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Embryology of the Female Genital Organs

Objectives:

- 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).
- Identify the incidence, clinical presentation, complication and management of the various types of congenital tract malformation including:
    a) Mullerian agenesis
    b) Disorder of lateral fusion of the mullerian ducts
    c) Disorder of the ventricle fusion of the mullerian ducts
    d) Defects of the external genitalia.
- List the steps that determine the sexual differentiation into male or female during embryonic development.
- List the causes of abnormal sexual development
- List the types of intersex
- Discuss the various types of intersex in term of clinical presentation, differential diagnosis and management.

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Embryology of the Female Genital Organs

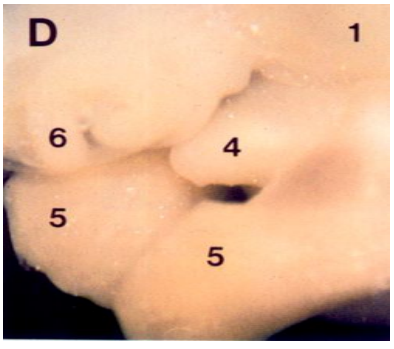
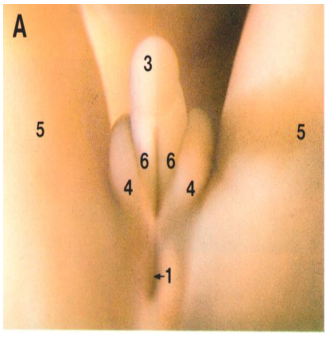
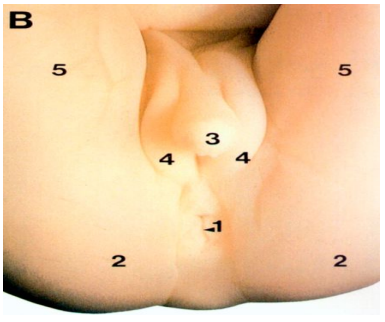
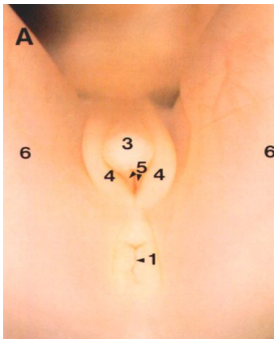
Sexual Differentiation

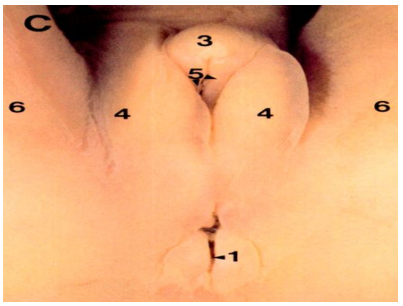
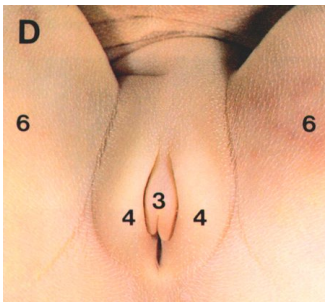
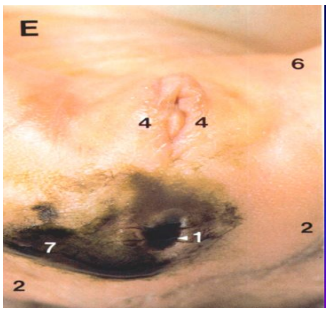
- The first step in sexual differentiation is the determination of genetic sex (XX or XY)

Females	Males
- Sexual development does not depend on the presence of ovaries (it depends upon the **absence of androgenic effect** to form the female genital tract) - If exposed to androgens in-utero will be musculanized (As in congenital adrenal hyperplasia and androgen secreting tumors of the mother or fetus) - The **masculinization** will occur in the **external genitalia despite an XX chromosome** , in other words androgenic masculinization will form ambiguous genitalia	- Sexual development depends on the presence of functioning testes and responsive end organs - The male sexual development depends upon the presence of androgens, testosterone , and functional receptors

