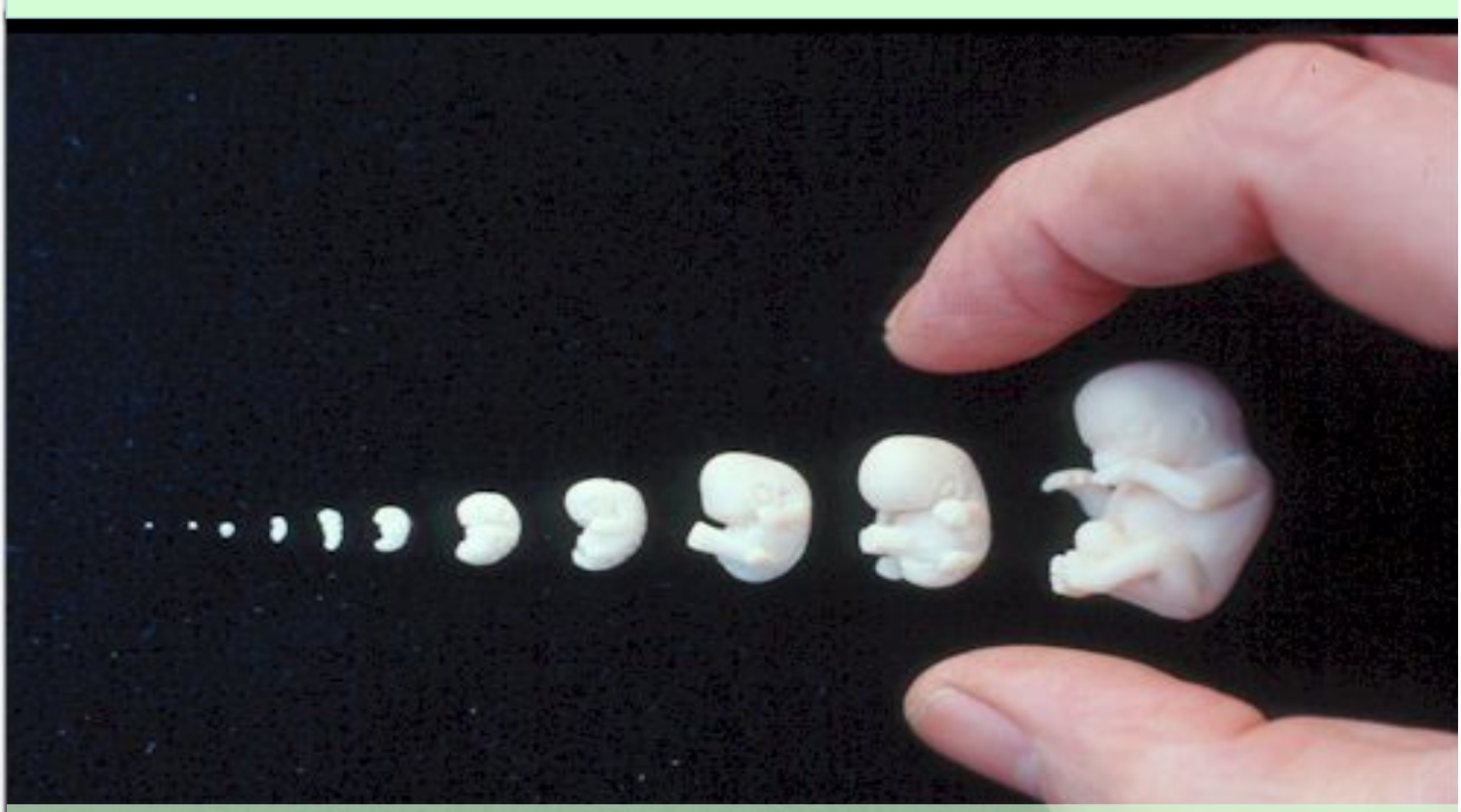


The Female Genital Tract; Embryology, Malformations and Intersex

Made by: Afnan Al-tamimi, Asma Al-Madhi and Dona Barakah

Sources: Hacker and Moore's Essentials of Ob/GYN, Slides and Wikipedia.

429 OB/GYN Team

EMBRYOLOGY OF THE FEMALE GENITAL TRACT

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.
- Male sexual development depends on the presence of functioning testes & responsive end organs.
- Females exposed to androgens in-utero will be musculanized.

EXTERNAL GENITAL ORGANS

1- THE UNDEFERENTIATED STAGE (4-8 WK)

The neutral genitalia includes:

1. Genital tubercle (phallus)
2. Labioscrotal swellings
3. Urogenital folds
4. Urogenital sinus

Before the 8th week of development, the appearance of the external genital area is the same in males and females.

Neutral genitalia are the primordia –origin- of the male and female external genitalia. In the next stage of development (sexual differentiation stage), neutral genitalia differentiate into male and female external genitalia (hence; the naming 'Neutral')

Primordia	*Female*	*Male*	*Major Determining Factors*
Urogenital sinus	▪ Vaginal contribution ▪ Skene's glands ▪ Bartholin's glands	▪ Prostate ▪ Prostatic utricle ▪ Cowper's glands	Presence or absence of testosterone, dihydrotestosterone (DHT), and 5α-reductase enzyme
Genital tubercle	Clitoris	Penis	
Urogenital folds	Labia minora	Corpora spongiosa	
Genital folds	Labia majora	Scrotum	

2- MALE AND FEMALE EXTERNAL GENITAL DEVELOPMENT (9-12 WK)

- By the 12th week of gestation, male and female genitalia start to be differentiated.
- In the absence of androgens; female external genitalia develop.
- The development of male genitalia requires the action of androgens, specifically DHT*.

