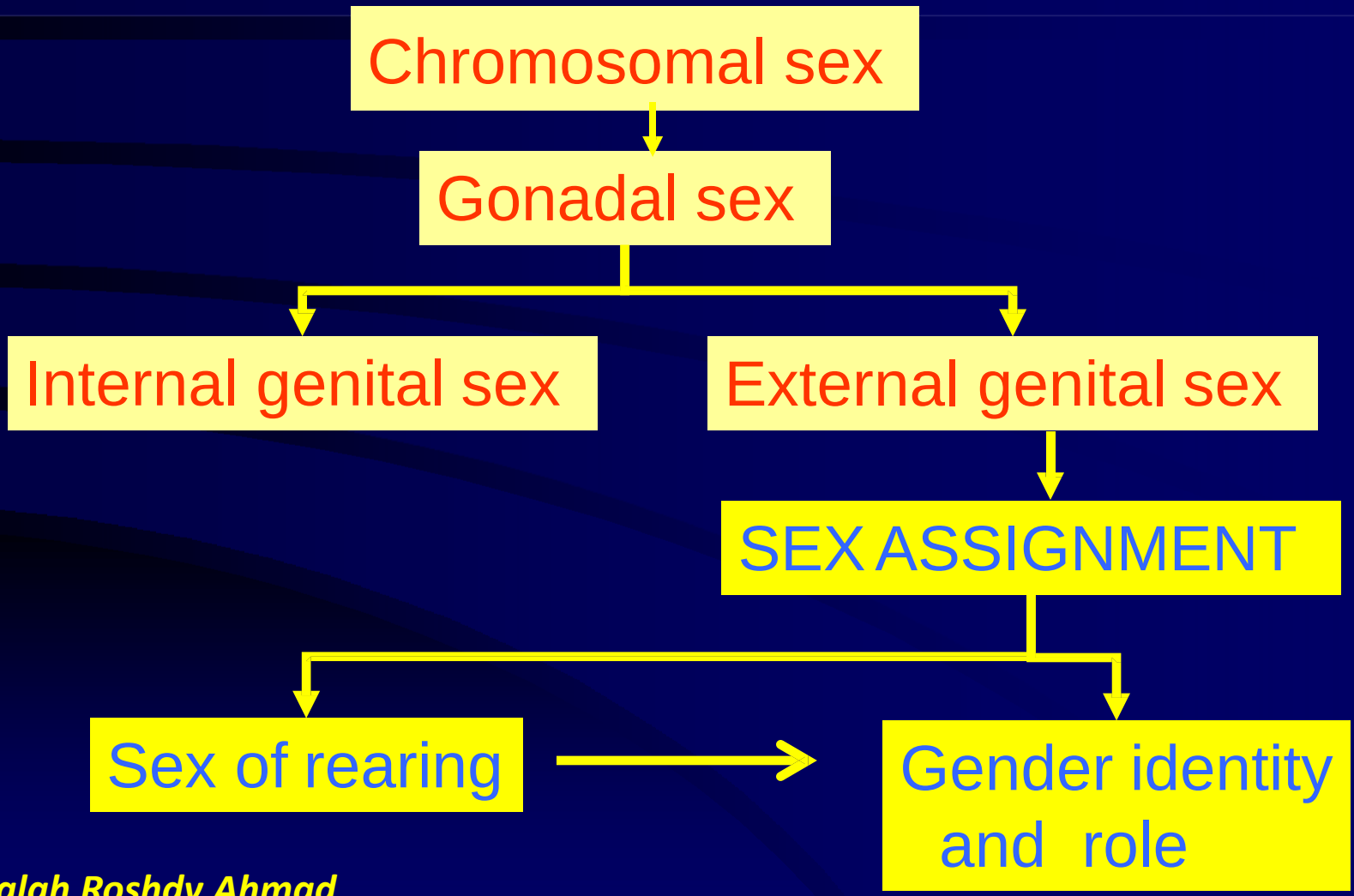


Figure 15.22 A. Transverse section of the ovary at the seventh week, showing degeneration of the primitive (medullary) sex cords and formation of the cortical cords. **B.** Ovary and genital ducts in the fifth month. Note degeneration of the medullary cords. The excretory mesonephric tubules (efferent ductules) do not communicate with the rete. The cortical zone of the ovary contains groups of oogonia surrounded by follicular cells.

Human sexual differentiation



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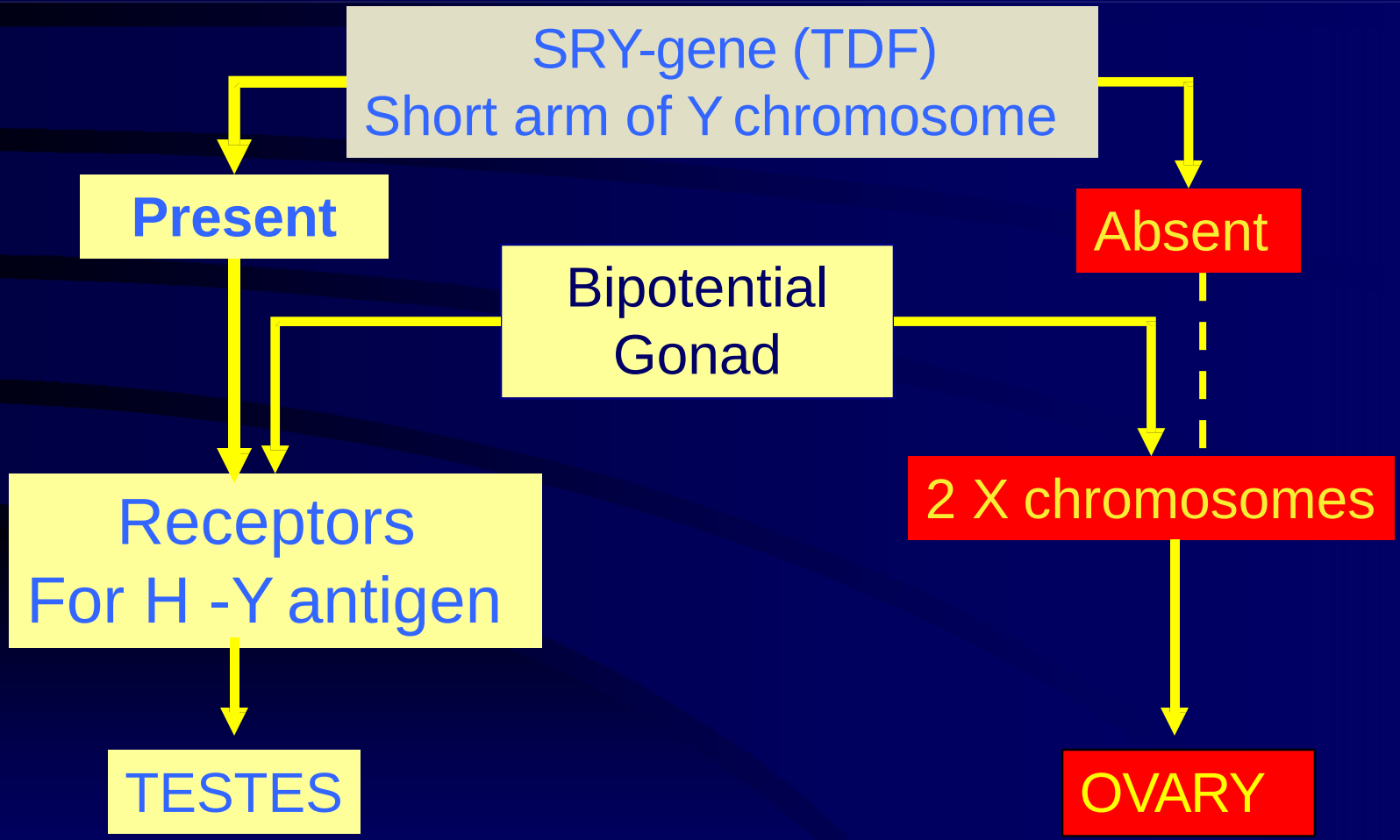
Gonadal development



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2- Development of the Genital Ducts.

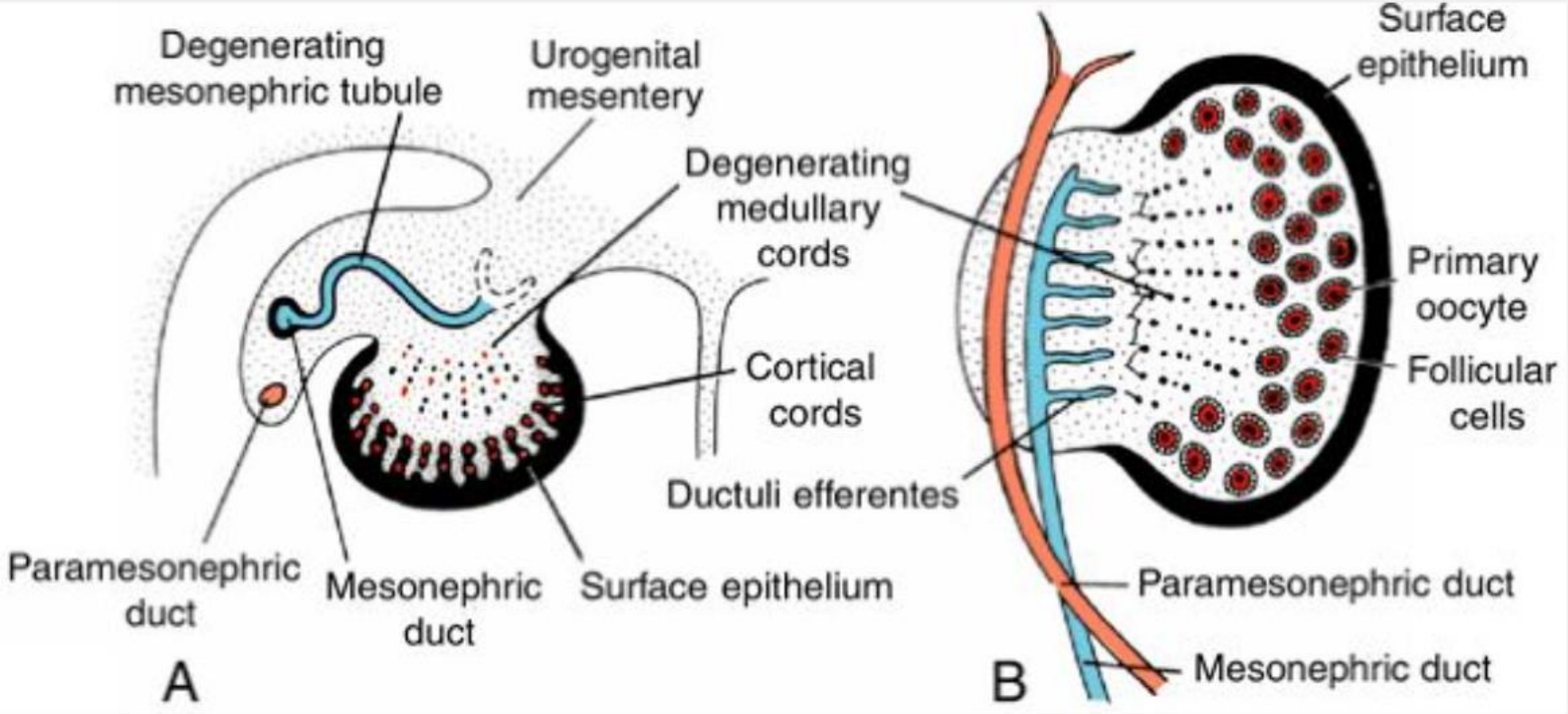

Testis
Müllerian inhibiting substance (Sertoli cells)
Testosterone (Leydig cells)
Paramesonephric ducts suppressed
Mesonephric ducts stimulated (efferent ductules, epididymis, vas deferens, seminal vesicles)
Dihydrotestosterone
External genitalia stimulated
Growth of penis, scrotum, and prostate
Ovary
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)

Development of the Genital Ducts.

- Initially, both male and female embryos have two pairs of genital ducts: mesonephric (wolffian) ducts and paramesonephric (müllerian) ducts. The paramesonephric duct arises as a longitudinal invagination of the epithelium on the anterolateral surface of the urogenital ridge.

Development of the Genital Ducts.

- Cranially, the duct opens into the abdominal cavity with a funnel-like structure. Caudally, it first runs lateral to the mesonephric duct, then crosses it ventrally to grow caudomedially



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Development of the Genital Ducts.

- In the midline, it comes in close contact with the paramesonephric duct from the opposite side. The two ducts are initially separated by a septum but later fuse to form the uterine canal.