Female External Genitalia

Undifferentiated Stage	Male & Female Genital Development
- **4-8 Weeks** - The neutral genitalia includes: - Genital tubercle (phalus) - Labioscrotal swellings - Urogenital folds - Urogenital sinus	- **9-12 Weeks** - By 12 weeks gestation male & female 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.

e 			
Indifferent Stage 1- Abdomen 4- Genital Tubercle 5- Leg bud 6- Midgut herniation to the umbilical cord	**Week 9** 1- Anus 2- Buttocks 3- Clitoris 4- Labioscrotal swelling (Labia majora) 5- Leg 6- Urogenital fold (Labia minora)	**Week 12** 1- Anus 2- Buttocks 3- Clitoris 4- Labioscrotal Swelling (Labia majora) 5- Leg 6- Urogenital fold	**Week 13** 1- Anus 2- Buttocks 3- Clitoris 4- Labia majora 5- Labia minora 6- Leg

			—
Week 17 1- Anus 2- Buttocks 3- Clitoris 4- Labia majora 5- Labia Minora 6- Leg	**Week 20** 1- Anus 2- Buttocks 3- Clitoris 4- Labia majora 5- Labia Minora 6- Leg	**Week 35** 1- Anus 2- Buttocks 3- Clitoris 4- Labia majora 5- Labia minora 6- Leg 7- Meconium	—

Female Internal Genitalia

Gonads	- Undifferentiated gonads begin to develop on the 5th wk - So if you are asked "When is the beginning of testicular or ovarian development?" at the beginning of the 5th week - Germ cells originate in the yolk sac & migrate to the genital ridge - In the absence of Y chromosome the undifferentiated gonad develops into an ovary - 45XO embryo the ovaries develop but undergo atresia → streak ovaries - The gonads develop from the mesothelium on the genital ridge → 1ry sex cords grow into the mesenchyme → outer cortex & inner medulla - **The ovary develops from the cortex & the medulla regress** - **The testes develop from the medulla & the cortex regress** - The development of the testes requires the presence of SRY gene (Sex Determining Region Y) found on Y chromosomes - The Ovary Contains 2 Million 1ry oocytes at birth.
Uterus & Fallopian Tubes	- 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 (8-11 wk), upper ⅔ of vagina - 12-16 wks → proliferation of the mesoderm around the fused lower part → muscular wall - In the male fetus the testes secretes mullerian inhibiting factor → regression of the mullerian ducts. - So if there is destruction of the testes for whatever reason , or if there is testicular agenesis--> no MIF -->you will have an individual with XY chromosomes but with a uterus and Fallopian tubes - It is important to remember that a functional or anatomic defect in the testes will lead to a deficiency in MIF!!
Vagina	- The caudal ends of the mullerian ducts from 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 doctor said that the following two points are IMPORTANT TO KNOW: - The upper ⅔ of the vagina → formed by mullerian tubercle - The lower ⅓ → urogenital sinus

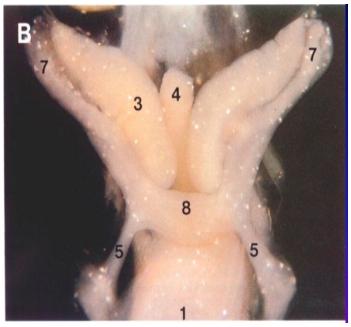
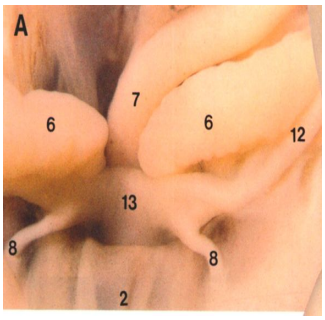
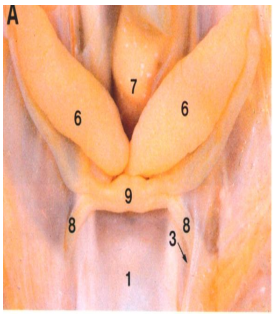
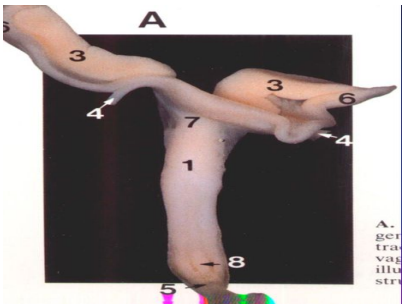
			