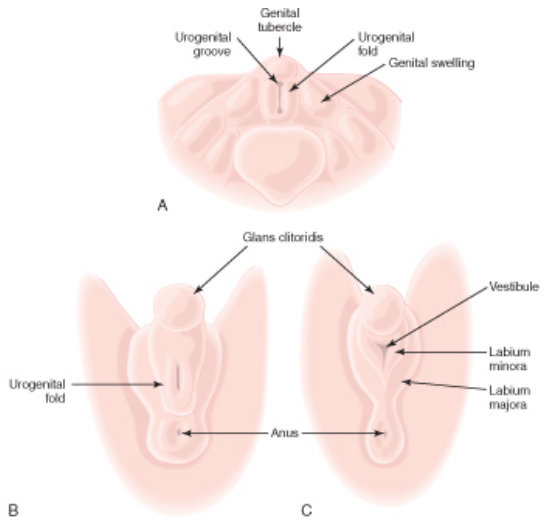
5-alpha reductase

Testosterone → DHT *Dihydrotestosterone.

Male genitalia require androgens.

If there is a deficiency in one of the androgens or enzymes required for their production, the male genitalia will fail to develop, or will develop abnormally.

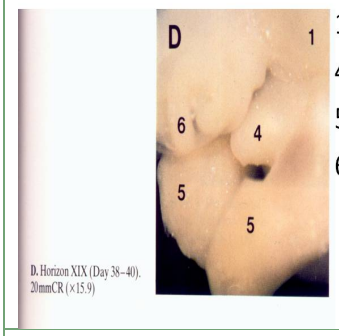
Sometimes, the defect is in the end-organ receptors (e.g. androgen insensitivity syndrome).



Development of the external female genitalia.
A: Indifferent stage (about 7 weeks). **B:** About 10 weeks.
C: About 12 weeks.

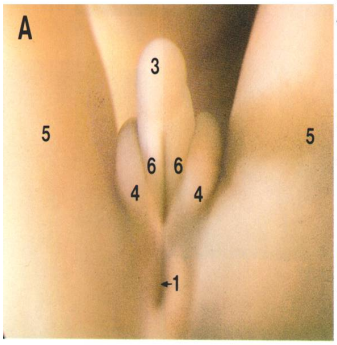
EXTERNAL GENITALIA

INDIFFERENT STAGE



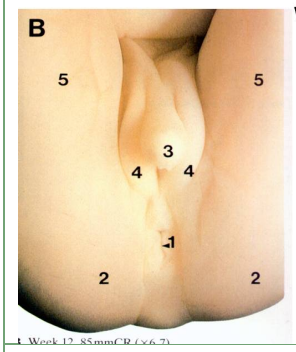
1-abdomen
4-genital tubercle
5-leg bud
6-midgut herniation to the umbilical cord

FEMALE EXTERNAL GENITALIA



Week 9
1-anus
2-buttocks
3-clitoris
4-labioscrotal swelling(labia majora)
5-leg
6-urogenital fold(labia minora)

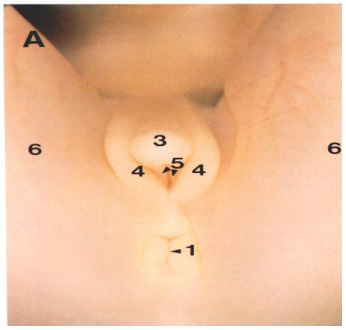
FEMALE EXTERNAL GENITALIA



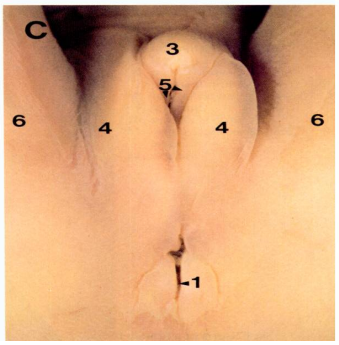
Week 12
1-anus
2-buttocks
3-clitoris
4-labioscrotal swelling(labia majora)
5-leg
6-urogenital fold(labia minora)

FEMALE EXTERNAL GENITALIA

Week 13
1-anus
2-buttocks
3-clitoris
4-labia majora
5-labia minora
6-leg

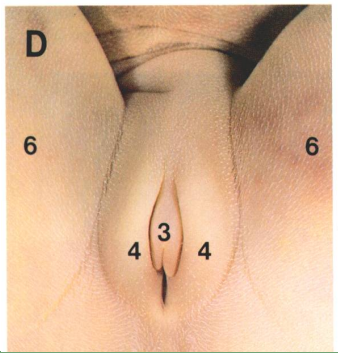


FEMALE EXTERNAL GENITALIA



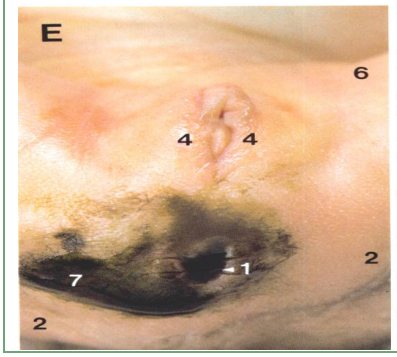
Week 17
1-anus
2-buttocks
3-clitoris
4-labia majora
5-labia minora
6-leg