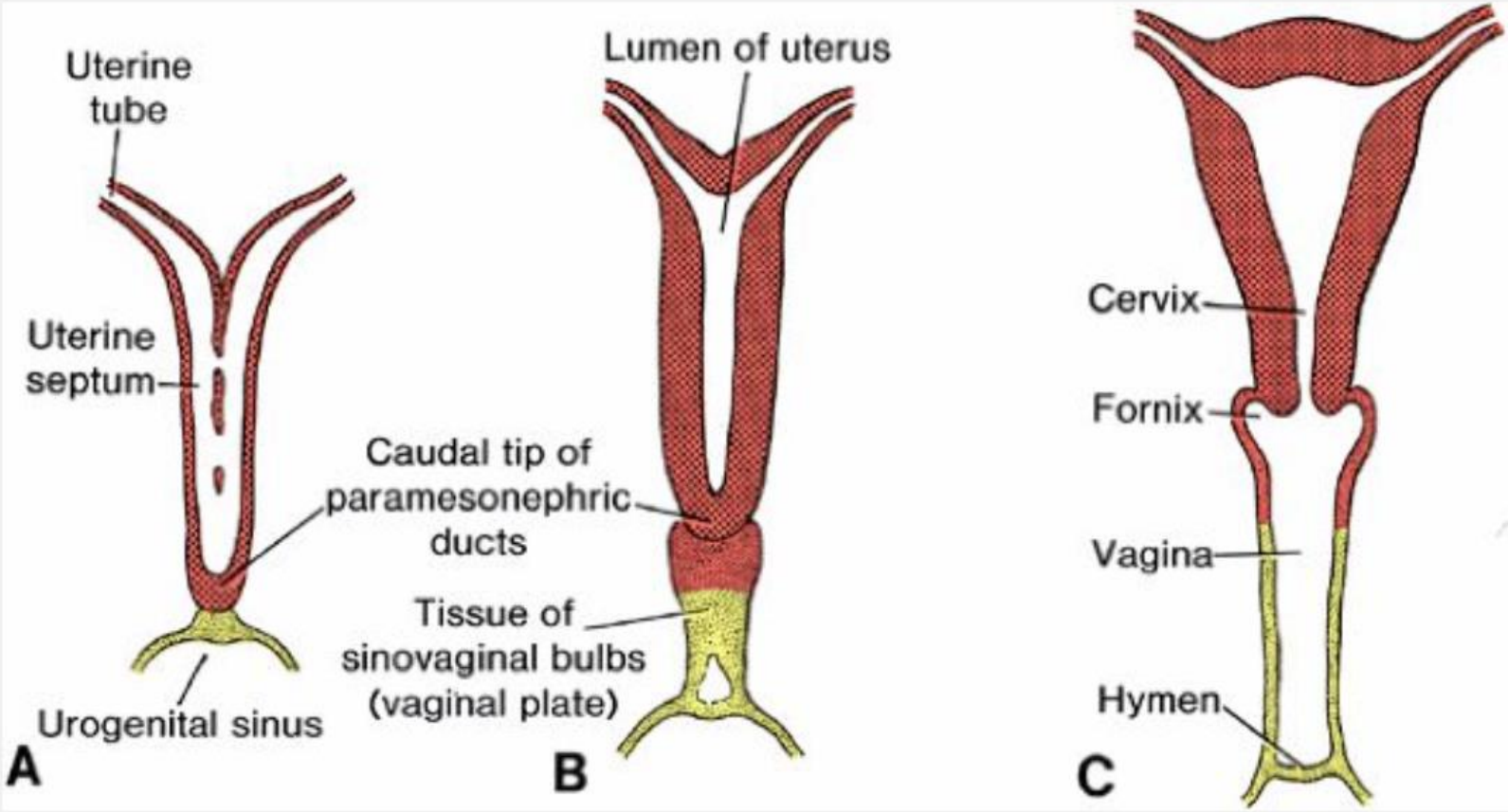


Figure 15.29 Formation of the uterus and vagina. **A.** 9 weeks. Note the disappearance of the uterine septum. **B.** At the end of the third month. Note the tissue of the sinovaginal bulbs. **C.** Newborn. The fornices and the upper portion of the vagina are formed by vacuolization of the paramesonephric tissue, and the lower portion of the vagina is formed by vacuolization of the sinovaginal bulbs.

Development of the Genital Ducts.

- The caudal tip of the combined ducts projects into the posterior wall of the urogenital sinus, where it causes a small swelling, the paramesonephric or müllerian tubercle. The mesonephric ducts open into the urogenital sinus on either side of the müllerian tubercle.

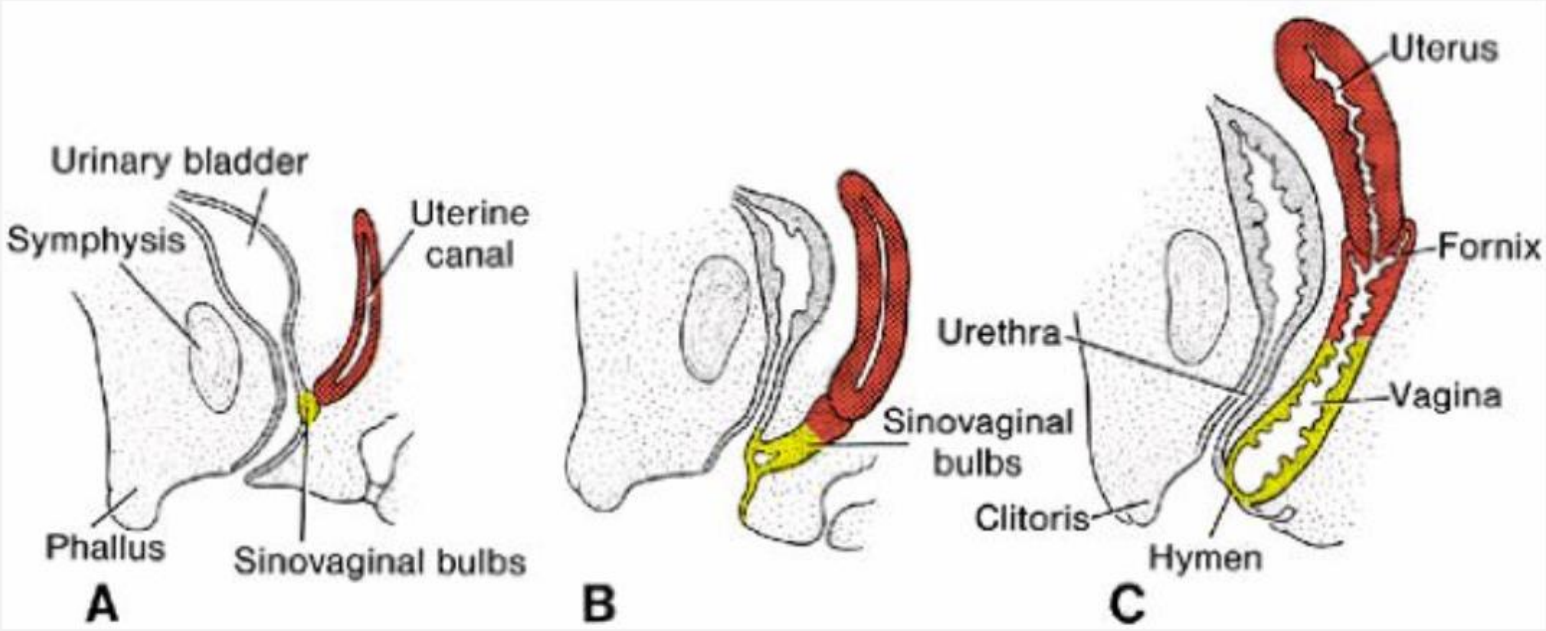


Figure 15.30 Sagittal sections showing formation of the uterus and vagina at various stages of development. **A.** Nine weeks. **B.** End of third month. **C.** Newborn.

Development of the Genital Ducts.

- The paramesonephric ducts develop into the main genital ducts of the female. Initially, three parts can be recognized in each duct: (a) a cranial vertical portion that opens into the abdominal cavity, (b) a horizontal part that crosses the mesonephric duct, and (c) a caudal vertical part that fuses with its partner from the opposite side.

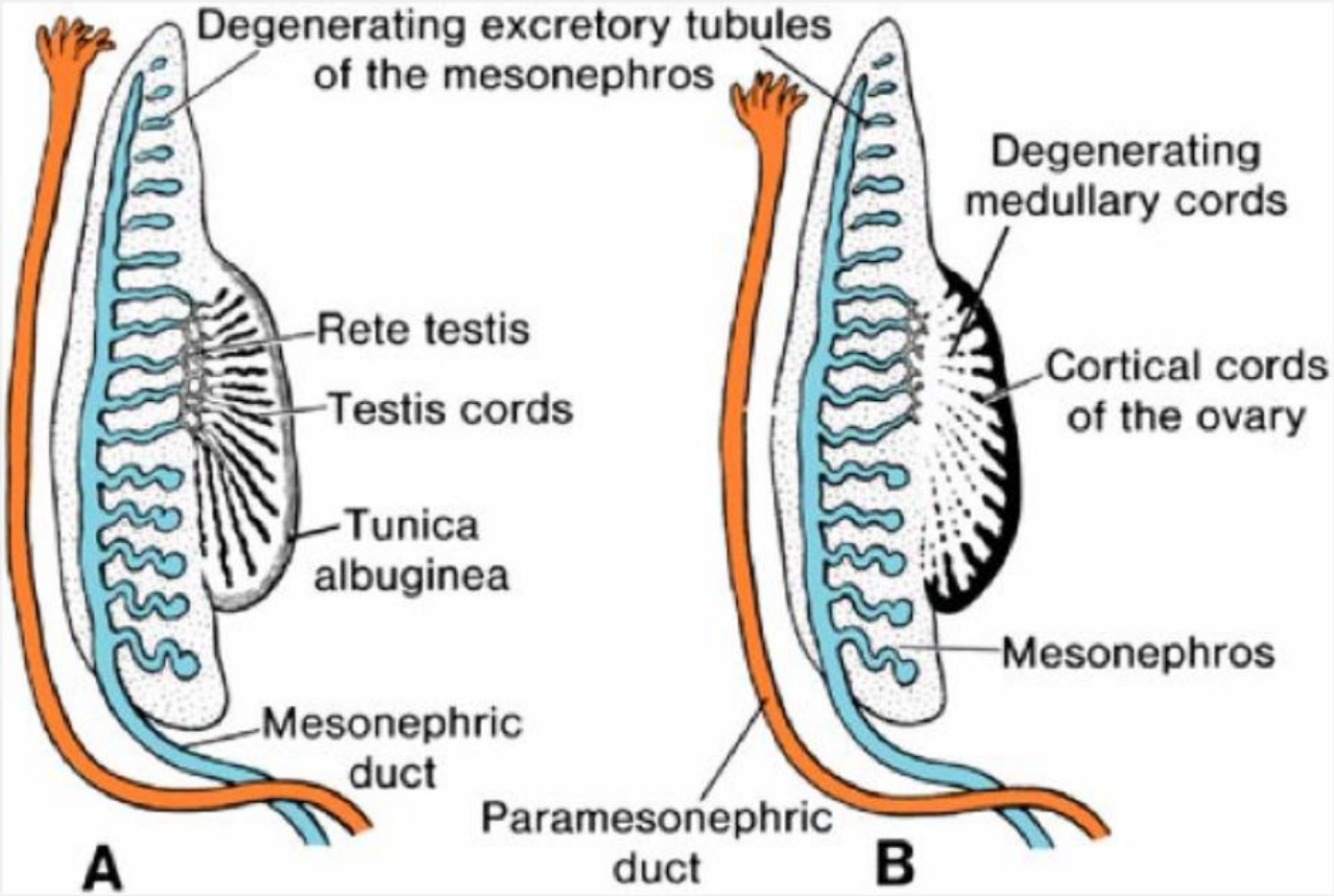


Figure 15.23 Genital ducts in the sixth week in the male **(A)** and female **(B).** The mesonephric and paramesonephric ducts are present in both. Note the excretory tubules of the mesonephros and their relation to the developing gonad in both sexes.

Development of the Genital Ducts.

- With descent of the ovary, the first two parts develop into the uterine tube and the caudal parts fuse to form the uterine canal. When the second part of the paramesonephric ducts moves medio-caudally, the urogenital ridges gradually come to lie in a transverse plane.

Development of the Genital Ducts.

- After the ducts fuse in the midline, a broad transverse pelvic fold is established. This fold, which extends from the lateral sides of the fused paramesonephric ducts toward the wall of the pelvis, is the broad ligament of the uterus.

Development of the Genital Ducts.

- The uterine tube lies in its upper border, and the ovary lies on its posterior surface.
- The uterus and broad ligaments divide the pelvic cavity into the uterorectal pouch and the uterovesical pouch.