Week 8 1- Bladder 2- Kidney 3- Ovary 4- Rectum 5- Round ligament of the uterus 6- Adrenal gland 7- Fallopian tube 8- Utero vaginal primordium	**Week 9** 2- Bladder 6- Ovary 7- Rectum 8- Round ligament 12- Uterine tube 13- Uterovaginal primordium	**Week 15** 1- Bladder 2- Clitoris 3- Vaginal process 4- 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 urogenital sinus) 6- Fallopian tube 7- Uterus 8- Vagina

TABLE 1-2
Male and Female Derivatives of Embryonic Urogenital Structures

Embryonic Structure	Derivatives	
	Male	Female
Labioscrotal swellings	Scrotum	Labia majora
Urogenital folds	Ventral portion of penis	Labia minora
Phallus	Penis	Clitoris
	Glans, corpora cavernosa penis, and corpus spongiosum	Glans, corpora cavernosa, bulb of the vestibule
Urogenital sinus	Urinary bladder Prostate gland Prostatic utricle Bulbourethral glands Seminal colliculus	Urinary bladder Urethral and paraurethral glands Vagina Greater vestibular glands Hymen
Paramesonephric duct	Appendix of testes	Hydatid of Morgagni Uterus and cervix Fallopian tubes
Mesonephric duct	Appendix of epididymis Ductus of epididymis Ductus deferens Ejaculatory duct and seminal vesicle	Appendix vesiculosis Duct of epoophoron Gartner's duct
Metanephric duct	Ureter, renal pelvis, calyces, and collecting system	Ureter, renal pelvis, calyces, and collecting system
Mesonephric tubules	Ductuli efferentes Paradidymis	Epoophoron Paroophoron
Undifferentiated gonad	Testis	Ovary
Cortex	Seminiferous tubules	Ovarian follicles
Medulla	—	Medulla
	Rete testis	Rete ovarii
Gubernaculum	Gubernaculum testis	Round ligament of uterus

Congenital Malformations of the Female Genital Tract

1. Mullerian Agenesis:

- Mayer- Rokitansky-Kuster-Huser Syndrome (unknown etiology)
- Failure of mullerian duct development → **absence** of the upper vagina, cervix and uterus (uterine remnants may be found)
- The uterine remnant may menstruate which will lead to the formation of a blood filled mass which must be removed !
- The ovaries & fallopian tubes are **present**
- Normal secondary characteristics (ex: normal breast development) indicate normal ovaries
- Normal 46XX female with normal external genitalia
- Pt presents with 1ry amenorrhea
- 47% have associated urinary tract anomalies (due to close proximity with genital tract), 12% skeletal anomalies.
- You must check for any renal anomalies (ex : single kidney) in these patients due to their common occurrence in these patients
- Urinary tract anomalies are detected by ULTRASOUND!
- If the patient presents with primary amenorrhea with normal secondary characteristics(normal breast development)---> the first thing you have to do is a CHROMOSOMAL ANALYSIS
- WHY? To differentiate androgen insensitivity syndrome which are XY from Rokitansky-Kuster-Huser syndrome which are XX!!
- Treatment → - Psychological counseling
  - Surgical→ Vaginoplasty, Vaginal dilators,
- Because these patients have vaginal agenesis of the upper two thirds of the vagina --> patient's vagina is too small for intercourse --> vaginoplasty or dilators are necessary for these patients to be able to have sexual intercourse
- The dilators must be used on a daily basis to yield results
- Surgery is favored over dilators because it is more accepted in our culture and because of the inconvenience of the dilators
- How is the vaginoplasty done in patients with Rukitansky -Kuster-Huser syndrome?
- A dissection is done between the urethra and the anus ,where the vagina is supposed to be , then skin is taken from the thighs and placed on a mould to form the walls of the vaginal canal
- Excision of uterine remnant (if it has functioning endometrium)