FEMALE EXTERNAL GENITALIA



Week 20
1-anus
2-buttocks
3-clitoris
4-labia majora
5-labia minora
6-leg

FEMALE EXTERNAL GENITALIA

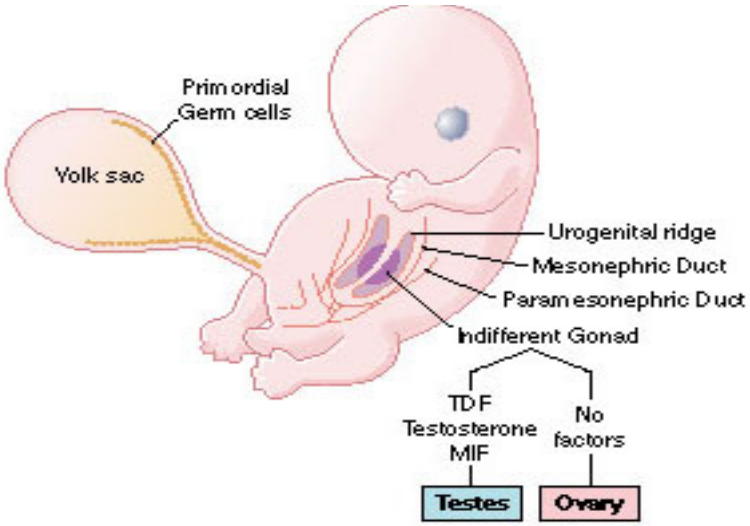


Week 35
1-anus
2-buttocks
3-clitoris
4-labia majora
5-labia minora
6-leg
7-meconium

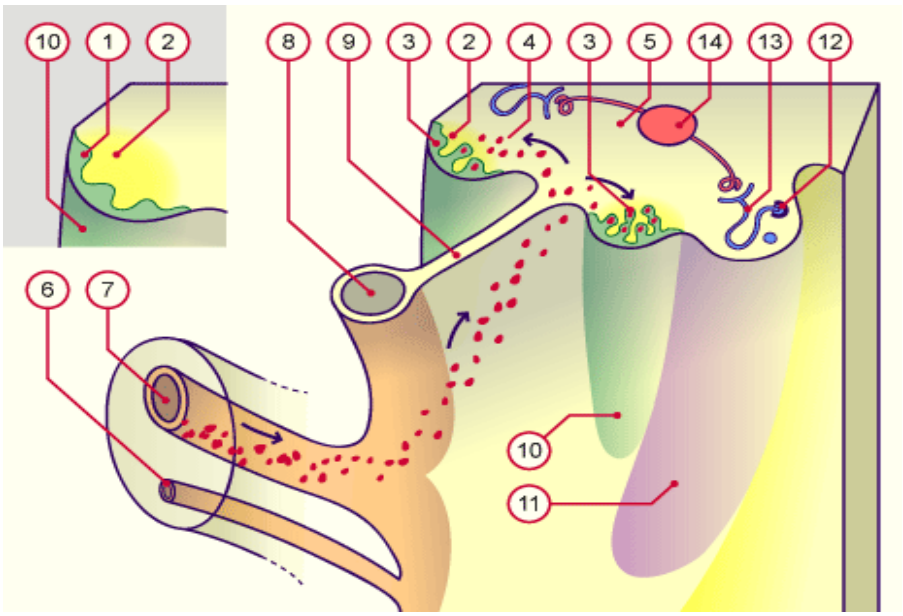
INTERNAL GENITAL ORGANS

1-GONADS

- **Undifferentiated gonads initiate its development on the 5th wk.**



In this picture 5 weeks embryo, the lining of the abdomen, which is illustrated in light purple, is one of the mesodermal ridges, which are called urogenital ridges
The smaller portion, which is illustrated by dark purple, is the part that will develop into a gonad but it have no gamat cells (germ cells).



- *The gamete (germ cells) originate in the lining of the yolk sac, which is the endoderm.*
- *Afterward; it migrate to the genital ridge*

1 Coelomic epithelium
2 Local mesenchyma (in proliferation)
3 Gonadal cord
4 Primordial germ cells (PGC)
5 Mesenchyma
6 Allantois
7 Omphalomesenteric duct
8 Intestine
9 Dorsal mesentery
10 Genital ridge
11 Nephrogenic cord
12 Mesonephric duct (Wolff)
13 Mesonephric tubule
14 Aorta

- **Development of Female Internal Genitalia:**
  - Requires the absence of:
  1. Androgens
  2. Mullerian inhibiting factor
  3. Inductor substance

  - In the absence of these 3 substances, the Mullerian ducts develop into the female internal genitalia, and the Wolffian duct regresses.

  - In the absence of the Y chromosome the undifferentiated gonad will leave it to develop into an ovary.

  - In a 45XO embryo, the ovaries develop; but they will undergo atresia → streak ovaries.

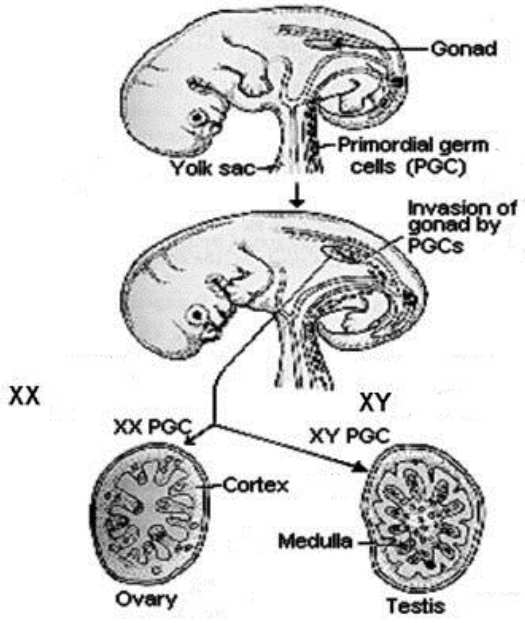
  - The gonads develop from the mesothelium on the genital ridge → primaryry sex cords grow into the mesenchyme → outer cortex & inner medulla.