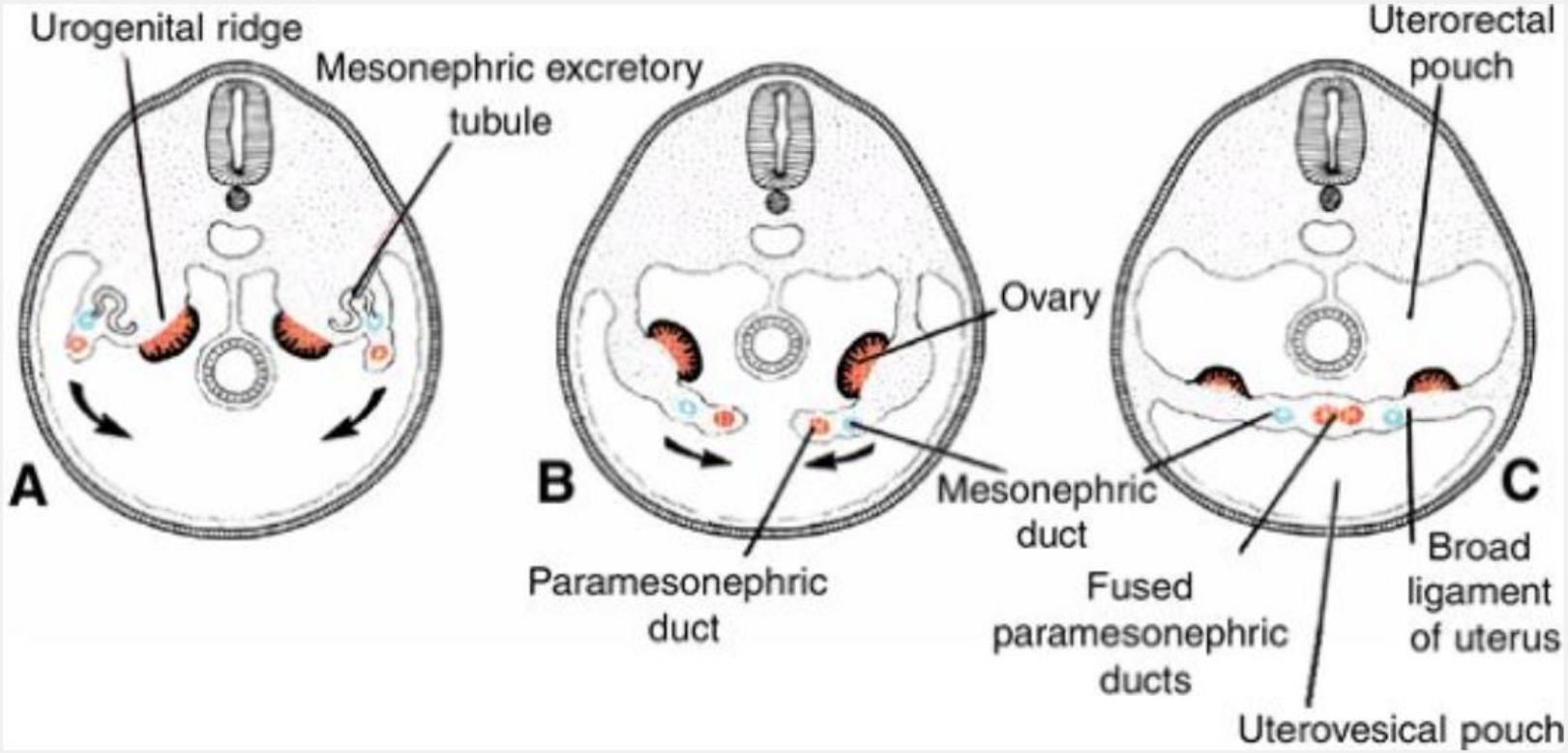


Figure 15.28 Transverse sections through the urogenital ridge at progressively lower levels. **A,B.** The paramesonephric ducts approach each other in the midline and fuse. **C.** As a result of fusion, a transverse fold, the broad ligament of the uterus, forms in the pelvis. The gonads come to lie at the posterior aspect of the transverse fold.

Development of the Genital Ducts.

- The fused paramesonephric ducts give rise to the corpus and cervix of the uterus. They are surrounded by a layer of mesenchyme that forms the muscular coat of the uterus, the myometrium, and its peritoneal covering, the perimetrium.

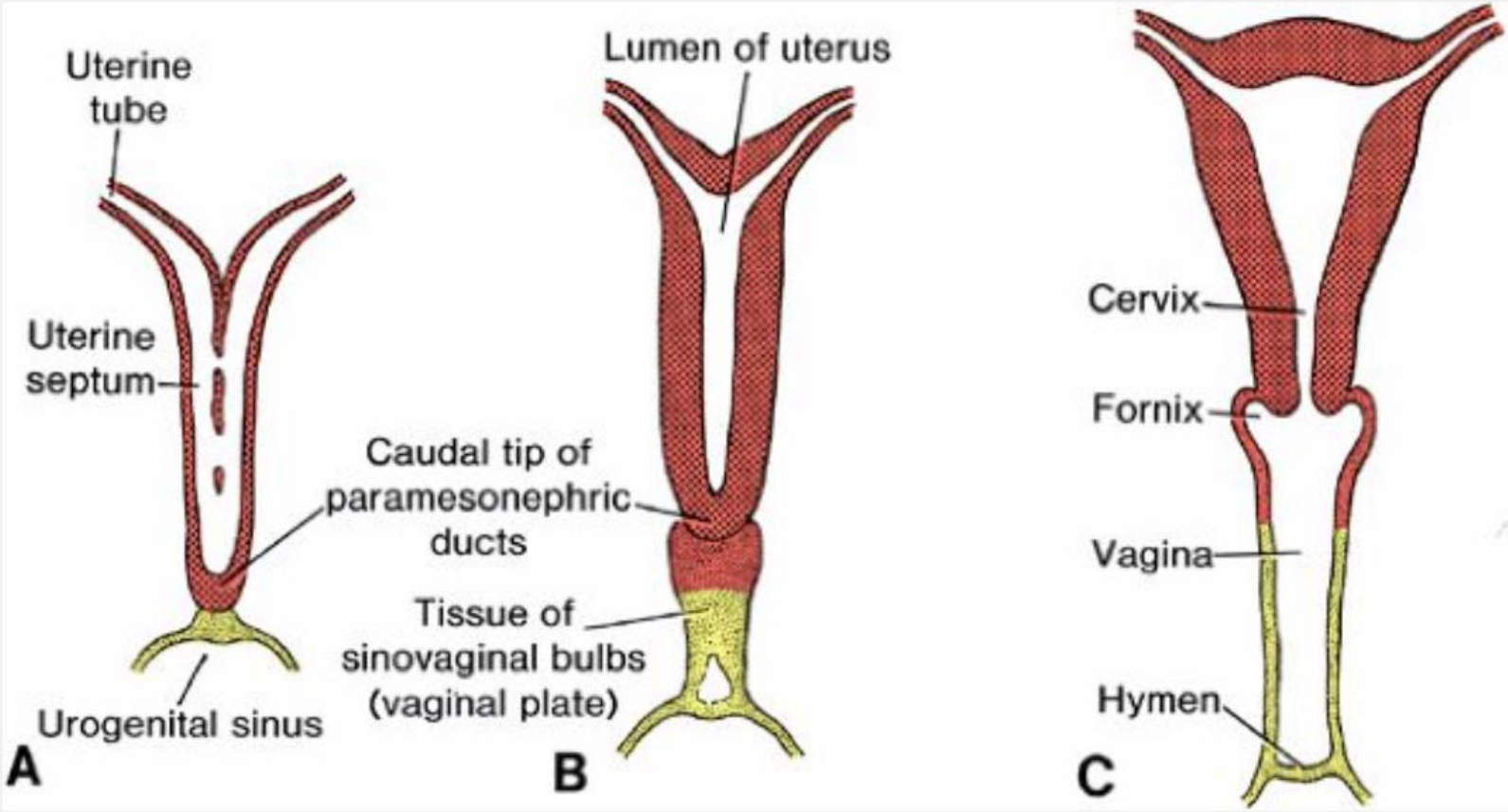
3- Development of the vagina and external genitalia

Development of the vagina

- Shortly after the solid tip of the paramesonephric ducts reaches the urogenital sinus, two solid evaginations grow out from the pelvic part of the sinus.
- These evaginations, the sinovaginal bulbs, proliferate and form a solid vaginal plate.

Development of the vagina

- Proliferation continues at the cranial end of the plate, increasing the distance between the uterus and the urogenital sinus. By the fifth month, the vaginal outgrowth is entirely canalized. The wing-like expansions of the vagina around the end of the uterus, the vaginal fornices, are of paramesonephric origin.



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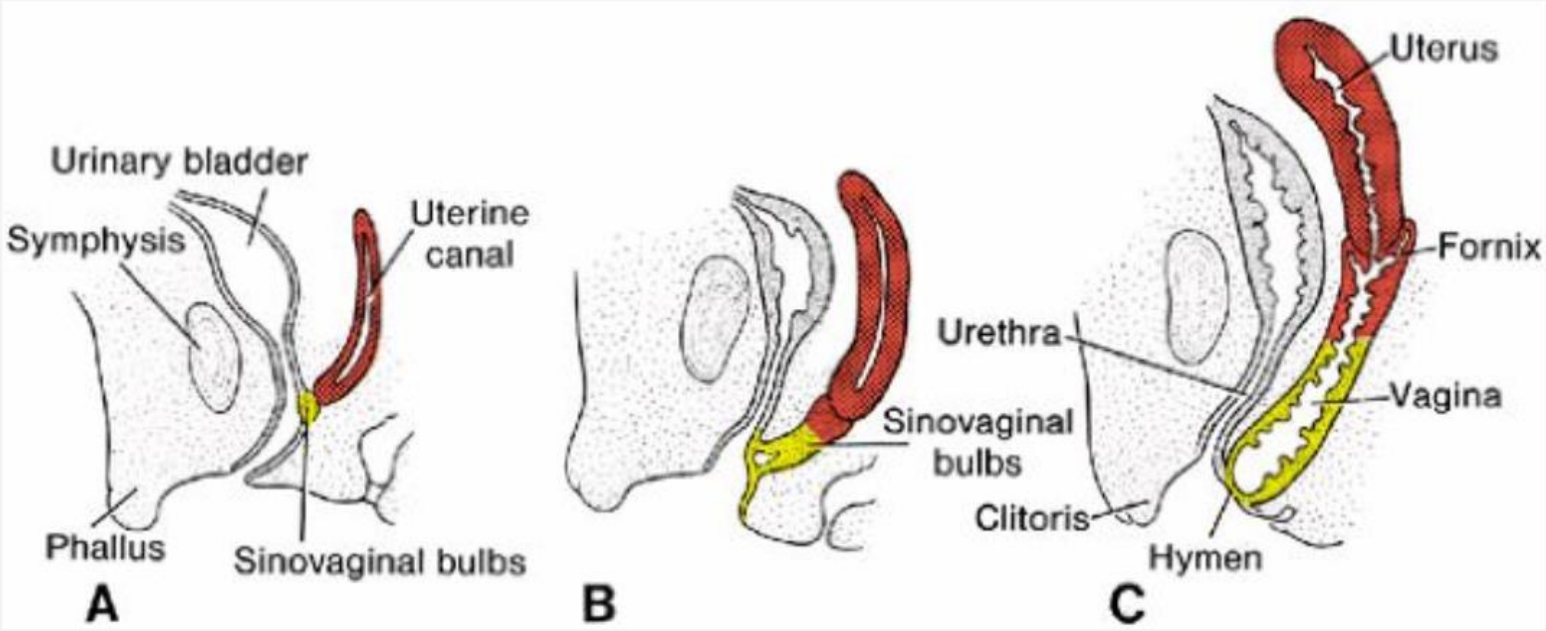

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Development of the vagina

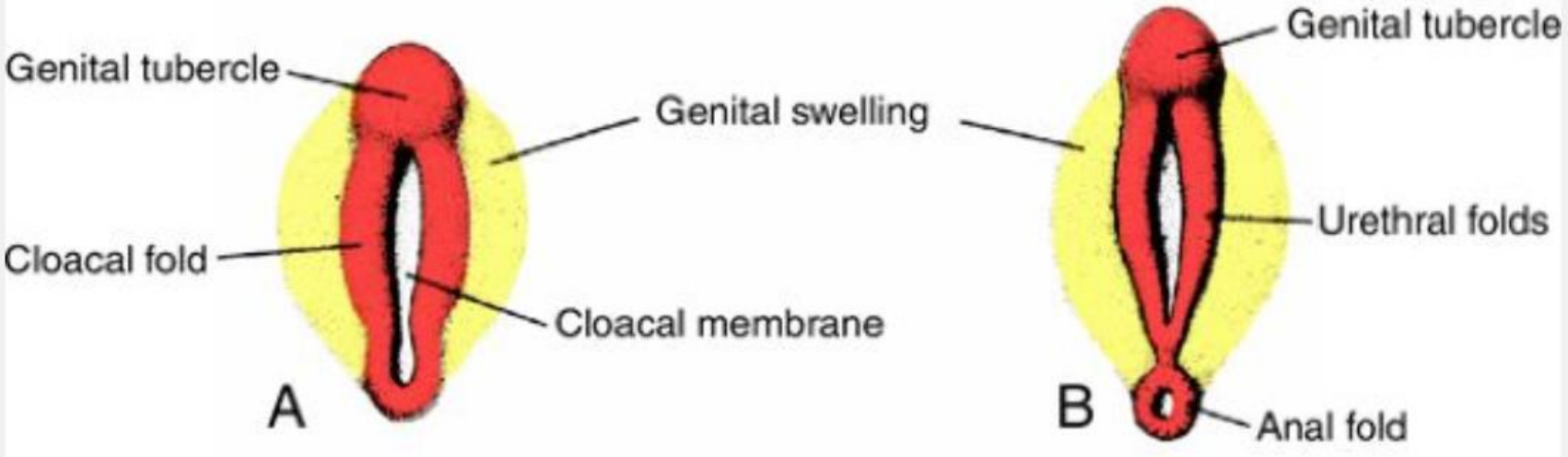
- Thus, the vagina has a dual origin, with the upper portion derived from the uterine canal and the lower portion derived from the urogenital sinus.

