433 Teams

OBSTETRICS & GYNECOLOGY

Embryology of the female genital organs, congenital malformation and intersex

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Objectives :

Embryology of the female genital organs:

- List the steps that determine the sexual differentiation into male or female during embryonic development.
- Describe the embryologic development of the female genital tract (internal and external).

Congenital Malformations of the Genital Tract :

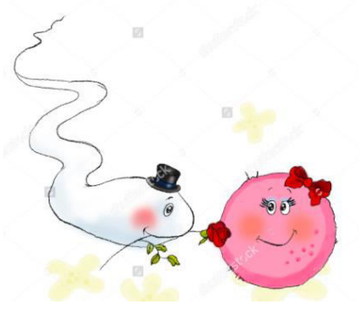
- Identify the incidence, clinical presentation, complication and management of the various types of congenital tract malformation including:
    - Mullerian agenesis
    - Disorder of lateral fusion of the mullerian ducts (Uterus didelphys, septate uterus, unicornuate uterus, bicornuate uterus).
    - Disorder of the ventricle fusion of the mullerian ducts
        - (Vaginal septum, cervical agenesis, dysgenesis)
    - Defects of the external genitalia.
        - Imperforate hymen
        - Ambiguous genitalia

List the steps that determine the sexual differentiation into male or female during embryonic development.

Intersex (Abnormal Sexual Development) :

- List the causes of abnormal sexual development
- List the types of intersex :
    - Masculinized female (congenital abdominal hyperplasia or maternal exposure to androgen)
    - Under masculinized male (anatomical or enzymatic testicular failure or endogen insensitivity)
    - True hemaprodites
- Discuss the various types of intersex in term of clinical presentation, differential diagnosis and management.

SEXUAL DIFFERENTIATION



- The first step in sexual differentiation is the **determination of genetic sex (XX or XY).**
- female sexual development does not depend on the presence of ovaries, like in turner syndrome (no ovaries but has normal external genitalia
- Male sexual development depend on the presence of functioning testes & responsive end organs
- Female exposed to **androgens** in- utero will be masculinized.

EXTERNAL GENITALIA

1-UNDEFERENTIATED STAGE (4-8 WK)

The neutral genitalia includes:

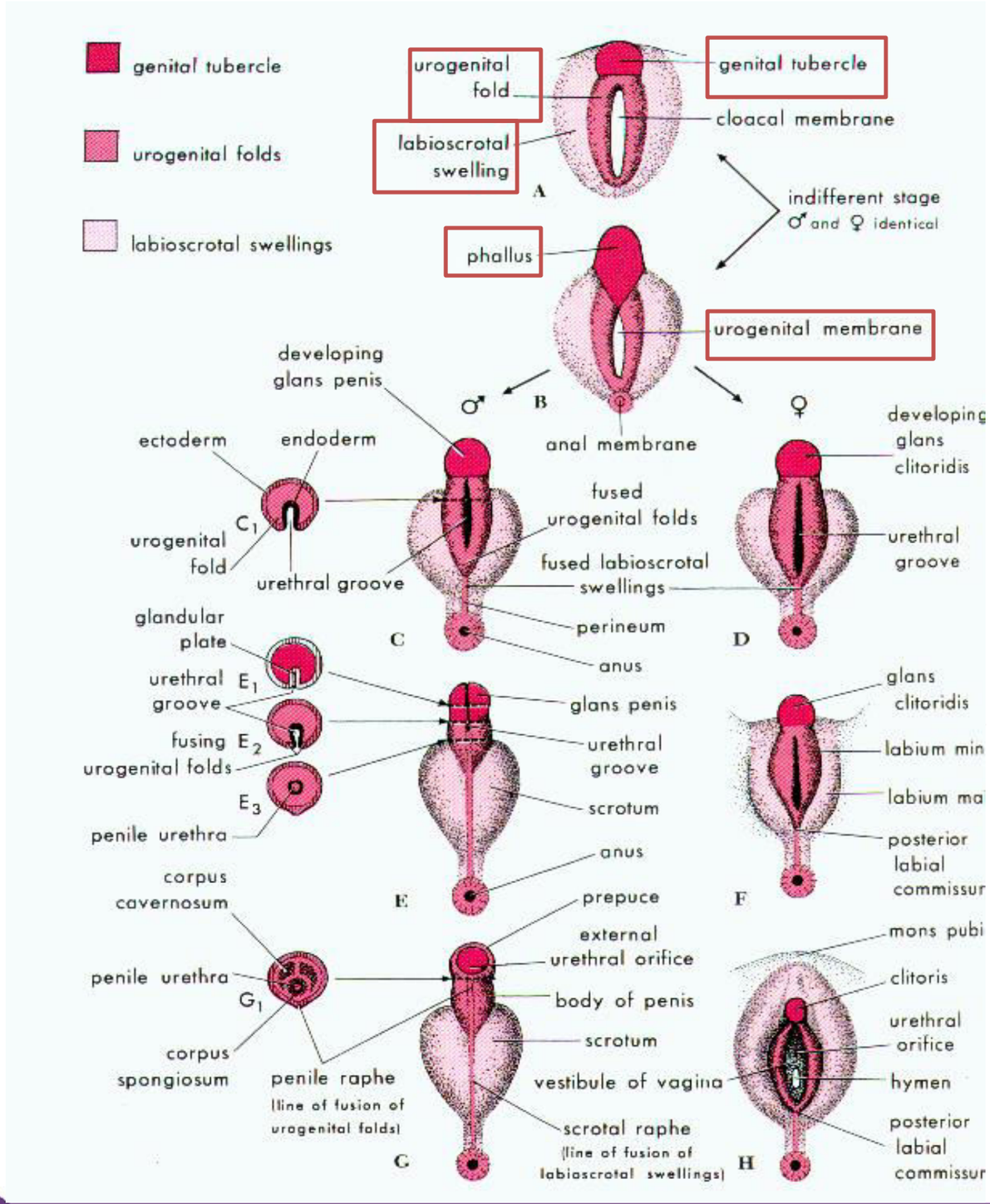
- genital tubercle (phalus)
- labioscrotal swellings
- urogenital folds
- urogenital sinus