  - The ovary develop from the cortex & the medulla regress
  - The testis develop from the medulla & the cortex regress
  - The ovary contains 2 million 1ry oocytes at birth

In the presence of a Y chromosome, the gonad will develop into testis while in the absence of this chromosome, it will become an ovary
(becoming an ovary is not because of the presence of the X chromosome but because of the absence of the Y chromosome)

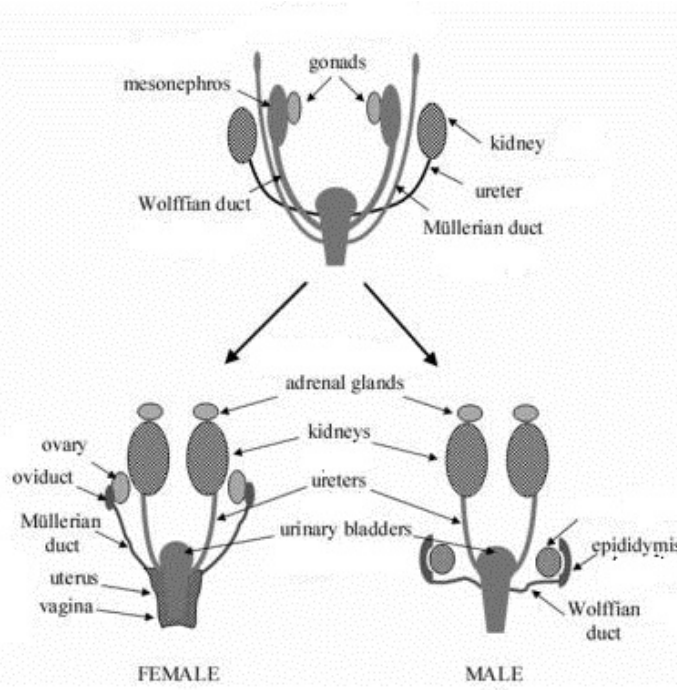
Why is that? The Y chromosome have a gene called SRY (Sex-determining Region Y) gene which codes for Testis Determining Factor (TDF) substance

The gonad is preprogramed to be an ovary unless there is TDF then it will become testes.



2-UTERUS & FALLOPIAN TUBES

- Happens through a process of 3:
  - Invagination of the coelomic epithelium on the craniolateral end of the mesonephric ridge → Paramesonephric ducts
  - Fusion of the two PMN ducts (mullerian ducts) → uterus, cervix & Fallopian tubes (at 8-11 wk.) (http://embryology.med.unsw.edu.au/Movies/genital/uterus2.mov)
  - 12-16 wks. → Proliferation of the mesoderm around the fused lower part → muscular wall
- **In the male fetus:** the testis secretes the mullerian inhibiting factor → regression of the mullerian ducts fusion

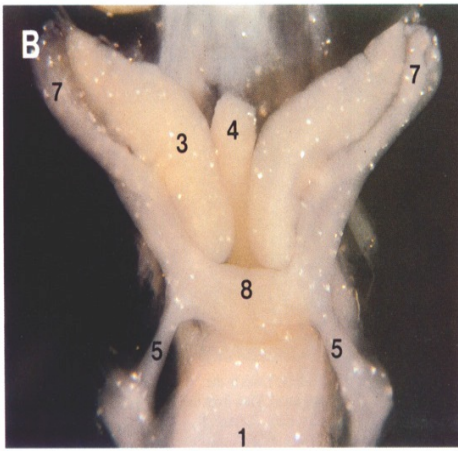


3-VAGINA

- The caudal ends of the mullerian ducts form the mullerian tubercle at the dorsal wall of the urogenital sinus
- Mullerian tubercle is obliterated → vaginal plate → 16-18 wk. the central core breaks down => vaginal lumen
- The upper 2/3 of the vagina → formed by → mullerian tubercle
- The lower 1/3 → urogenital Sinus

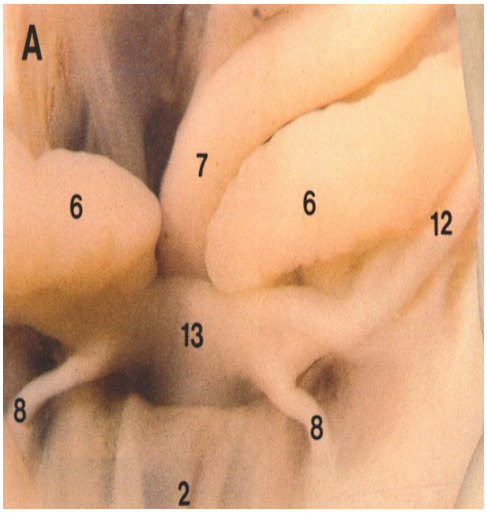
Week 8

1-bladder
2-kidney
3-ovary
4-rectum
5-round Ligament of the uterus
6-adrenal gland
7-Fallopian tube
8-utero vaginal primordium



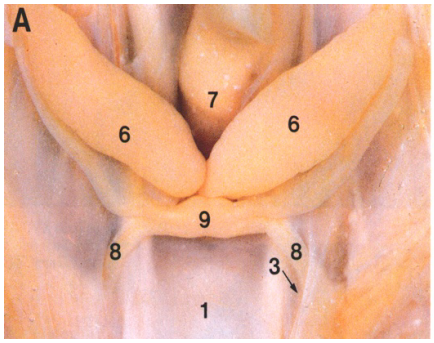
Week 9

2-bladder
6-ovary
7-rectum
8-round ligaments
12-uterine tube
13-uterovaginal primordium



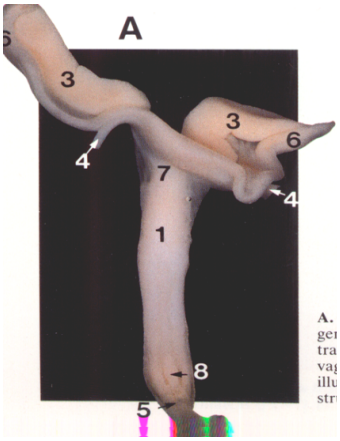
Week 15

1-bladder
2-clitoris
3-vaginal process
4-labia majora
5-leg
6-ovary
7-rectum
8-uterine round ligament
9-uterovaginal primordium