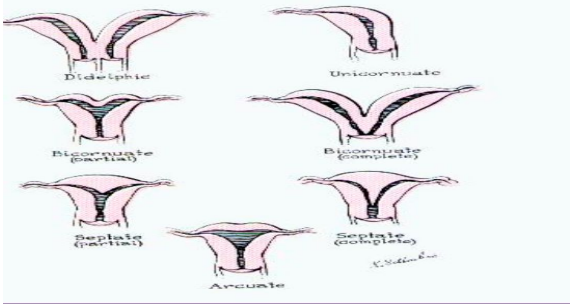
2. Disorders of Lateral Fusion of the Mullerian Duct

- Incidence 0.1-2% , 4% of infertile patients, 6-10% recurrent abortion patient
- Most patients can conceive without difficulty
- Fusion of the Müllerian ducts normally occurs in the midline to form the uterus , cervix and the upper two thirds of the vagina
- **Increased incidence of**

1. Recurrent abortions
2. Premature birth
3. Fetal loss
4. Fetal malpresentation
5. Cesarean Section
6. Cx incompetence

- **Clinical Presentation:**

- Shortly after menarche → if these is obstruction to uterine blood flow. (Patient presents with mass due to accumulation of blood in the uterus)
- Difficulty in intercourse → Longitudinal vaginal septum
- Dysmenorrhea or menorrhagia
- Abnormality detected on D&C (incidental)
- U/S, Laparoscopy or laparotomy (done for other reasons "incidental")
- Palpable mass
- Complications of pregnancy (For example : the patient may present with preterm labor ,especially if she has a bicornuate uterus)
- HSG→ during infertility or RFL investigations
- Hystosalpingogram is done when the patient is being assessed for infertility
- A possible situation : Patient has an abortion so when we try to do evacuation , we discover that there are two vaginas , two uterus

Non Obstructive Malformations of the Mullerian Ducts -Abnormalities are seen by a hystosalpingj ogram -Arcuate form is simple with only a dimple at the top	

A-Uterus didelphys	B- Bicornuate uterus
- Complete duplication of the uterus,cx & vagina (due to failure of fusion of the two mullerian ducts) - Increased pregnancy wastage - Dx→ HSG or at laparoscopy/ laparotomy - Rx→ If affecting pregnancy outcome → surgical correction (Metroplasty)	- Incomplete fusion of the two mullerian ducts - Increased pregnancy wastage - Dx→ HSG or at laparoscopy/ laparotomy - Rx→ If affecting pregnancy outcome → surgical correction (Metroplasty) - Partial Bicornuate has a dimple in the middle - Complete bicornuate: severe and presents with early recurrent abortions - Heart shaped!
C- Septate Uterus	**D- Unicornuate uterus**
- External contour of the uterus is normal but there is intrauterine septum of varying length & thickness. - Septate uterus will lead to RECURRENT abortions because the embryo sometimes implants on the septum - Easily treated if partial : remove septum by HYSTERSOCOPY (uterus is reached by a hysterscope then the septum is cut) - Surgery for a completely septate uterus is more complex : laparotomy is done and we call it a metroplasty where we join the uterus (only done in women with early pregnancy loss or RECURRENT fetal loss) - **Worst pregnancy outcome** - Dx ⟶ Both HSG & Laproscopy - RX ⟶ Hysteroscopic excision of the septum -	- Due to the development of only one mullerian duct. - Almost all pts have associated single kidney - Pregnancy outcome⟶ similar to pts with didelphic uteri - Usually the baby survives but certain complications sometimes occur: (preterm labor and late pregnancy loss) - Dx⟶ HSG or Surgery - Rx ⟶ **NO** corrective surgery If the pt has associated cx incompetence⟶ cx cerclage
E-Unicornuate with rudimentary horn	
A. Non-communicating horn 90% - Present with cyclic pelvic pain, mass, ectopic pregnancy in the rud horn or endometriosis. - Rx⟶ Surgical excision	**B. Communicating horn** - Present with ectopic pregnancy in the rud horn or increased pregnancy wastage.