2-♂ & ♀ EXTERNAL GENITAL DEVELOPMENT (9-12 WK)

- By **12 week** gestation ♂ & ♀ genitalia can be differentiated
- In the **absence of androgens** female external genitalia develop
- The development of male genitalia requires the **action of androgens**, specifically **DHT**

Testosterone → 5 alpha reductase → DHT

DEVELOPMENT OF MALE & FEMALE EXTERNAL GENITALIA



- **Male**:

stimulated by **TESTOSTERONE**

1. The **phallus** enlarges to form **Penis**.
2. The **Urogenital folds** fuse to form the **spongy (penile) urethra.**
3. The **labioscrotal** swellings (folds) fuse to form **scrotum**.

- **Female**:

Estrogen produced by both the placenta and the fetal ovaries has a role in feminization of the external genitalia.

1. he **phalls** elongates slightly to form the **Clitoris**.- not as the size of the penis.
2. The **Urogenital folds do not fuse** and form the **Labia Minora**.
3. The Labioscrotal Folds form the **Labia Majora**

INTERNAL GENITAL ORGANS

1. Gonads:

- Undifferentiated gonads begin to develop on the **5th week.**
- Germ cells originate in the yolk sac & migrate to the genital ridge.
- In **the absence of Y chromosome** the Undifferentiated gonad develop into an **ovary.**
- In the **presence Y chromosome (SRY gene** (sex determining region Y) the Undifferentiated gonad develop into **testes** .
- **45XO (**turner's syndrome)embryo the ovaries develop but undergo atresia ➔**streak ovaries.**
- The gonads develop from the mesothelium on the genital Ridge ➔ primary sex cords grow into the mesenchyme ➔ outer **cortex & inner medulla.**
- The **ovary** develop from the **cortex** & the medulla regress.
- The **testes** develop from the **medulla** & the cortex regress.
- The ovary contains 2 million 1primary oocytes* at birth but only about 300,000 primordial follicles are present by 7 years of age.

*The oogonia enter the prophase of the **first meiotic division** and are then called **primary oocytes**

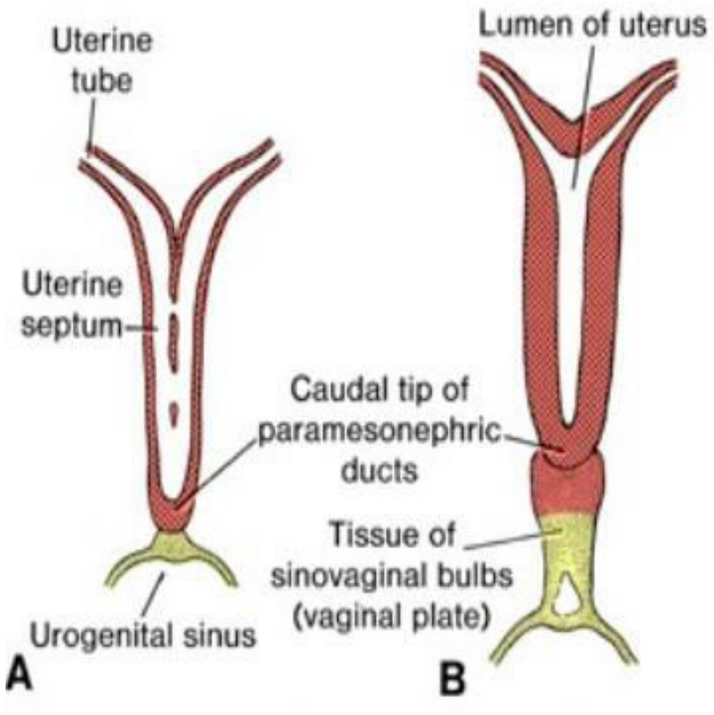
2. UTERUS & FALLOPIAN TUBES:

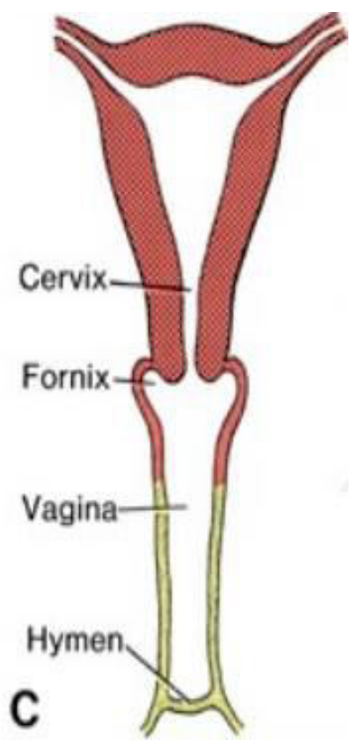
- Invagination of the coelomic epithelium on the craniolateral end of the mesonephric ridge ➔ **Paramesonephric ducts.**
- In the **male** fetus the testes secrete the **mullerian inhibiting factor** ➔ **regression of the mullerian ducts.**
- Fusion of the two **PMN ducts (mullerian ducts)**due to absence of MIS (Müllerian Inhibiting Substance) ➔ **uterus, cervix & Fallopian tubes** (**at 8-11 week**).
- 12-16 weeks ➔ proliferation of the mesoderm around the fused lower part ➔ muscular wall

INTERNAL GENITAL ORGANS

3. Vagina:

- The caudal ends of the mullerian ducts form the mullerian tubercle at the dorsal wall of the urogenital Sinus.
- **Mullarian tubercle** is obliterated ➔ vaginal plate ➔ 16-18 week the central core breaks down ➔ vaginal lumen.
- The **upper 2/3 of the vagina** ➔ formed by **mullerian tubercle.**
- The **lower 1/3 ➔ urogenital sinus.**
- **the hymen is usually perforated by the time delivery occurs.**