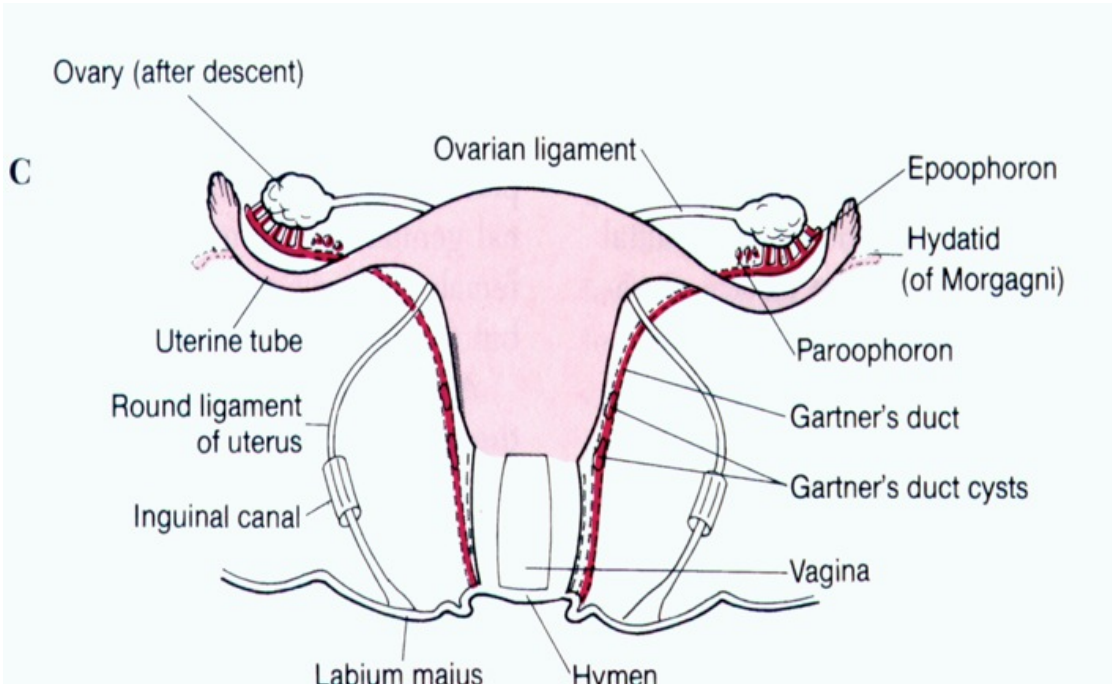


Week 13

(Dissected genital tract)
1-body of uterus
2-clitoris
3-ovary
4-round ligament
5-solid epithelium (vagina meets the urogenital sinus)
6-fallopian tube
7-uterus
8-vagina



FEMALE INTERNAL GENITAL ORGANS (IN A NEWBORN)



CONGENITAL MALFORMATIONS

MULLERIAN DEFECTS

1) MULLERIAN AGENESIS

- It is a congenital malformation characterized by:
    - A failure of the müllerian ducts to develop
    - This results in a missing uterus, cervix and variable malformations of the upper portion of the vagina.
    - The ovaries and the fallobian tubes are present.
- It is the second most common cause of primary amenorrhea after gonadal failure (such as from Turner syndrome).
- The condition is also called **MRKH** or **Mayer-Rokitansky-Küster-Hauser Syndrome**, named after four scientists.
- The patient will be:
    - Normal 46XX female with normal *external genitalia*
    - Have a normal hormonal profile due to normal ovaries
    - Have short vaginas and may present with dyspareunia
    - Present with Amenorrhea
    - As there is no uterus; she may not be able to carry a pregnancy unless through IVF and surrogacy (get an another woman to carry and deliver her child)
    - 47% have associated urinary tract anomalies
    - 12% have associated skeletal anomalies
- Treatment:
    - Psychological Counseling
    - Surgery; ***Vaginoplasty***, *excision of uterine remnants (if they were functional) and Vaginal Dilators*

2) DISORDERS OF 'LATERAL FUSION' OF MULLERIAN DUCTS

INCIDENCES

- A prevalence of 0.1-2%
- Most patients can conceive without difficulty, but it still remains the reason to 4% of infertile patents and 6-10% of patients with recurrent abortions.
- Having such disorders, will increase the incidence of:
    - Recurrent abortions
    - Premature birth
    - Fetal Loss
    - Fetal Malpresentations
    - C-sections
    - Cervical incompetence

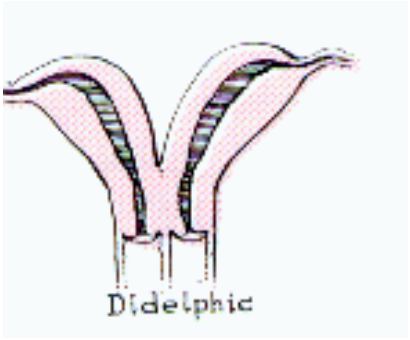
CLINICAL PRESENTATION

- Patients present shortly after menarche (if there was an obstruction to the uterine blood flow)
- Longitudinal Vaginal Septum → difficulty in intercourse
- Dysmenorrhea or menorrhagia
- When doing D & C; abnormalities will be detected
- Diagnosed by US, laparoscopies or laparotomies

- Palpable mass on examination
- Complications of pregnancy result
- Infertility and Rapid Fetal Loss (RFL) investigations → Hysterosalpingogram (HSG) → detected