Development 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 slightly elevated cloacal folds.

Development of external genitalia

- Cranial to the cloacal membrane the folds unite to form the genital tubercle. Caudally the folds are subdivided into urethral folds anteriorly and anal folds posteriorly


Genital tubercle
Genital swelling
Cloacal fold
Cloacal membrane
A
Genital tubercle
Urethral folds
B
Anal fold

Development of external genitalia

- In the meantime, another pair of elevations, the genital swellings, becomes visible on each side of the urethral folds. These swellings later form the scrotal swellings in the male and the labia majora in the female.
- At the end of the sixth week, however, it is impossible to distinguish between the two sexes.

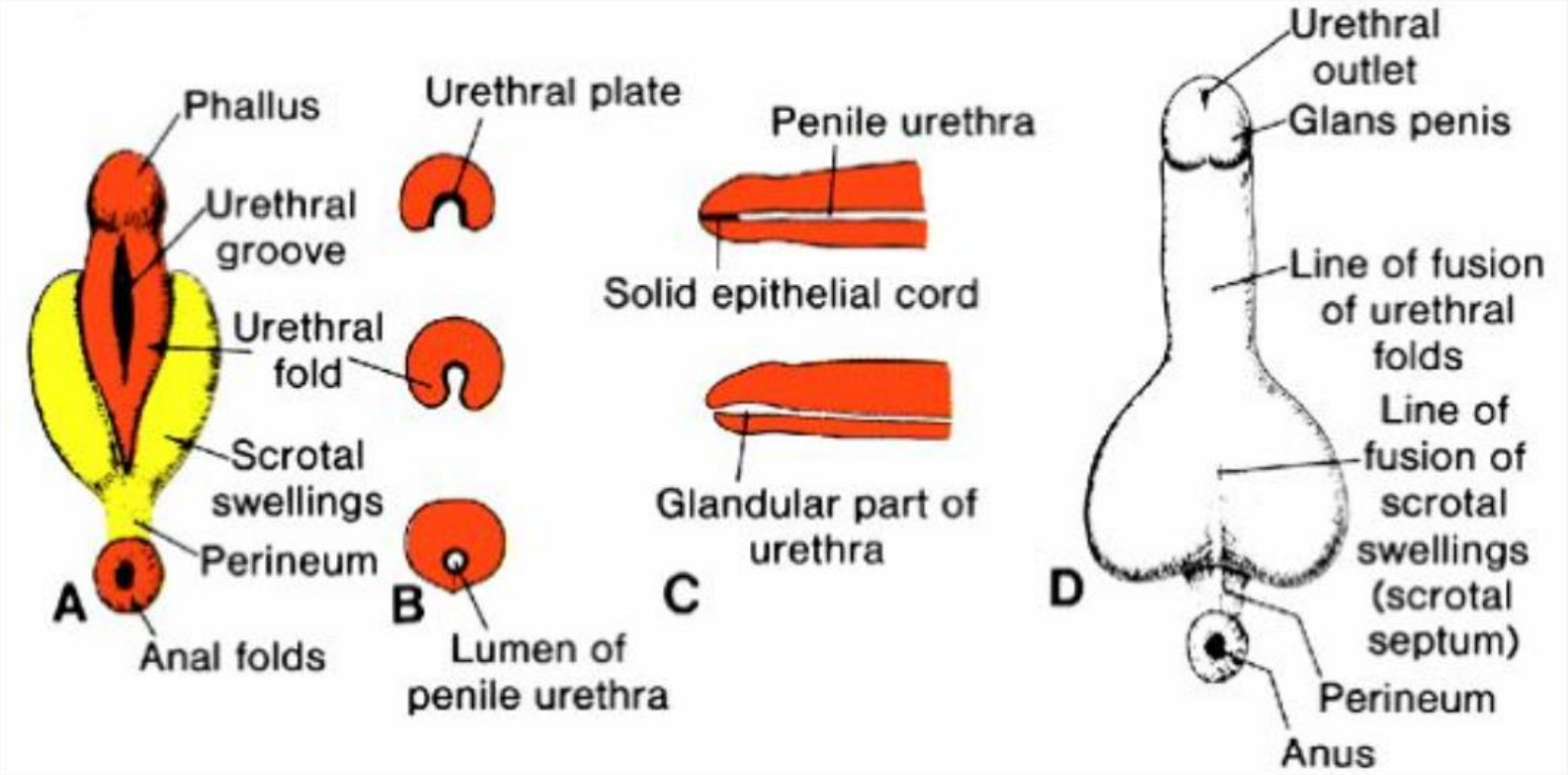


Figure 15.33 A. Development of external genitalia in the male at 10 weeks. Note the deep urethral groove flanked by the urethral folds. **B.** Transverse sections through the phallus during formation of the penile urethra. The urogenital groove is bridged by the urethral folds. **C.** Development of the glandular portion of the penile urethra. **D.** Newborn.

Development of external genitalia

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

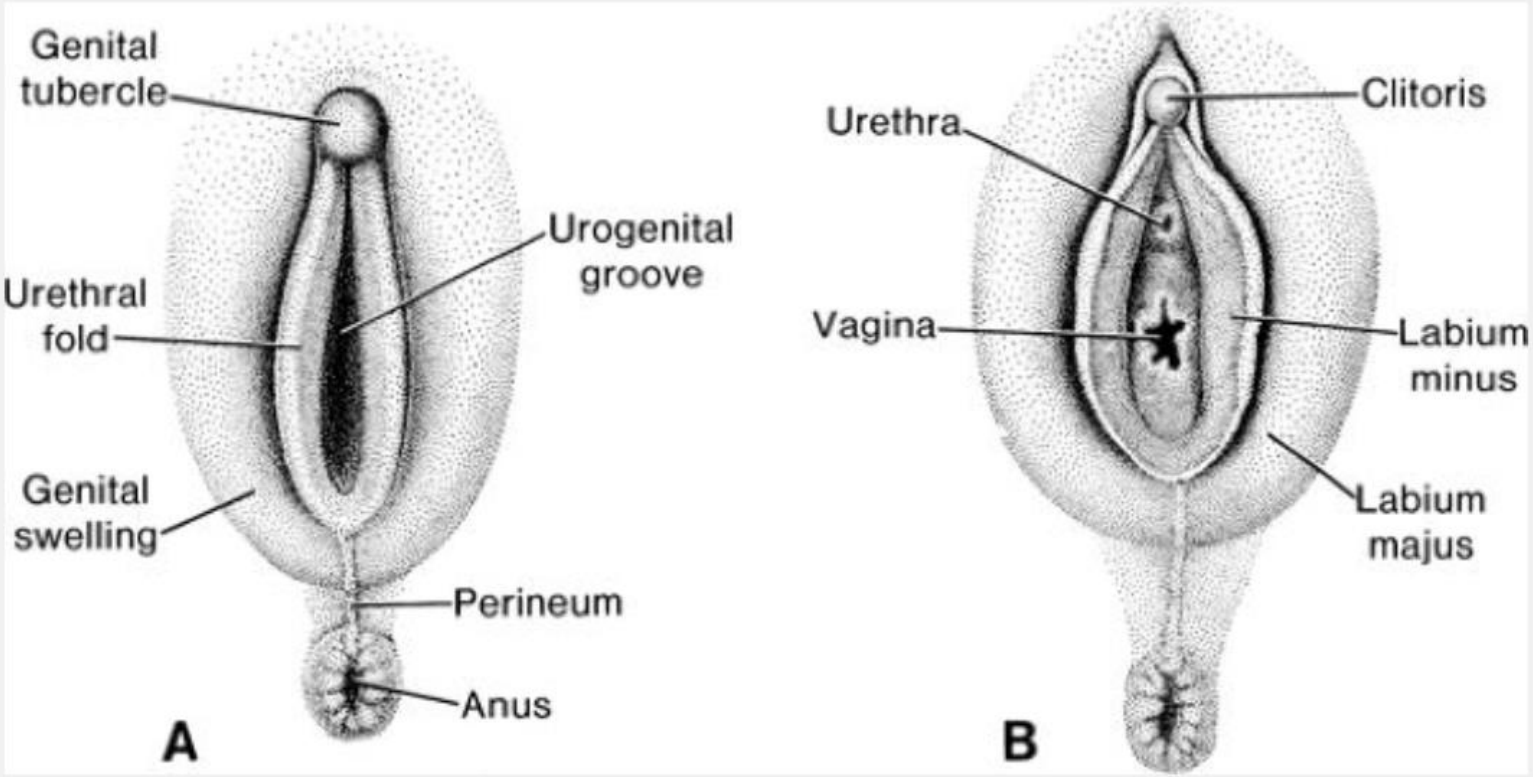


Figure 15.36 Development of the external genitalia in the female at 5 months **(A)** and in the newborn **(B).**

Formation of the External Genitalia

End of Part 1

Thank you

Part 2: Congenital Malformations

A- THE OVARIES

Cong. malformations of the ovaries

1. Ovarian agenesis: Absent ovaries or rudimentary (Streak gonads).
   - Usually underlying chromosomal abnormality (e.g. Turner Syndrome).
   - C/P: primary amenorrhea, infertility.
   - Unilateral agenesis in a normal female is extremely rare and usually asymptomatic. (more likely due to torsion with atrophy, particularly in the prenatal period). It may be accompanied by ipsilateral renal or ureteric agenesis and/or malformation of the ipsilateral fallopian tube.

Cong. malformations of the ovaries

2. Ovarian dysgenesis:

- This could be partial or pure.
- Can be present with different karyotypes, i.e. 46XO, 46XY or 46XX.
- Gonads can possess both ovarian and testicular structure (Ovotestis).
- Condition results in wide spectrum of phenotypes of intersex or hermaphroditism.
- Consensus statement on management of intersex disorders in 2006 replaced the old nomenclature with the term Disorders of Sex Development (DSD)

Cong. malformations of the ovaries

3. Supernumerary ovary: (rare)

- An ectopic ovary that has no connection with the broad, ovarian, or infundibulo-pelvic ligaments.
- 1 case in 29,000 patients (Wharton 1959)
- May be located in the pelvis, retroperitoneum, paraaortic area, colonic mesentery, or omentum.
- Aberrant migration of part of the genital ridge after incorporation of germ cells describes one theory.

Cong. malformations of the ovaries

4. Accessory ovary :

- Excess ovarian tissue nearby and connected to a normally placed ovary.
- approximately 1 case in 93,000 patients (Wharton 1959).
- Can be associated with additional congenital defects, most frequently involving the genitourinary tract.

Cong. malformations of the ovaries

5. Ovarian maldescent:
   - Incidence of 0.2%–0.5%
   - May be uni- or bilaterally and can be associated with Müllerian malformations.
   - Ovaries may be found in an ectopic position along its migration pathway from the lumbar region to the ovarian fossa. [The paracolic gutters is a common location of ovarian maldescent above the pelvic brim]
   - Rarely, ovaries may descend too far down as far as the inguinal canal.

Management

- Investigations:

Laboratory investigations: Usually associated with hypergonadotrophic hypogonadism.

Imaging: Ultrasonography 2D and 3D, Computed tomography and Magnetic resonance imaging.