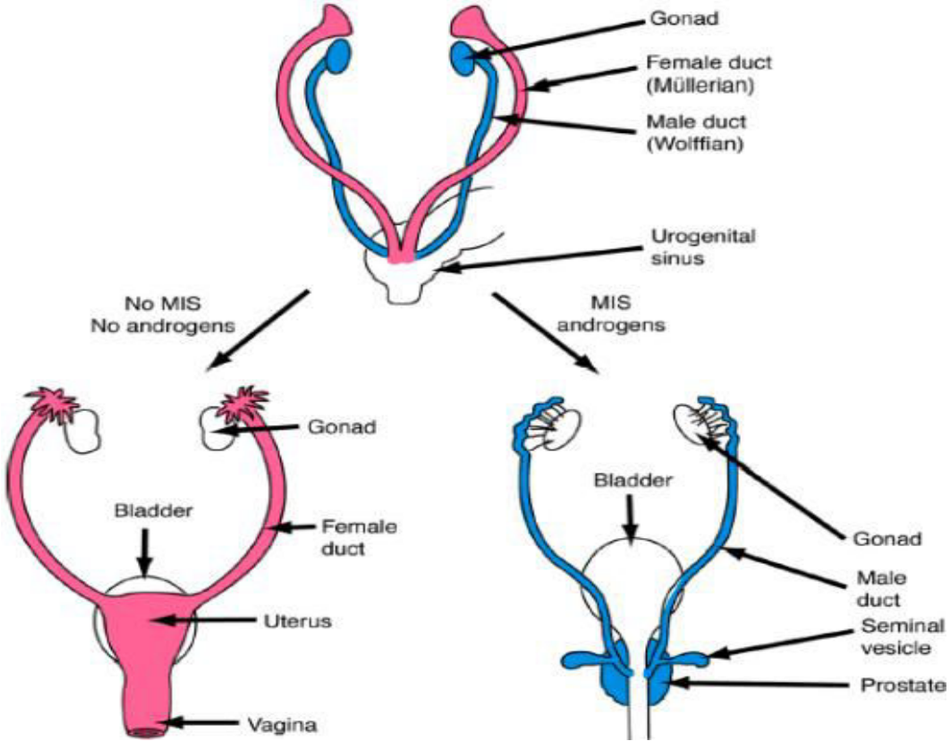


TABLE 3-1

STRUCTURAL HOMOLOGUES IN MALES AND FEMALES

Primordia	Female	Male	Major Determining Factors
Gonadal			
Germ cells	Oogonia	Spermatogonia	Sex chromosomes
Coelomic epithelium	Granulosa cells	Sertoli cells	
Mesenchyme	Theca cells	Leydig cells	
Mesonephros	Rete ovarii	Rete testis	
Ductal			
Paramesonephric (müllerian) duct	Fallopian tubes Uterus Superior ⅔ of vagina Gartner duct	Hydatid testis	Absence of Y chromosome
Mesonephric (wolffian) duct Mesonephric tubules	Epoöphoron Paroöphoron	Vas deferens Seminal vesicles Epididymis Efferent ducts	Testosterone Müllerian inhibiting factor
External Genitalia			
Urogenital sinus	Vaginal contribution Skene glands Bartholin glands	Prostate Prostatic utricle Cowper glands Penis Corpora spongiosa Scrotum	Presence or absence of testosterone, dihydrotestosterone, and 5α-reductase enzyme
Genital tubercle Urogenital folds Genital folds	Clitoris Labia minora Labia majora		

Congenital Malformations of the Genital Tract :

1. Müllerian Dysgenesis or Agenesis : Mayer –Rokitansky-Kuster-Huser syndrome

Patients with:

- ✓ **primary amenorrhea**
- ✓ breast development.
- ✓ 46, XX karyotype.
- ✓ **Normal external genitalia**
- ✓ **The ovaries & fallopian tubes are present**
- ✓ **Absence of upper vagina cervix and/or uterus (uterine reminants may be found)**
- ✓ 47% have asociared urinary tract anomalies such as a unilateral solitary kidney or a double renal collecting system
- ✓ 12% skeletal anomalies

Causes:

müllerian defects that cause obstruction of the vaginal canal

Diagnosis :

- **Ultrasonography and rectal examination** may indicate the absence of a uterus, indicating müllerian agenesis or the Mayer-Rokitansky-Küster- Hauser syndrome. This syndrome is characterized by a **failure of the müllerian ducts to fuse**.
- On occasion, the ovaries are not visible on ultrasonography because they have not descended into the pelvis. In these cases, CT or MRI may reveal them well above the pelvic brim.
- Because these patients may have renal abnormalities Therefore, an **intravenous pyelogram** or other diagnostic radiographic study should be obtained to confirm a normal urinary system.

Management:

- **psychological counseling**
- surgical ⇨ **vaginoplast*** (Creation of a neovagina by McIndoe vaginoplasty, using a split-thickness skin graft)
- **vaginal dilators** *(Creation of a neovagina by Frank method useing dilation of the vaginal pouch with vaginal forms (usually thermoplastic acrylic resin [Lucite] dilators) over the course of weeks to months)
- excision of utrine reminant (if it has functioning endometrium)

*Both of these methods should be performed close to the time when the patient anticipates having vaginal intercourse.

Congenital Malformations of the Genital Tract :

2. DISORDERS OF LATERAL FUSION OF THE MULL DUCTS:

Most patient can conceive without difficulty

- **↑ Incidence of:**

recurrent abortions, premature birth, fetal loss, fetal mal-presentation, C-Section , Cervical incompetence