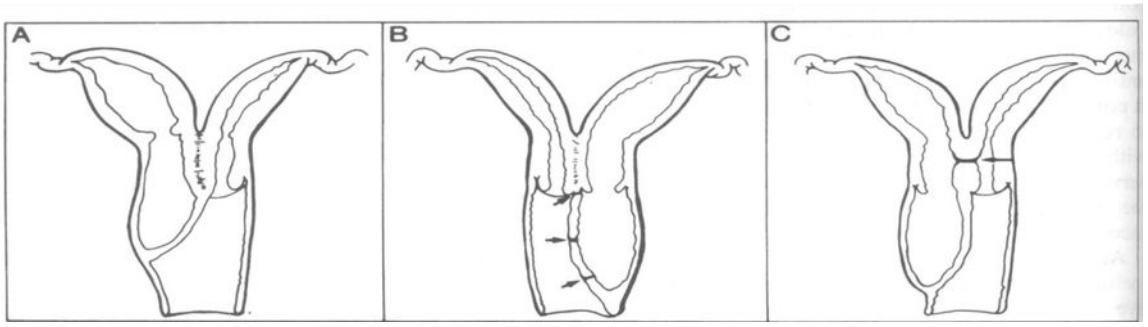
• Important clinical point:
- How does one differentiate between septate and bicornuate uterus ? You have to do a hystosalpingogram PLUS an ultrasound or laparoscopy
- On ultrasound :You will notice that in the septate :the uterus will be normal from the outside inside you will see the septum
- If you do a HSG: both the septate and bicornuate will look the same (the uterus is separated from the top)
• The ultrasound and the laparoscopy will show if the outer part is normal --> septate /if not --> bicornuate

3. Disorders of Vertical Fusion of the Mullerian Ducts

A. Vaginal Septum - Faults in the junction between the mullerian tubercle & the urogenital sinus(the point of meeting remains obliterated ,forming a septum) → could be very thick or thin - 85% in upper two thirds the vagina - Pt presents with 1ry amenorrhea, hematocolpos (A collection of blood in the upper vagina, must be opened to release the blood) , mass or cyclic abdominal pain. - Increased incidence of endometriosis - Rx → Surgical excision	**B. Cx Agenesis/ Dysgenesis** - Very rare - Difficult, unsuccessful surgical correction - Rx→ Hysterectomy

4. Unusual Configuration of Vertical/ Lateral Fusion Defects

- Combined lateral & vertical defects
- Do not fit in other categories
- Example: Double uterus with obstructed hemivagina

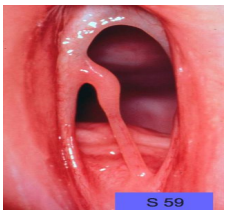
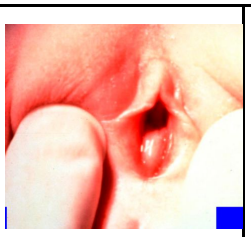
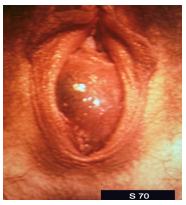


A. Complete Vaginal Obstruction -Double uterus :one is obstructed and the other one is patent - The patent part allows menstruation to occur (this may lead to a late diagnosis because the woman is menstruating) - Patient will present with pain + mass	B. Incomplete Vaginal Obstruction -The fenestration allows for infection to occur • So incomplete vaginal obstruction is actually worse!	C. Comp Obstruction with Comm Double uterus