Others: laparoscopy in limited cases

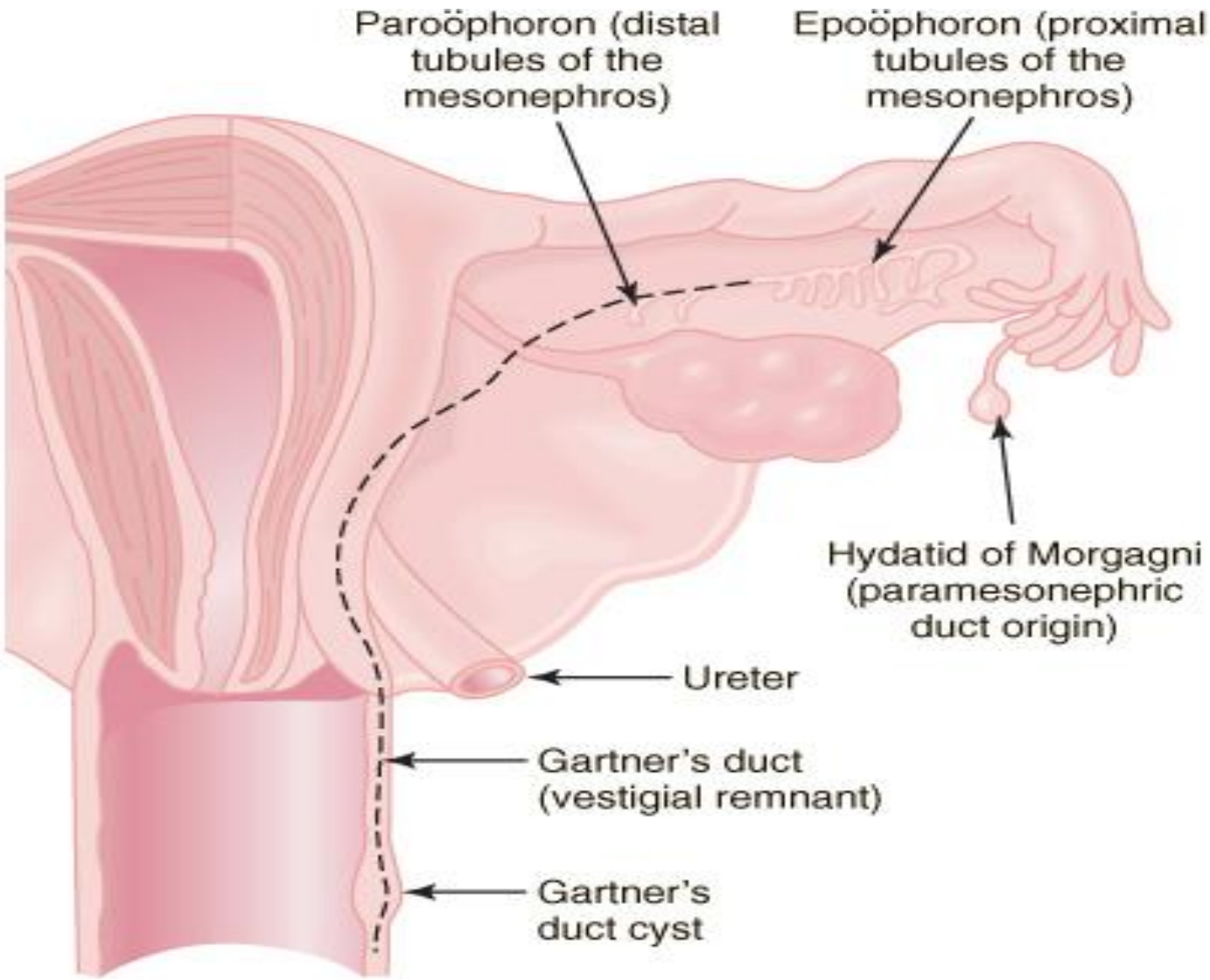
Management

- Treatment:
- According to the severity.
- Removal of dysgenetic gonads for fear of malignant transformation.
- Hormone replacement for complete physical development and psychological support.
- Genetic counselling is beneficial.
- Stem cell research may provide treatment options in the future.
- Oocyte donation (Not done in Egypt and Sunni countries).

B- THE FALLOPIAN TUBES

Cong. malformations of the tubes

1. Accessory ostia.
2. Complete or segmental absence of the fallopian tube.
3. Embryonic cystic remnants: remnants o the mesonephric duct in the female include a few blind tubules, the ***epoophoron***, in the mesovarium, and similar ones, collectively called the ***paroophoron***, adjacent to the uterus which may develop into clinically identifiable cysts.



Remnants of the mesonephric (wolffian) ducts that may persist in the anterolateral vagina or adjacent to the uterus within the broad ligament or mesosalpinx.

C- OTHER MULLERIAN ANOMALIES

Cong. malformations of the uterus

- Because nearly 57 percent of women with uterine defects have successful fertility and pregnancy, the true incidence of congenital müllerian defects may be significantly understated.
- Nahum (1998) found that the prevalence of uterine anomalies in the general population was 1 in 201 women or 0.5 percent.
- Dreisler and colleagues (2014) found uterine anomalies in nearly 10 percent of 622 women from the general population undergoing saline infusion sonography.

Cong. malformations of the uterus

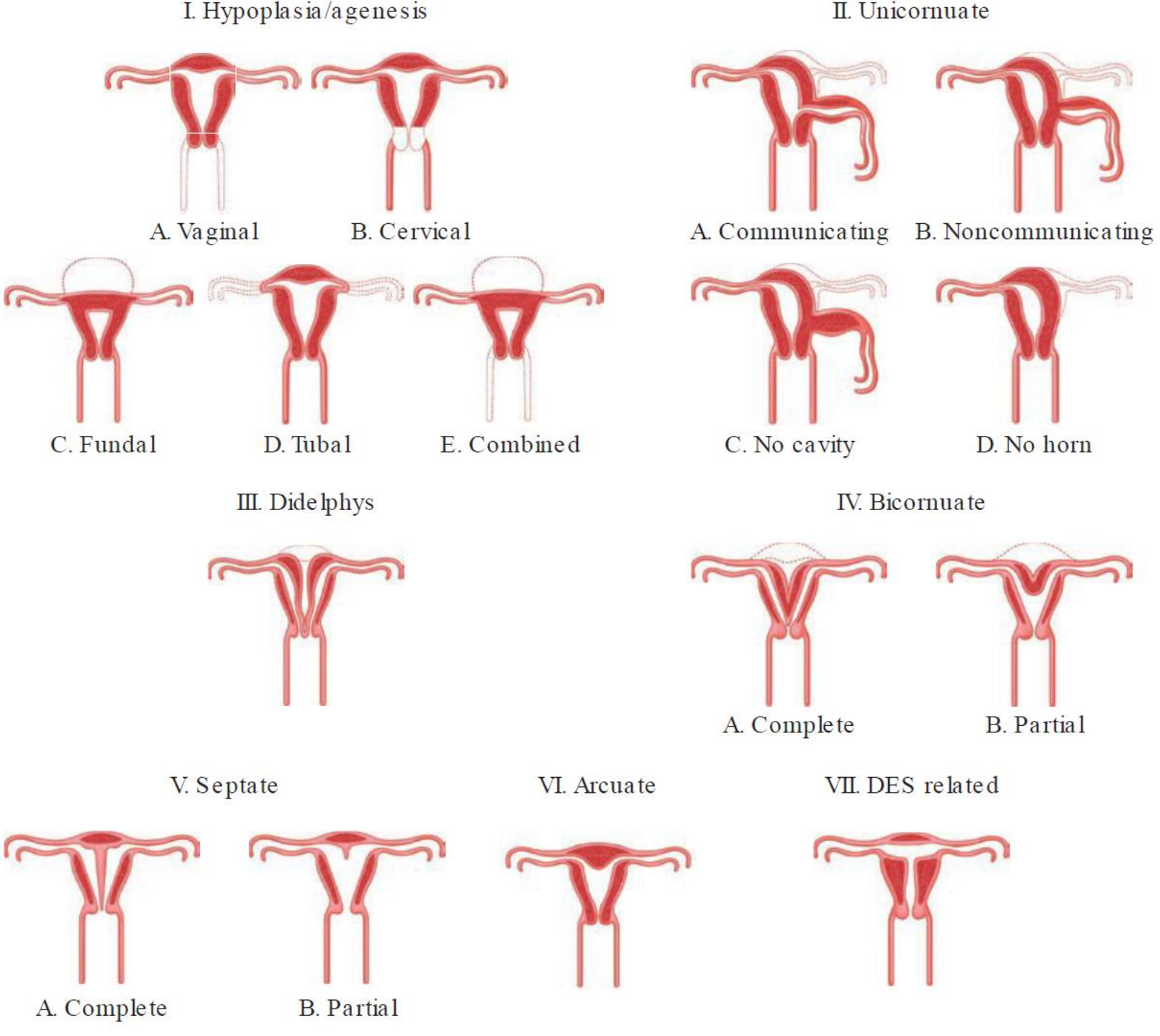
- Müllerian defects are associated with renal anomalies in 30-50 % of cases, Spinal anomalies in 10-12 %.

Cong. malformations of the uterus

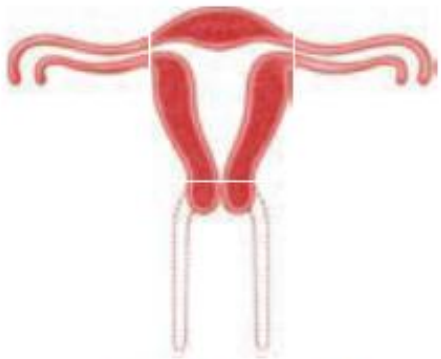
- Anatomic uterine defects have long been recognized as a cause of obstetric complications like: recurrent pregnancy loss, preterm labor, abnormal fetal presentation.
- Some uterine septal defects has also been linked to infertility.

Cong. malformations of the uterus

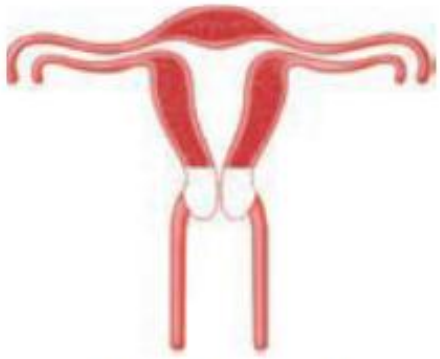
- Mostly result from either failure or abnormal union of both Mullerian tubes.
- Failure of canalization of part of Mullerian tubes give rise to some obstructive types.


I. Hypoplasia/agenesis
A. Vaginal
B. Cervical
C. Fundal
D. Tubal
E. Combined
II. Unicornuate
A. Communicating
B. Noncommunicating
C. No cavity
D. No horn
III. Didelphys
IV. Bicornuate
A. Complete
B. Partial
V. Septate
VI. Arcuate
VII. DES related
A. Complete
B. Partial