- **Cause:**

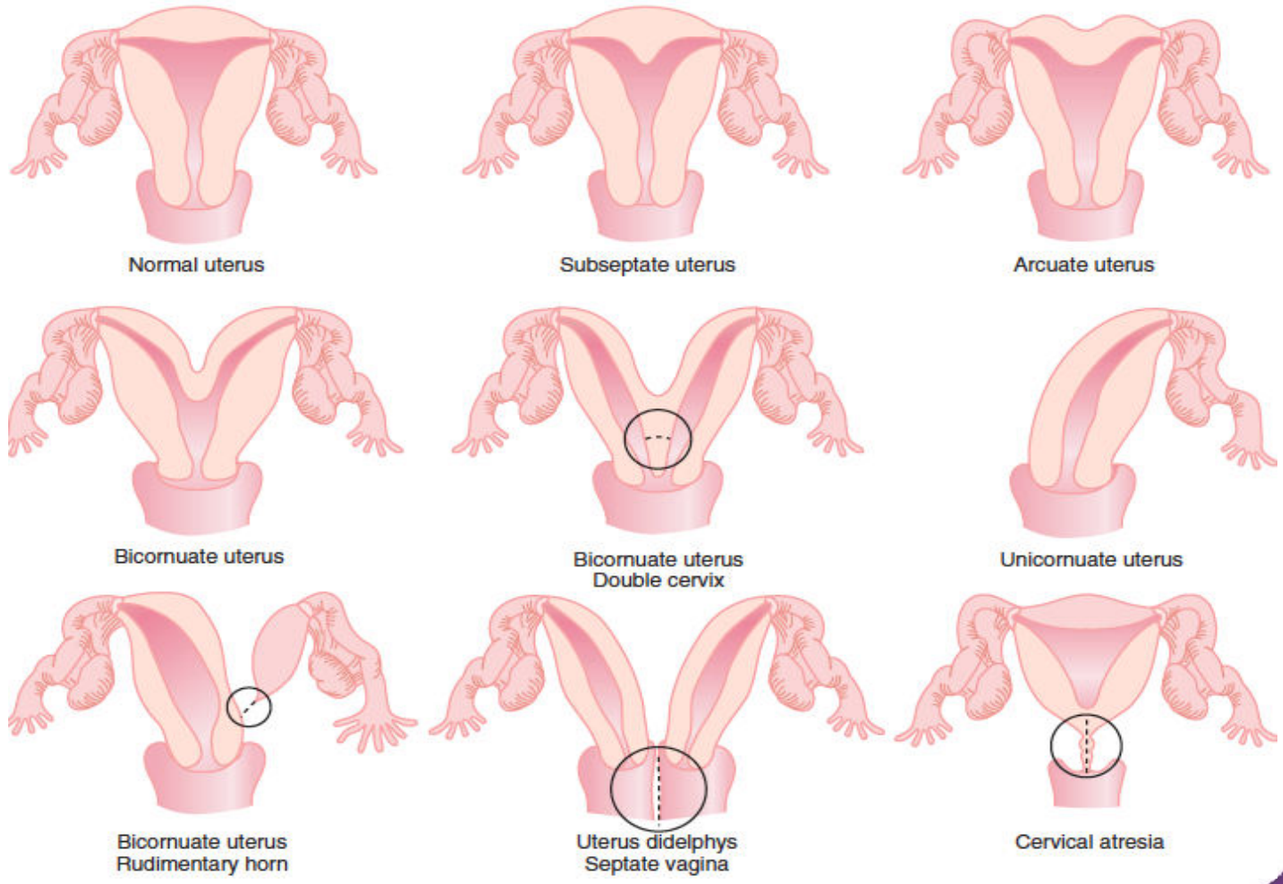
Early maternal exposure to certain drugs such as diethylstilbestrol(DES) which increase the risk of a small T-shaped endometrial cavity or cervical deformity.

- **Clinical Presentation:**

✓ **Patient present shortly after menarche** ⇨if there is obstruction to uterine blood flow
✓ Difficulty in intercorse ⇨ longitudinal vaginal septum
✓ Dysmenorrhea or menorrhagia
✓ Abnormality detected on D&C
✓ U/S, laparoscopy or laparotomy
✓ Palpable mass
✓ Complications of pregnancy

- **Investigations:**
- HSG-hysterosalpingogram-during infertility

or Recurrent Fetal Loss



*All of these conditions occur in normal karyotypic and phenotypic females

Types:	A. Uterus didelphys	B. Bicornuate uterus	C. Septate uterus	D. Unicornuate uterus	E. Unicurnuate with rudimentary horn
Cause	**failure of fusion of the two Mull ducts**	**Incomplete fusion of the two Mull ducts**	**Incomplete dissolution of the midline fusion**	**Failure of formation lead to development of only one Mull duct**	**<u>1) Noncommunicating horn 90%</u>** Present with: ✓ cyclic pelvic pain. ✓ Pelvic mass. ✓ **Ectopic pregnancy in the horn .** ✓ Endometriosis. Rx ⇨ **surgical excision**
Presentation	**two separate uterine bodies, each with its own cervix and attached fallopian tube and vagina.(Complete duplication)** ↑ pregnancy wastage	↑ pregnancy wastage	External contour of the uterus is normal but there is **intrauterine septum of varying length & thickness** Worst pregnancy outcome	Almost all patient have associated **single kidney.** ↑ pregnancy wastage	
Diagnosis	**HSG or at laparoscopy / laparotomy**		**HSG >shows 2 cavities laparoscopy> normal shape ouside**	**HSG or surgery**	**2) <u>Communicating horn :</u>** Present with **ectopic pregnancy in the rud horn** ↑ pregnancy wastage
Management	**<u>If affecting pregnancy outcome</u> ⇨ surgical correction (metroplasty)**		**Hysroscopic excision of the septum**	**<u>NO corrective surgery</u> ⇨** if pt has associated **cervix incompetence** ⇨ **<u>cervix cerclage*</u>**	