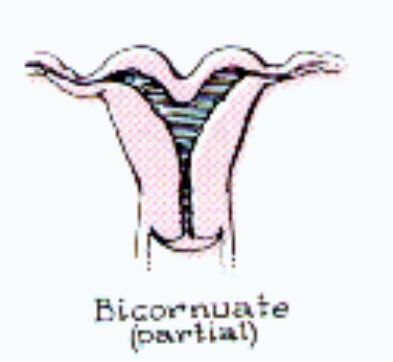
TYPES

1. *Uterus Didelphus*



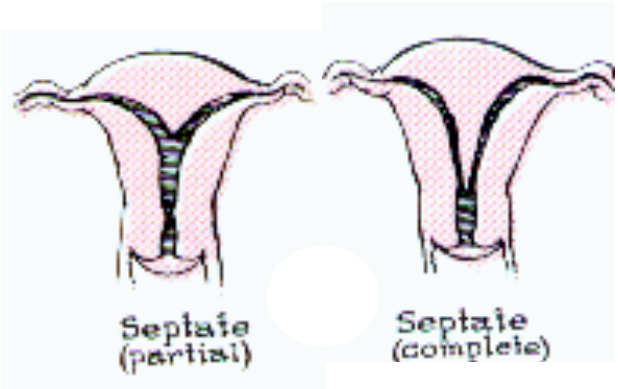
- *The two mullerian ducts fail to fuse;*
- *Complete duplication of the uterus, cervix and vagina*
- *Each uterus has a single horn linked to the ipsilateral fallopian tube that faces its ovary.*
- *Presentation:*
  - *Asymptomatic*
  - *Reproductive problems and pregnancies will be lost → diagnosis is by transvaginal examination, HSF, laparotomy or laparoscopy.*
  - *It is important to differentiate it from vaginal septum (as a septum's treatment is removal, which doesn't work in didelphus).*
- *Treatment;* ***Metroplasty*** *(surgical correction, if it affects pregnancies outcome)*

2. *Biconrnuate Uterus*



- *The two mullerian ducts fuse, but incompletely.*
- *Only upper part fusion is altered.*
- *Results in a heart-shaped uterus.*
- *Considered as an incomplete didalphus.*
- *It has a single vagina and cervix, and two-horns of the upper part of the uterus.*
- *Its presentation, diagnosis and treatment are same.*

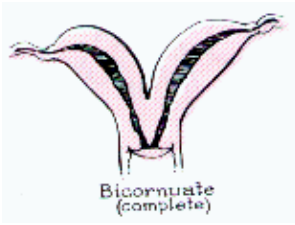
3. *Septate Uterus*



- *The uterine cavity is partitioned by a longitudinal septum with a varying length and thickness.*
- *The outside of the uterus has a normal typical shape.*
- *This partition may involve only the superior part of the cavity (incomplete septum), or a subseptate uterus, or less frequently the total length of the (complete septum) and a double cervix.*
- *The septation may also continue caudally into the resulting in a "double vagina".*
- *Patients present with worst outcomes*
- *Treatment;* ***hysteroscopic excision of the septum***

4. *Unicornuate Uterus*

- *Results from the development of only one mullerian duct while the other mullerian duct remains in a rudimentary state.*
- *It is sometimes called hemi-uterus has a single horn linked to the ipsilateral fallopian tube that faces its ovary.*
- *A unicornuate uterus has a single cervix and vagina.*
- *Almost all the patients have associated single kidney.*
- *Presentation:*
  - *May be asymptomatic; normal pregnancy may occur.*
  - *While other patients are at a higher risk for pregnancy loss.*
  - *Similar to patients with didelphic uteri in pregnancy outcome.*
- *Diagnosed by HSG or surgery no corrective surgical treatment is available*
- *When cervical incompetence occurs, it is corrected by "cervical cerclage".*



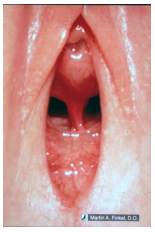
5. *Unicornuate with a Rudimentary Horn*

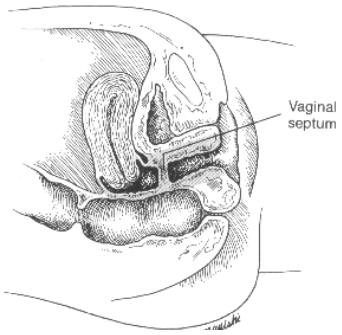
- **Non-communicating horn 90%**
  - *Present with cyclic pelvic pain, mass, ectopic pregnancy in the rudimentary horn or endometriosis.*
  - *Treatment; surgical excision*
- **Communicating horn**
  - *Present with ectopic pregnancy in the rudimentary horn*
  - *There's an increased pregnancy wastage*

3) DISORDERS OF 'VERTICAL FUSION' OF MULLERIAN DUCTS

VAGINAL SEPTUM

- A longitudinal vaginal septum develops during embryogenesis when there is an incomplete fusion of the lower parts of the two mullerian ducts
- The mullerian tubercle and the urogenital sinus fail to join
- As a result, there's a double vagina that could be very thick or thin
- 85% of it is in the upper two third of the vagina
- Presentation:
  - Primary amenorrhea
  - Hematocolpus or a mass
  - Cyclic abdominal pain
- Incidence of endometriosis increases along with it
- Treatment; surgical excision.