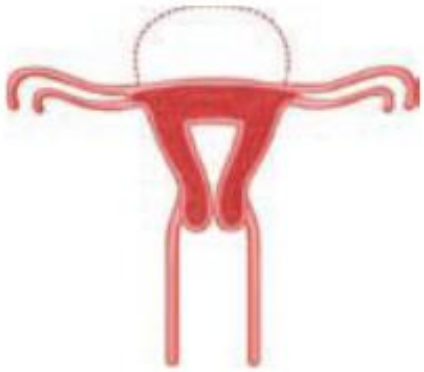
I. Hypoplasia/agenesis



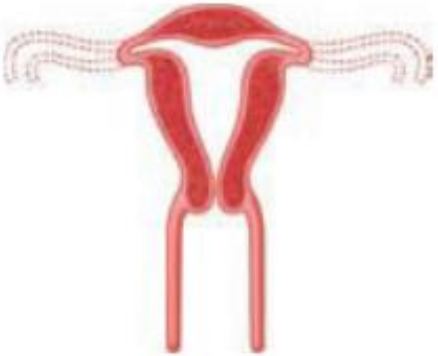
A. Vaginal



B. Cervical



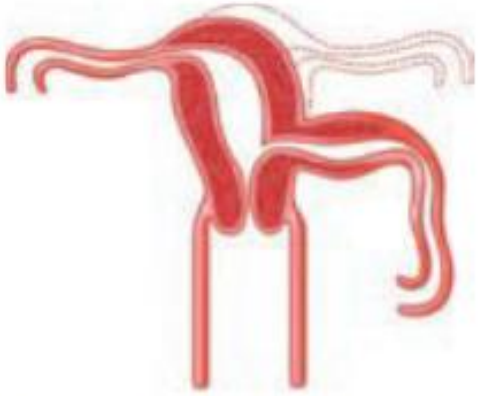
C. Fundal



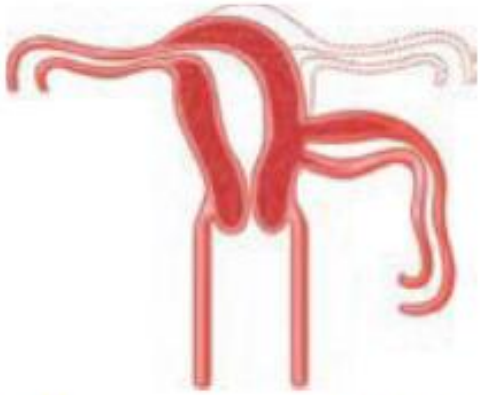
D. Tubal

E. Combined

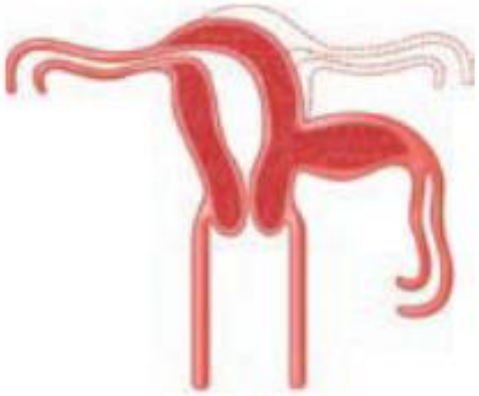
II. Unicornuate



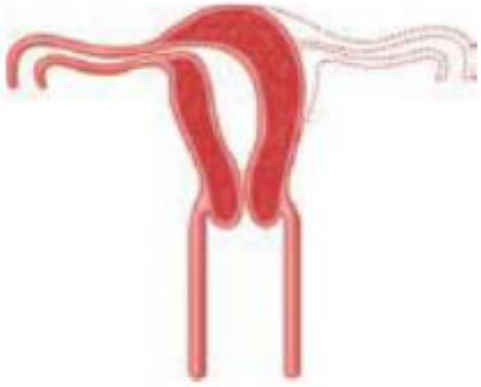
A. Communicating



B. Noncommunicating

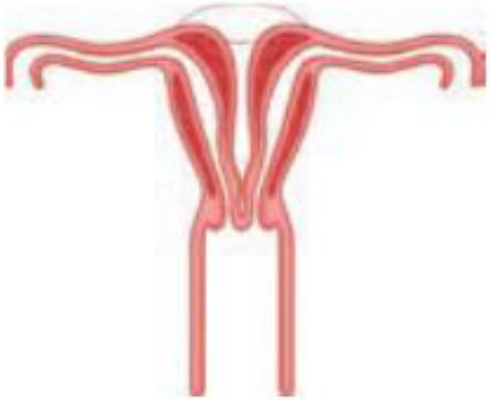


C. No cavity

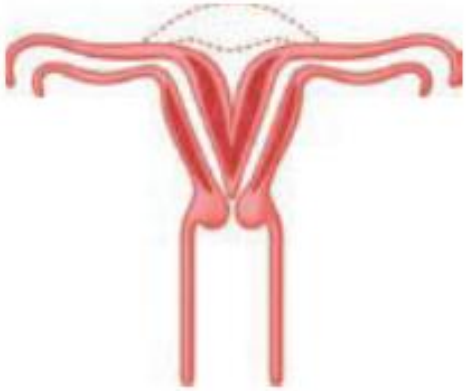


D. No horn

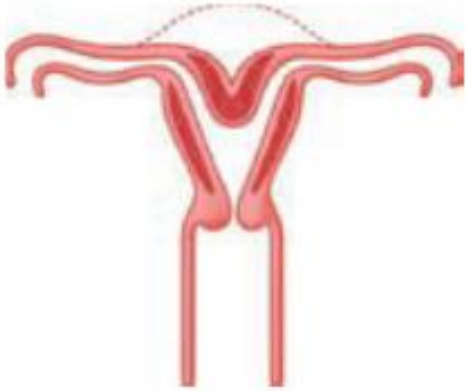
III. Didelphys



IV. Bicornuate



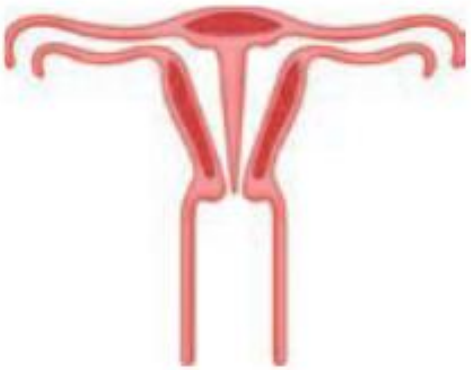
A. Complete

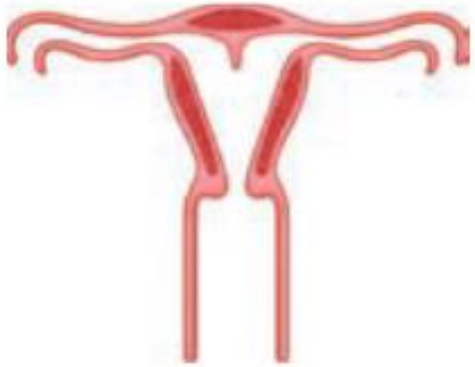


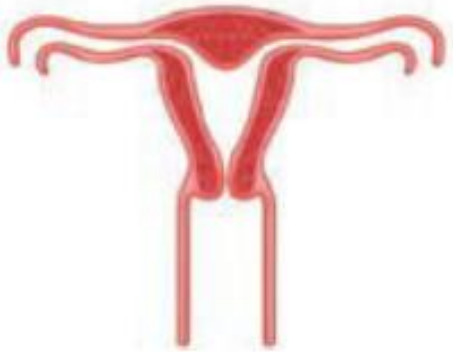
B. Partial

V. Septate

VI. Arcuate



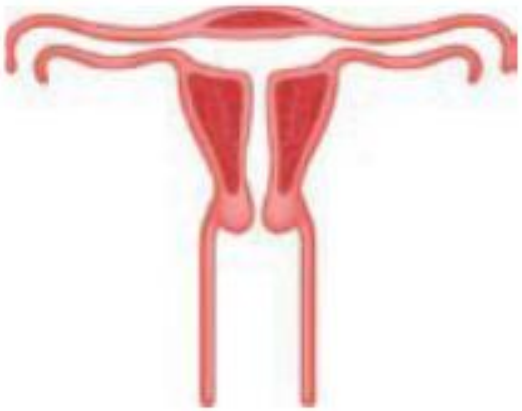


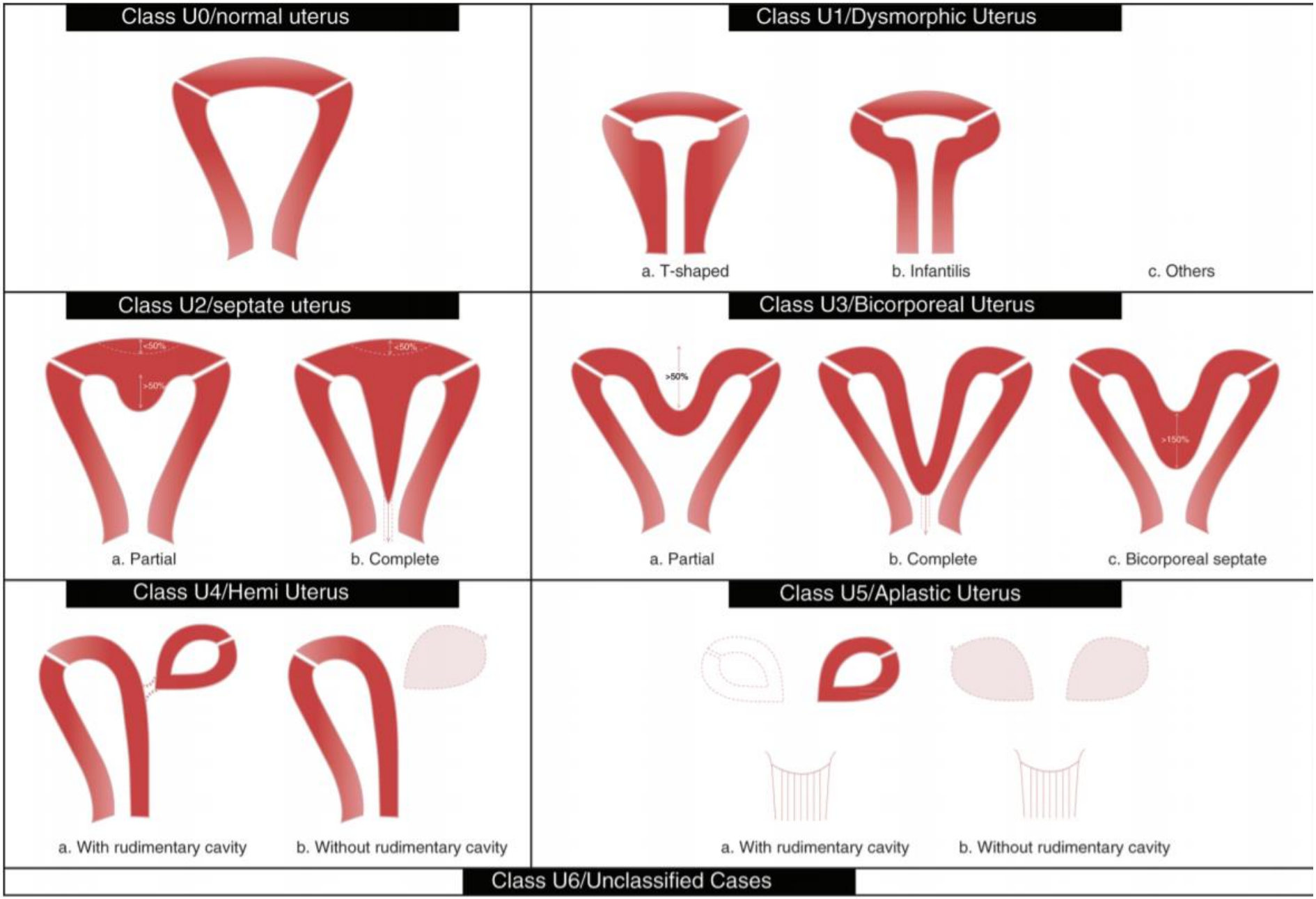


A. Complete

B. Partial

VII. DES related




Class U0/normal uterus
Class U1/Dysmorphic Uterus
a. T-shaped
b. Infantilis
c. Others
Class U2/septate uterus
<50%
>50%
a. Partial
b. Complete
Class U3/Bicorporeal Uterus
>50%
>150%
a. Partial
b. Complete
c. Bicorporeal septate
Class U4/Hemi Uterus
a. With rudimentary cavity
b. Without rudimentary cavity
Class U5/Aplastic Uterus
a. With rudimentary cavity
b. Without rudimentary cavity
Class U6/Unclassified Cases

ESHRE/ESGE classification
Female genital tract anomalies

	Uterine anomaly		Cervical/vaginal anomaly
	Main class	***Sub-class***	***Co-existent class***
U0	Normal uterus		
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	
U2	Septate uterus	**a.** Partial **b.** Complete	
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate	
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity/no horn)	
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	
U6	Unclassified malformations		

C0	*Normal cervix*
C1	*Septate cervix*
C2	*Double 'normal' cervix*
C3	*Unilateral cervical aplasia*
C4	*Cervical aplasia*
V0	*Normal vagina*
V1	*Longitudinal non-obstructing vaginal septum*
V2	*Longitudinal obstructing vaginal septum*
V3	*Transverse vaginal septum and/or imperforate hymen*
V4	*Vaginal aplasia*