*“procedure in which stitches are used to close the cervix during pregnancy to help prevent pregnancy loss or premature birth”

Congenital Malformations of the Genital Tract :

3. DISORDERS OF VERTICALE FUSION OF THE MULLERIAN DUCTS

A. Vaginal Septum:	B. Cervix Agenisis / Dysgenisis: rare
• **Failure in the junction between the Mull, Tubercle & the urogenital sinus ⇨ could be very thick or thin**. • 85% in **upper two third of the vagina**. • Patient present **primary amenorrhea, hematocolpus*, mass or cyclic abdominal pain.** • ↑ incidence of endometriosis. • Rx ⇨ **surgical exision**.	• **complete lack of development of the paramesonephric system**. • Difficult, unsuccessful surgical correction . • Rx ⇨ hysterectomy .Because we can't create a functional cervix and the blood we accumulate in the uterus

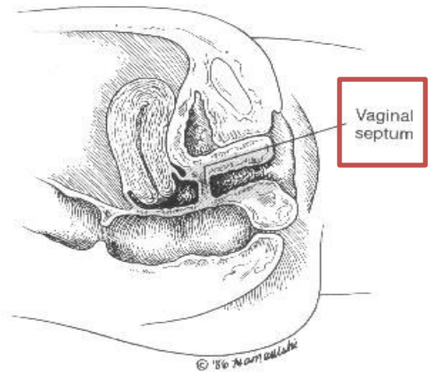
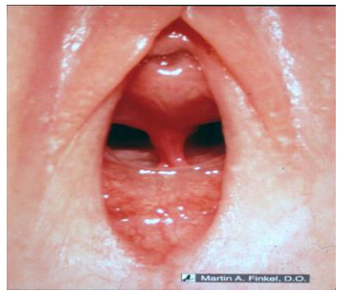


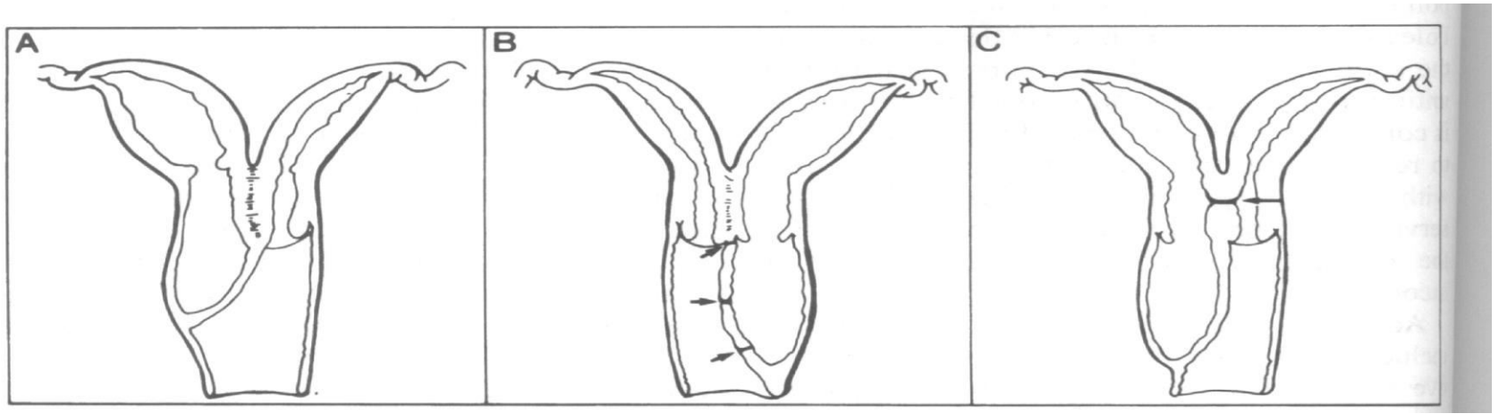
FIGURE 10-7
Diagram of transverse vaginal septum.