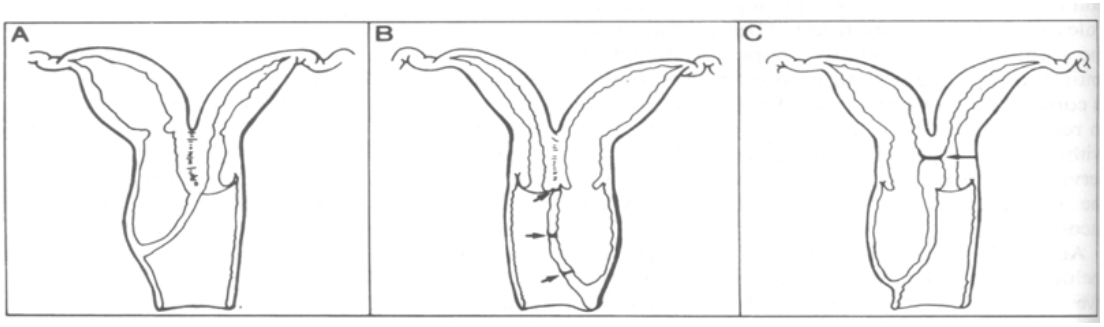


CERVICAL AGENESIS/DYSGENESIS

- A very rare condition
- Treatment; Hysterectomy (surgical correction is difficult and unsuccessful).

4) UNUSUAL CONFIGURATION OF 'VERTICAL/LATERAL FUSION' DEFECTS

- Combined lateral and vertical defects that doesn't fit in other categories
- Examples; double uterus with an obstructed hemivagina.



A- complete vaginal obstruction. B- incomplete vaginal obstruction. C- completed obstruction with a common double uterus

EXTERNAL-GENITALIA DEFECTS

AMBIGUOUS GENITALIA

- Congenital adrenal hyperplasia is a cause
- Hermaphrodites is another

DEFECTS OF CLITORIS

- An uncommon condition called bifid clitoris
- Clitoromegaly; a hypertrophied clitoris due to androgen excess' effect

IMPERFORATE HYMEN

- The hymen normally forms at the junction of the urogenital sinus and the sinovaginal bulbs.
- Presentation:
  - Primary amenorrhea
  - Cyclic abdominal pain
  - Hematocolpus or hematometria
- Treatment; a cruciate incision made in the middle of the hymen to open up for menstrual blood.

INTERSEXUALITY

DEFINITION

An abnormal sexual development.

It is the presence of intermediate or atypical combinations of physical features that usually distinguish female from male. This is usually understood to be congenital, involving chromosomal, morphologic, genital and/or gonadal anomalies, such as diversion from typical XX-female or XY-male presentations, genital ambiguity, or sex developmental differences e.g. phenotype is opposite to the genotype.

CAUSES

1. SEX CHROMOSOME ABNORMALITY

Mosaicism associated with gonadal dysgenisis , e.g. Turner syndrome: **turner mosaicim (45XO/46XY).**

2. TESTIS IS INCAPABLE OF PRODUCING TESTOSTERONE

e.g. **Testosterone Biosynthetic Defects:**

Testosterone is produced from cholesterol through a number of biochemical conversions. In some individuals, one of the enzymes needed for these conversions is deficient. In such cases, patients are unable to make normal amounts of testosterone despite the presence of a testis. Testosterone Biosynthetic Defects affect 46,XY individuals and can be complete or partial, which leads to newborns who appear either completely female or ambiguous, respectively.
46XY → testis develop → Testosterone Biosynthetic Defect → **no androgens** due to enzyme deficiency → **Wolffian Ducts regress** → **MIF produced normally** → Mullerian Ducts regress → **external genitalia are female**

3. END ORGANS INCAPABLE OF UTILIZING TESTOSTERONE

e.g. **5α reductase** deficiency → failure of testosterone binding to **receptors** (**androgen insensitivity**).

46 XY → testes develop →Testosterone produced but no DHT produced → Wolffian Ducts develop →MIF produced normally →Mullerian Ducts regress →ambiguous external genitalia

4. DEFICIENT PRODUCTION OF MIF (Mullerian Inhibiting Factor)

Female internal genital organs (uterus & tubes) in an otherwise **normal Male**.

Persistent müllerian duct syndrome (PMDS) is a form of **internal male pseudo-hermaphroditism** caused by a deficiency of müllerian-inhibiting factor (MIF). Müllerian derivatives (i.e., fallopian tubes, uterus, upper part of the vagina) are present in otherwise normal; 46 XY male.
PMDS **patients are both karyotypically and phenotypically male, with normal development of secondary sex characteristics.** That's why the diagnosis is made after **incidental finding** in most of the cases.

5. MUSCULANIZATION OF THE FEMALE EXTERNAL GENITALIA

Due to **high androgen** levels, e.g. **Congenital adrenal hyperplasia** (CAH) and exposure to androgens in utero.

The patient is female (46 XX), has ovaries and female internal organs, but externally she looks like a male (enlarged clitoris , fusion of labioscrotal folds, hypospadiac urethral meatus, hirsutism…etc).

46XX → ovaries develop → Mullerian Ducts develop → excessive adrenal (or exogenous) androgens → ambiguous external genitalia

6. (46 XX) MALE

Due to the presence of a gene, the **SRY gene** (**S**ex determining **R**egion **Y**).

46 XX male syndrome (also called de la Chapelle syndrome, for a researcher who characterized it in 1972) is a rare sex chromosomal disorder. Usually it is caused by **unequal crossing over between X and Y-chromosomes** during **meiosis in the father**, which results in the **X-chromosome containing** the normally male **SRY gene**. When this X combines with a normal X from the mother during fertilization, the result is an XX male.

SRY (**S**ex-determining **R**egion **Y**) is a sex-determining gene on the **Y-chromosome**. This gene encodes a transcription factor for a protein called the **"SRY protein"** which initiates **male sex determination**. **Translocation** of part of the **Y-chromosome containing this gene to the X-chromosome causes XX male syndrome.**

7. TRUE HERMAPHRODITISM

The presence of **BOTH** testicular & ovarian tissue in the **same individual**.
E.g. Klinefelter's syndrome (47 XXY).