U ***C*** ***V***

Cong. malformations of the uterus

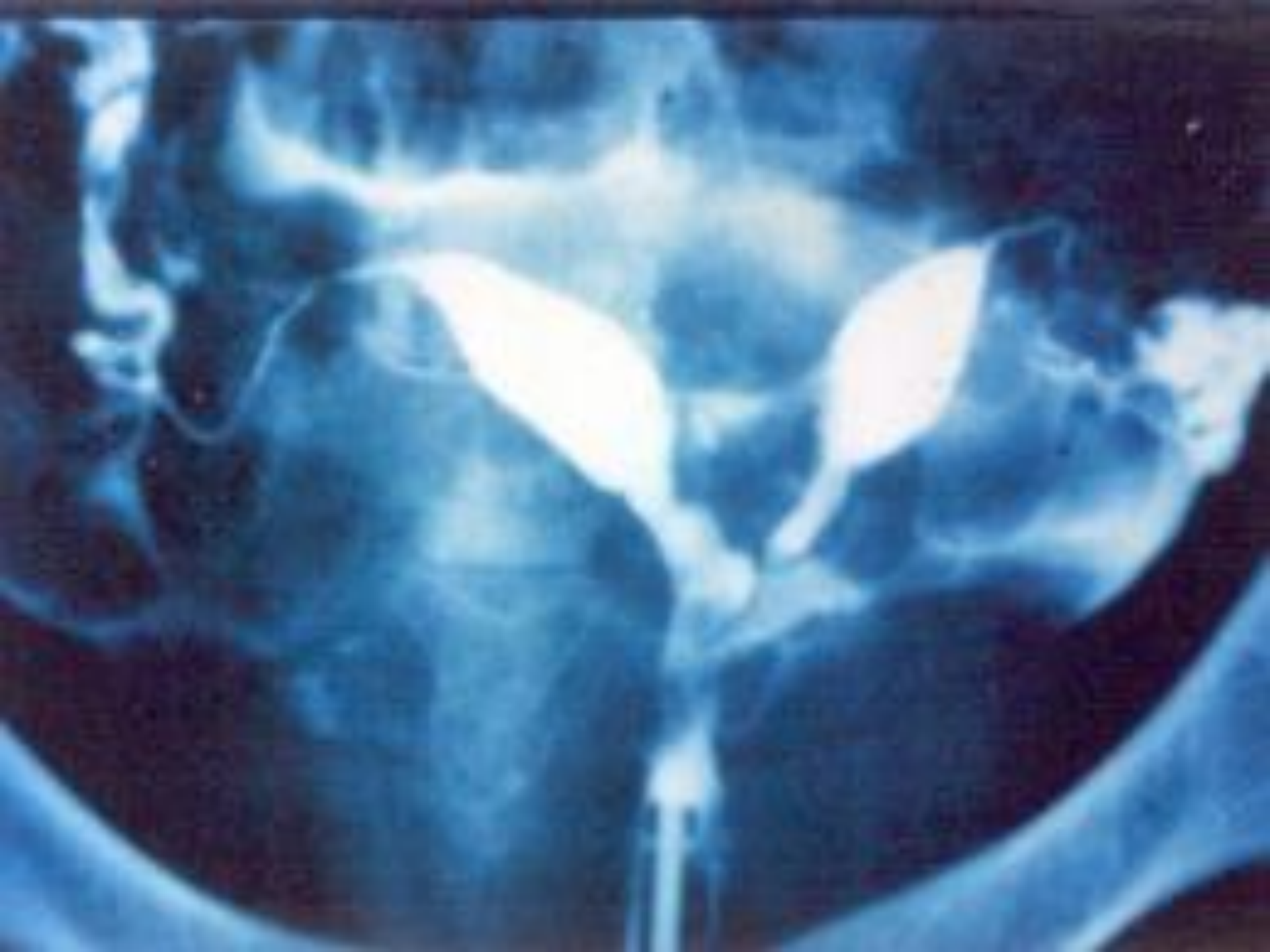
- Clinical picture:
  - Asymptomatic.
  - Recurrent pregnancy loss.
  - Preterm labour.
  - Malpresentation of the fetus.
  - Chronic pelvic pain and dysmenorrhea (i.e unicornate) maybe acute with superimposed infection.
  - Amenorrhea in cervical agenesis.
  - Infertility in obstructive lesions and Septate uterus.

Cong. malformations of the uterus

- Some times uterus is small in size (infantile uterus) in cases of hypogonadism (2ndry hypoplasia). Look for other 2ndry sexual characters during clinical evaluation.
- Mullerian agenesis: **Mayer**–**Rokitansky**–Küster–Hauser **syndrome** (MRKH) is characterized by a failure of the Müllerian duct to develop, resulting in a missing uterus and variable degrees of vaginal hypoplasia of its upper portion.

Cong. malformations of the uterus

- Investigations:
  - U/S : 2D and 3D. 3D is important in definitive diagnosis.
  - Hysterosalpingogram HSG.
  - MRI.
  - Combined hysteroscopy, laparoscopy.



Cong. malformations of the uterus

- Treatment:
  - Surgical management:
    - Hysteroscopic septum excision.
    - Metroplasty.
    - Uterine transplantation.
  - Conservative management.
  - Cerclage (No evidence).

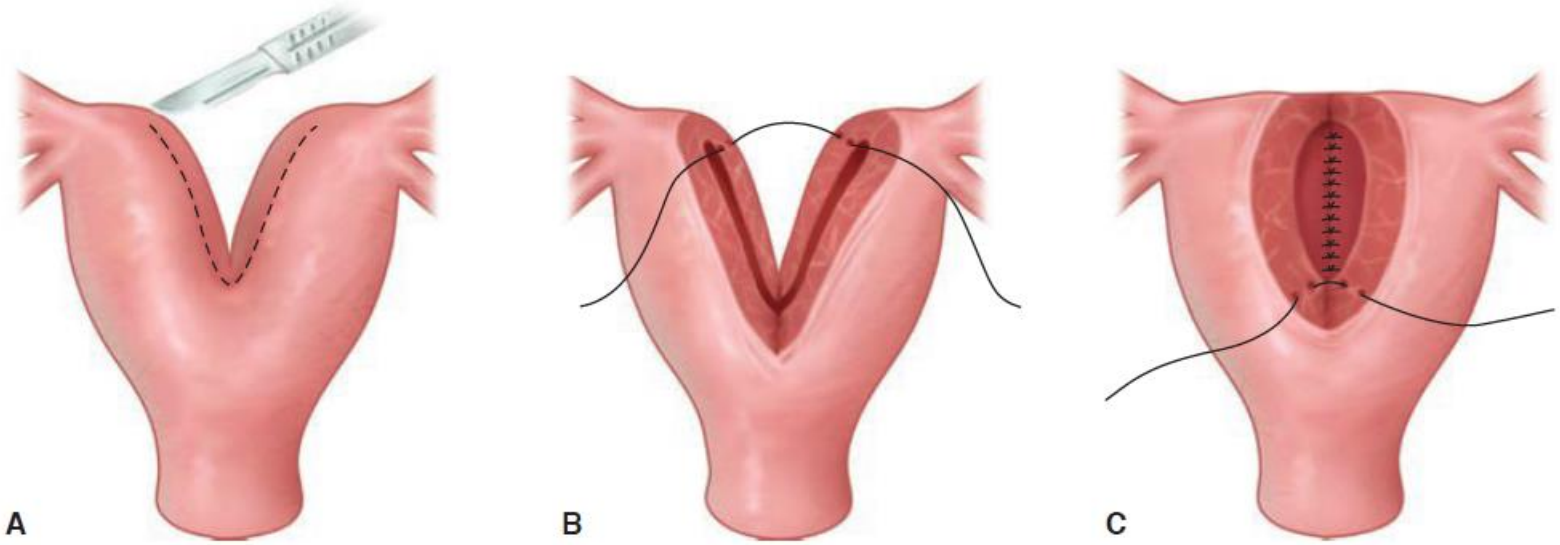
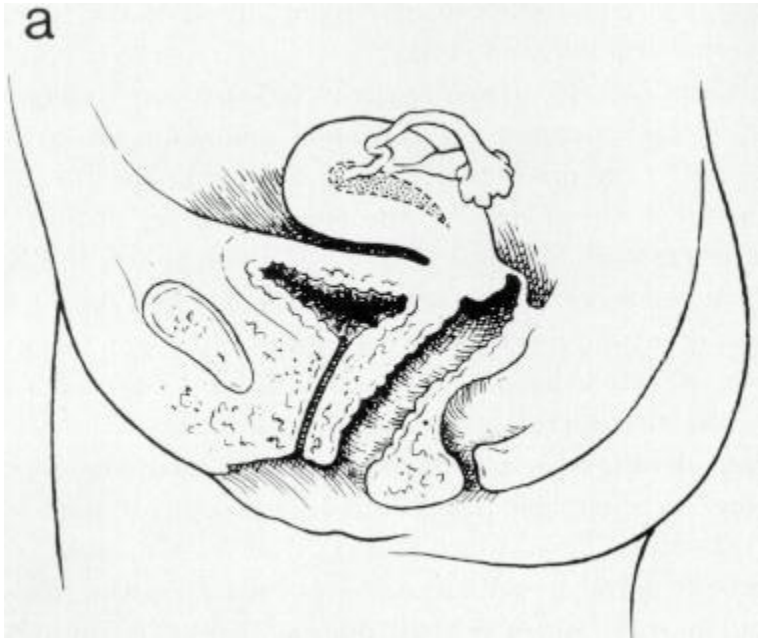


FIGURE 18-12 Strassman metroplasty is one of several techniques of bicornuate uterus repair. **A.** Excision of intervening uterine wall. **B.** Reapproximation of posterior uterine wall with a layer of myometrial sutures. **C.** Reapproximation of the anterior wall is closed similarly. Following placement of myometrial sutures, a layer of subserosal sutures is placed in the anterior and posterior walls.

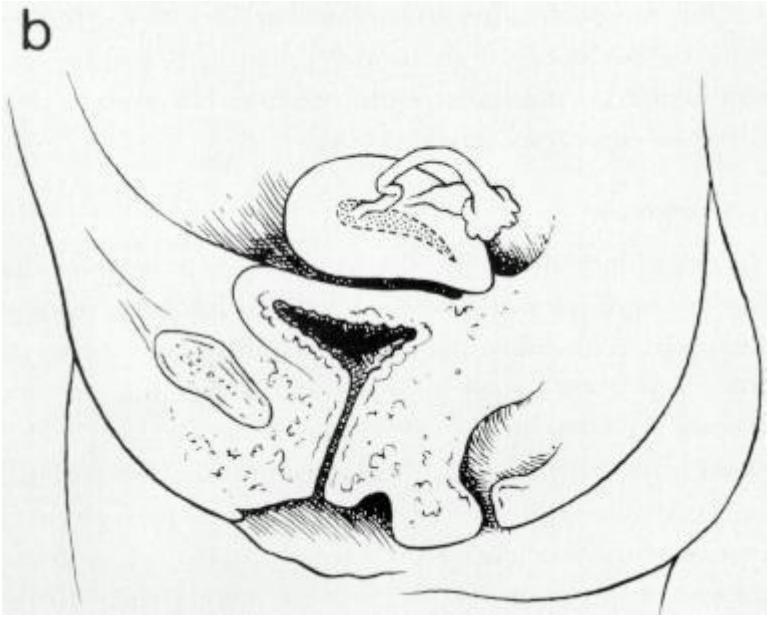
THE VAGINA AND HYMEN

Cong. malformations of the vagina and hymen

- Aplasia or hypoplasia.
- Transverse vaginal septum.
- Longitudinal vaginal septum.
- Imperforate hymen.



a, Isolated congenital cervical atresia with normal vaginal development. **b,** Congenital cervical atresia with complete vaginal agenesis



Isolated congenital cervical atresia with normal vaginal development. **b,** Congenital cervical atresia with complete vaginal agenesis

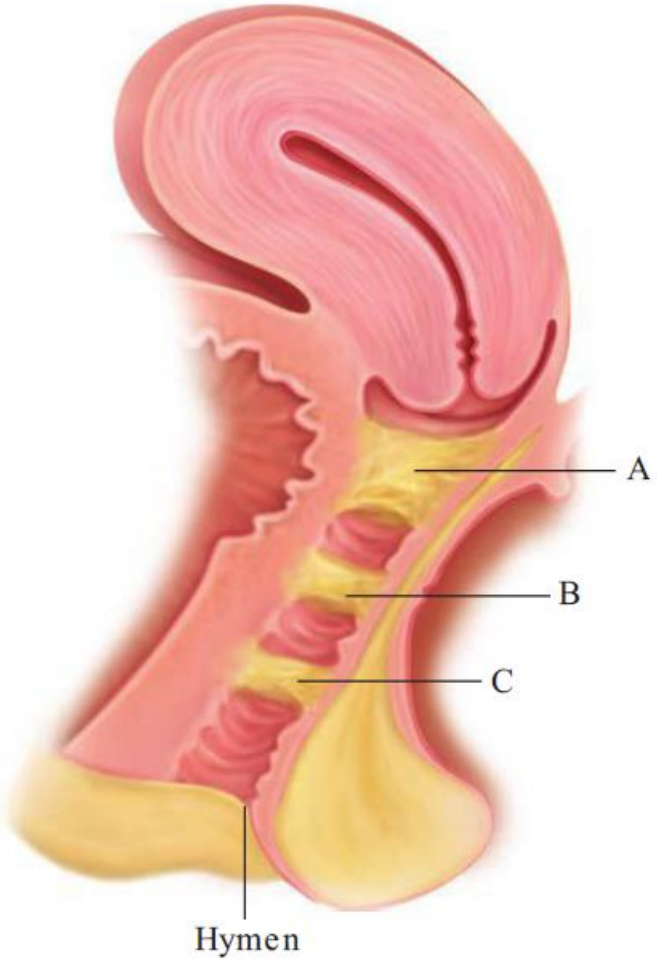


FIGURE 18-8 Potential locations of transverse vaginal septa are indicated and marked **(A–C)**. (Reproduced with permission from Rock JA, Zacur HA, Dlugi AM, et al: Pregnancy success following surgical correction of imperforate hymen and complete transverse vaginal septum, Obstet Gynecol 1982 Apr;59(4):448–451.)