Before the surgical excision make sure it's just a vaginal septum not Uterus didelphys

- **UNUSUAL CONFIGRATION OF VERTICAL/LATERAL FUSION DEFECTS:**

✓ Combined lateral & verticle defects
✓ Do not fit in other categories
✓ EXAMPLE, **double uterus with obstructed hemi-vagina**



A-Complete vaginal obstruction Will cause hematocolpos and hematometra

B-Incomplete vaginal obstruction

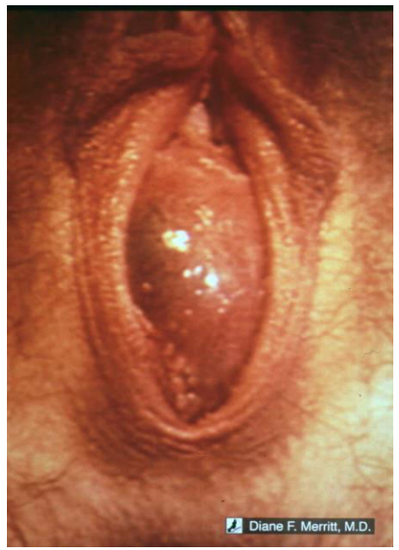
C-Complete vaginal obstruction with double uterus

***Hematocolpos:Collection of blood in the vagina.**
Hematometra: collection of blood in the uterus.

Congenital Malformations of the Genital Tract :

4. DEFECTS OF THE EXTERNAL GENITALIA:

Ambigious genitalia	Defects of the clitoris	Hermaphrodites	imperforate hymen:
• Most common cause : congenital adrenal hyperplasia.	• bifid clitoris : rare • Hypertrophied(Clitoromegaly)* ⇨ **androgen effect.** • Clitoral agenesis : result from the failure of the genital tubercle to develop • Incomplete development of the genitalia can result in a cloaca with no separation of the bladder and the vagina . *determined by the relative size of the clitoris in relation to the other vulvar structure	The presence of testicular and ovarian tissue in the same individual.	• the mildest form of these canalization abnormalities. • After birth, a **bulging, membrane-like structure may be noticed in the vestibule, usually blocking egress of mucus** and **a midline cystic mass on rectal examination** • An imperforate hymen should be suspected in adolescents who ***report monthly dysmenorrhea in the absence of vaginal bleeding (1ry amenorrhea)*** **or hematocolpus /hematometra** • Dx: Ultrasonography confirms the presence of **a normal uterus and ovaries.** • Rx: hymenectomy/**cruciate incision**



Mucocele: babies with imperforate hymen will have mucus collected in the vagina.
when there is bluish fluid collected behind the hymen then it is usually blood (at the age of menarche)

Intersexuality

Pseudo hermaphrodites: Male

1-Sex chromosome abnormality: Mosaicism associated with gonadal dysgenisis ⇨ 45XO/46XY

2-Testis incapable of producing testosterone

3-End organs incapable of utilizing testosterone eg. 5α reductase deficiency, failure of testosterone binding to receptors (androgen insensitivity)

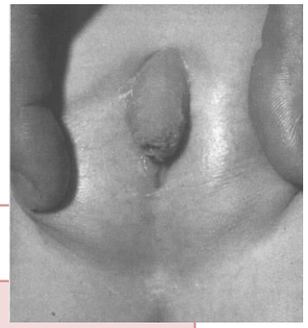
4-Defficient production of MIF ⇨ ♀ internal genital organs in other wise normal ♂

Pseudo hermaphrodites: Female

5-Musculanization of the ♀ external genitalia due to ↑↑ androgen eg. Congenital adrenal hyperplasia

True hermaphroditism ⇨ the presence of testicular & gonadal tissue in the same individual

Rarely 46XX male due to the presence of a gene the SRY gene (Sex determining Region Y)



1-MUSCULINIZED FEMAE (FEMALE PSEUDOHERMAPHRODITES): 46XX

-Exposed to androgens in utero ⍰ varying degrees of musculinization of the external genitalia

A-CONGENITAL ADRENAL HYPER PLASIA (CAH) The most common cause of female intersex

Deficiencies of the various enzymes required for **cortisol & aldosterone biosynthesis** (**21-hydroxylase (most common)** , 11β-hyroxilase ,3βhydroxisteroid dehydrogenase)

⇨ ✖cortisone &aldosterone,↑Androgen

✓ Affected **female** may present **at birth with ambiguous genitalia:**

- **Enlargement of the clitoris**
- **Excessive fusion of the genital folds obscuring the vagina & urethra**
- **Thickening and rugosity of the labia majora resembling the scrotum.**

✓A dangerous **salt losing syndrome** due to **deficiency of aldosterone** may occure .

✓ **Delayed menarche & menstrual irregularities**

INVESTIGATIONS:

✓ Karyotyping

✓ **↑17-α hydroxiprogestrone.**

✓ **17-ketosteroids** (androgens) in urine.