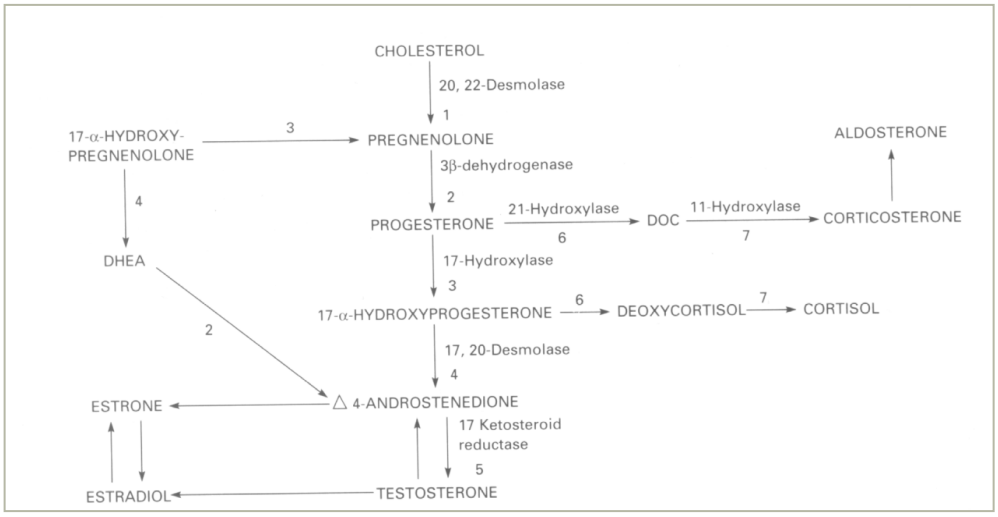
CONDITIONS

1. MUSCULINIZED PSEUDOHERMAPHRODITES ♀ (FEMALE PSEUDOHERMAPHRODITES)

- 46 XX Female + has ovaries.
- Cause: The female baby was 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.
- Causes are due to; **Deficiencies** of the various enzymes required for cortisol & aldosterone biosynthesis (**21-hydroxylase, 11β-hyroxilase** and **3βhydroxisteroid dehydrogenase**).
- 21-hydroxylase deficiencies is the commonest defect 90%.
- A dangerous salt losing syndrome due to deficiency of aldosterone may occur in some patients.
- Delayed menarche & menstrual irregularities (depending on the degree of musculinization).



❖ PRESENTATION

- Affected females ♀ may present **at birth** with:
  - Ambiguous genitalia
  - Enlargement of the clitoris
  - Excessive fusion of the genital folds obscuring the vagina & urethra
  - Thickening & rugosity of the labia majora resembling the scrotum

❖ INVESTIGATIONS

- Karyotyping.
- 17-α-hydroxiprogestrone levels (will be high).
- 17-ketosteroids (androgens) in urine.
- Electrolytes.
- US

❖ TREATMENT

- Cortisol or its synthetic derivatives → suppress the adrenals → less androgen production.
- Corrective surgery:
  - Clitroplasty (neonatal period).
  - Division of the fused labial folds (delayed till puberty).

B. EXPOSURE OF THE MOTHER TO ANDROGENS

- Rare
- Happens due to:
  - Androgen secreting tumors , e.g. luteoma, arrhenoblastoma.
  - Drugs
- Musculanization of female child; with a mother whom is exposed to methyl testosterone.

2. UNDERMUSCULINIZED PSEUDOHERMAPHRODITES♂(Male Pseudohermaphrodites)

A. ANATOMICAL TESTICULAR FAILURE

❖ PURE GONADAL DYSGENISIS

- Normal chromosomes 46XY
- Variable features – severe - mild (normal ♀ , ♀ with mild musculinization)
- Uterus present

❖ MOSAICISM 45X/46XY

- Variable features (normal ♀, ambiguous genitalia, nearly normal ♂)

B. ENZYMETIC TESTICULAR FAILURE

❖ ENZYMETIC DEFECTS IN THE BIOSYNTHESIS OF TESTOSTERONE

- These defects are usually incomplete → Varying degrees of musculinization of the external genetalia.
- Uterus & tubes are absent (MIF produced by the testes)

C. ENDORGAN INSINSITIVITY

❖ 5-ALPHA REDUCTASE DEFICIENCY

1. Autosomal recessive
2. Formation of the ♂ external genitalia requires 5α REDUCTASE.
3. Testosterone converted to dihydrotestosterone by this enzyme.
4. Formation of the internal wolffian structures respond directly to testosterone
5. External genitalia ♀ with mild musculinization
6. Absent uterus (because of MIF).
7. At puberty → increased testosterone secretion → virilization

❖ COMPLETE ANDROGEN INSENSITIVITY (testicular feminization)

ETIOLOGY:

- Lack of androgen receptors → complete (classical TF).
- Receptors are present but low in number or inactive → incomplete androgen insensitivity.

CLINICAL FEATURES (in complete androgen insensitivity):

1. Normal Female ♀ external genitalia with blind vagina.
2. **Absent uterus** (due to MIF produced by testes).
3. **Breast** development.
4. Present with **primary amenorrhea**. (because of their external appearance they are considered females until investigations reveals the truth !)
5. **Testes found** in abdomen or inguinal canal.
6. Normal ♂ Testosterone level.

TREATMENT:

- Gonadectomy after puberty due to increased incidence of malignant changes (5%)
- Estrogen replacement

❖ *INCOMPLETE ANDROGEN INSINSITIVITY*

- Ambiguous genitalia with varying degrees
- Breast development
- Musculinization at puberty

3. TRUE HERMAPHRODITES

❖ *HAVE BOTH OVARIAN & TESTICULAR TISSUE:*

- Ovotestis 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

❖ *KLINEFELTER SYNDROME*

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