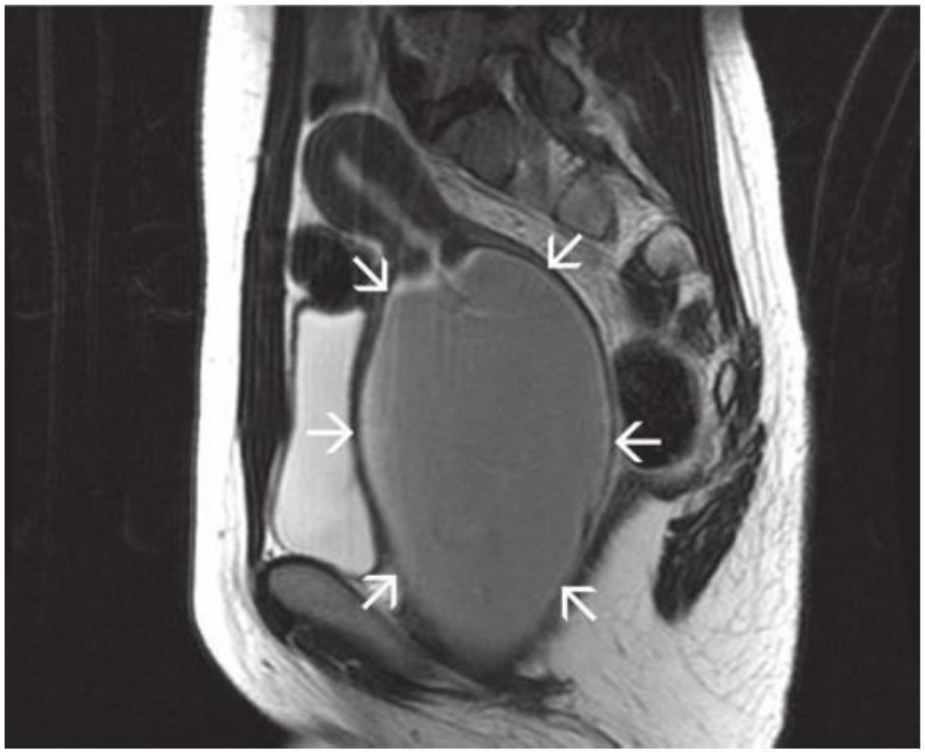
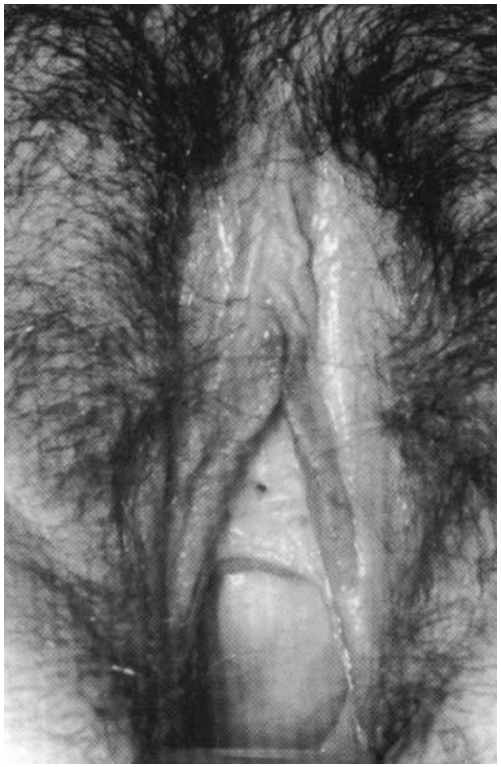
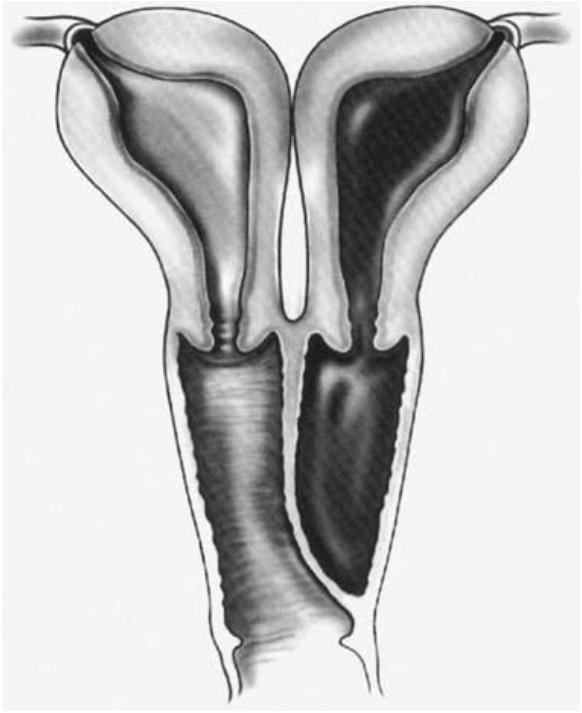
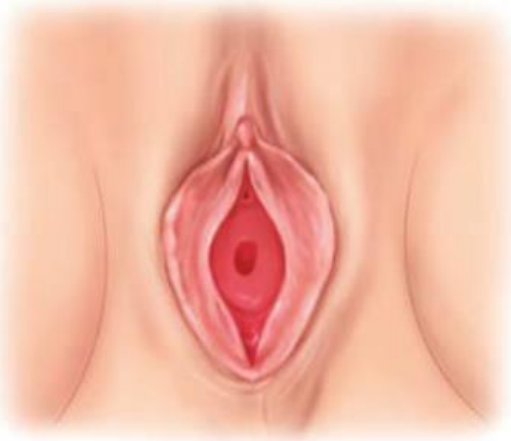


FIGURE 18-9 Magnetic resonance image of complete low transverse septum with obstruction. Marked hematocolpos is identified (arrows) in this 13-year-old female. The relatively low signal intensity on the T2-weighted images is consistent with subacute blood. The uterus is seen above the hematocolpos. (Used with permission from Dr. Doug Sims.)

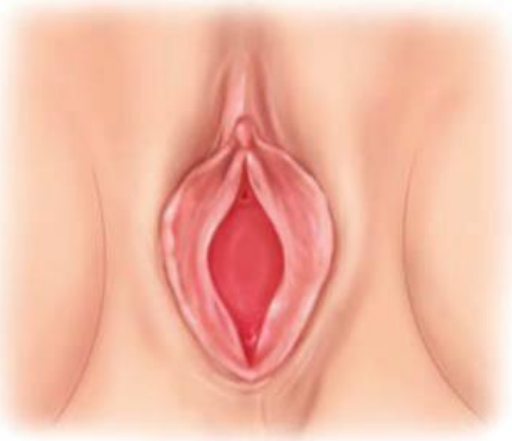


Bulging mass in a complete obstructive longitudinal vaginal septum

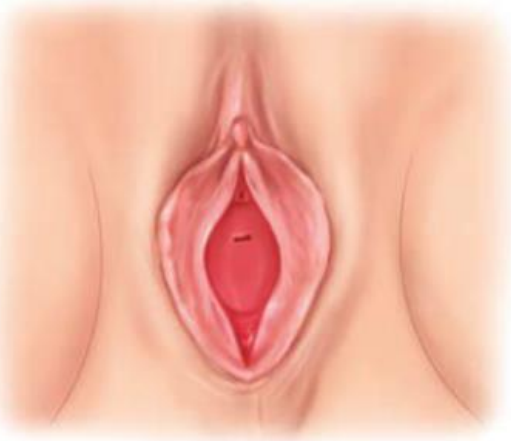




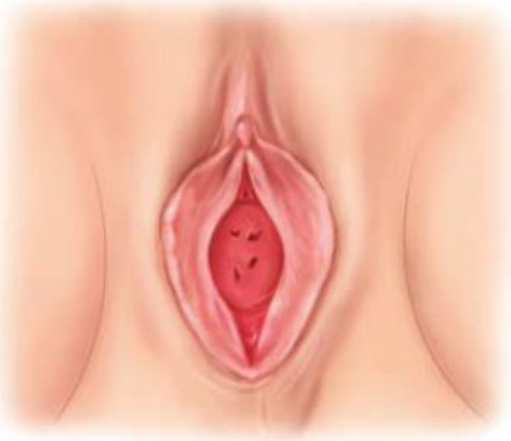
A Normal



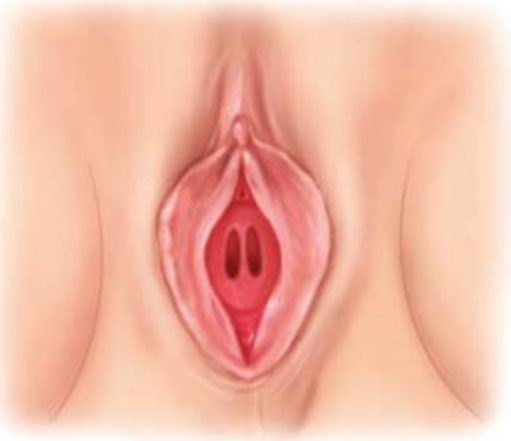
B Imperforate



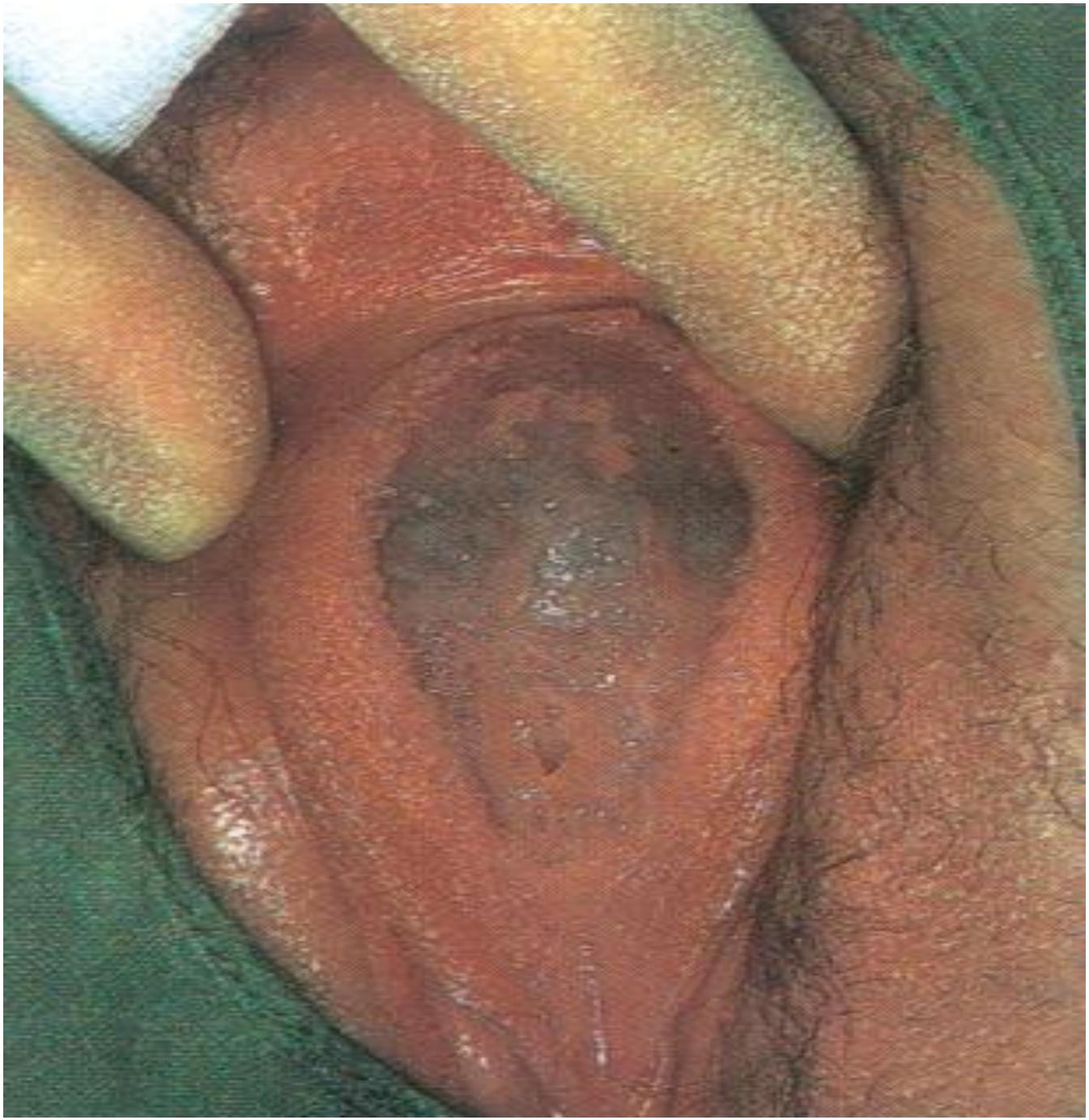
C Microperforate



D Cribriform



E Septate



Cong. malformations of the vagina and hymen

- Treatment is mainly surgical.
  - Excision of the septum.
  - Hymenotomy.
  - Etc.

Thank you