✓ Electrolytes

✓ U/S for internal organs

Management:

1. **Cortisol** or its synthetic derivatives (**hormone replacement**) ⇨ **suppress the adrenals⇨ lower androgen production.**
2. **Corrective surgery.**
   - ***Clitroplasty*** (at the **neonatal period** to reduce the size of it)
   - Division of the fused labiocsrotal folds to create the vagina (**delayed till puberty**)

B-EXPOSURE OF THE MOTHER TO ANDROGENS **Rare**

-**Androgen secreting tumours** , eg. Luteoma,arrhenoblastoma

-**Drugs**

2-UNDERMUSCULINIZED Male(Male PSEUDOHERMAPHRODITES)

A-ANATOMICAL TESTICULAR FAILURE:(testes are not developed at all or developed abnormally)

1.Normal chromosomes 46XY :

-Pure gonadal dysgenisis. (gonadal not devolped)
variable features – mild-severe
(normal female , female with mild musculinization)
*uterus present (if testes are not secreting MIF)

2.Mosaicism 45X/46XY :

Variable features:
(normal female, ambiguous genitalia, nearly normal male)

B-Enzymatic testicular failure :

- Enzymatic defects in the **biosynthesis of testosterone**
- Varying degrees of musculinization of the external genetalia
- **Uterus & tubes ⇨ absent** (**MIF produced by the testes**)

C-End-organ insensitivity

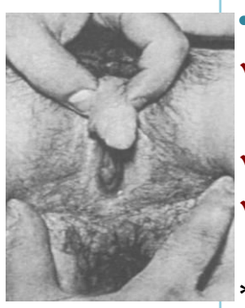
1.5α reductase deficiency (Autosomal recessive):

- Formation of **the male external genitalia** requires: **Testosterone**

5α REDUCTASE dihydrotestosterone

- Formation of the **internal wollfiane* structures** respond directly to **testosterone**
- **Clinical feature:**

✓ **External female genitalia with mild masculinization**
✓ **Absent uterus**
✓ **At puberty ⇨ ↑ testosterone secretion ⇨ virilization** (male 2dry characteristics)



*embryonic structures that develop into the internal male reproductive organs attached to the testicles

2.Androgen insensitivity (TESTICULAR FEMINIZATION): 46,XY

Complete (classical TF): *Lack of androgen receptors.*

✓ **Normal female external genitalia with blind vagina****.
✓ **Absent uterus.**
✓ **Breast development*****.
✓ **Present with 1ry amenorrhea.**
✓ **Testes found in abdomen (pelvic sidewalls) or inguinal canal.**
✓ **Normal male Testosterone level.**

Treatment:

✓ **Gonadectomy** after puberty due to ↑incidence of malignant change(5%).
✓ **Oestrogen replacement.**

incomplete androgen insinsitivity: Receptors are present but low in NO. or inactive.

✓ **Ambiguous genitalia with varying degrees.**
✓ **Breast development*****.
✓ **Musculinization at puberty.**

**(In utero, müllerian-inhibiting hormone (MIH) is produced, which results in absence of the uterus and fallopian tubes)
***(is caused by the testicular secretion of estrogens and by the conversion of circulating androgen to estrogens in the liver and elsewhere)

3-TRUE HERMAPHRODITES

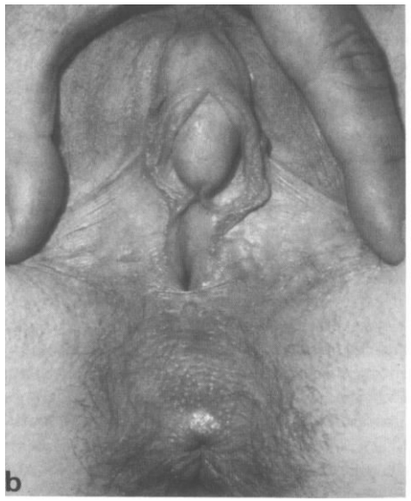
- The affected child has some degree of **both female and male development externally and internally.**
- Can occurs with:

✓ Ovo-testes on one side & ovary or testes on the other
✓ Ovary on one side & testes on the other
✓ Bilateral ovotestes

- Varying degrees of sexual ambiguity
- KARYOTYPING:
  - **-46XX ⇨ most common**
  - -46XX/XY
  - -46XY
  - -46XY/47XXY

Ex: Klinefelter Syndrome:

✓ **47XXY**
✓ **Normal male external genitalia**
✓ **Tall stature**
✓ **Gynecomastia**
✓ **Azospermia (infertility)**



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