5. Defects of the External Genitalia

- Ambiguous genitalia → congenital adrenal hyperplasia hermaphrodites
- Defects of the clitoris → Uncommon → bifid clitoris
  Hypertrophied→ androgen effect
- **Imperforate Hymen (on examination bulging membrane filled with blood)**
  - Hymen is formed at the junction of the urogenital sinus & sinovaginal bulbs
  - Pt presents with 1ry amenorrhea with cyclic abdominal pain or hematocolpos / hematometra
  - Rx → Cruciate incision

Important images in this lecture:

		
This is a picture of a vaginal tag that easily excised	This is a patient with an imperforate hymen ,but in childhood it presents as a mucocele (a mucous collection)	Imperforate hymen Bulging membrane +bluish discoloration (can be confirmed by ultrasound (blood collecting in the vagina) • Simple treatment : incision to drain the blood • Cruciate incision (cross shaped) and remove elliptical part of tissue so that it doesn't close again.

Intrsexuality

Abnormal Sexual Development :

1. Sex chromosome abnormality Mosaicism associated with gonadal dysgenesis → 45X/46XY
2. Testis incapable of producing testosterone
3. End organs incapable of utilizing testosterone e.g. 5α reductase deficiency, failure of testosterone binding to receptors (androgen insensitivity)

Why does 5 alpha reductase lead to abnormal external genatalia ?
Because we need Dihydrotestosterone (which is formed by 5- alpha reductase) to act on the receptors for normal external male genitalia to form

• The external genitalia is dependent on the effect of androgens
• In androgen insensitivity syndrome (testicular feminization syndrome) :the problem is in the receptors thus androgens cannot act to form male external genitalia (uterus and vagina are formed instead)
• Females with CAH will have ambiguous genitalia (virilized)

4. Deficient production of MIF → female internal genital organs in otherwise normal males

-The Müllerian inhibiting factor is produced from testes in males but the testes have an abnormal development (non functional) -->gonadal dysgenesis--> Müllerian duct will develop

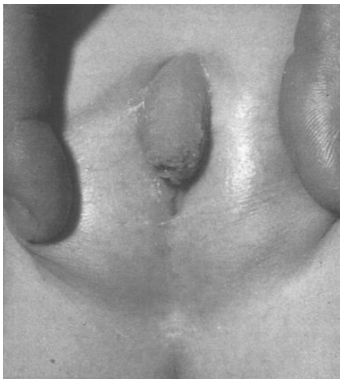
5. Masculinization of the female external genitalia due to increased androgen e.g. congenital adrenal hyperplasia
6. Rarely 46XX male due to the presence of a gene the SRY gene (Sex Determining Region Y)
7. True hermaphroditism → the presence of testicular & gonadal (ovarian) tissue in the same individual

1. Masculinized Pseudohermaphrodites

- 46 XX
- Exposed to androgens in utero → varying degrees of masculinization of the external genitalia

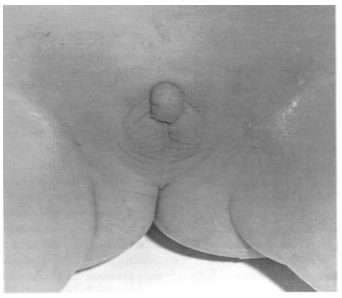
A. Congenital Adrenal Hyperplasia (CAH):

- The most common cause of female intersex.
- Deficiencies of various enzymes required for cortisol & aldosterone biosynthesisx (**21-hydroxylase**, 11β-hyroxilase, 3β hydroxysteroid dehydrogenase)
- Pathophysiology of CAH:
- If one of the enzymes needed in cortisol synthesis is deficient, precursors will build up and synthesis will be shunted towards androgen synthesis.
- 21-hydroxylase deficiency is the commonest defect 90%
- Affected female may present at birth with ambiguous genitalia:
  1. Enlargement of the clitoris
  2. Excessive fusion of the genital folds obscuring the vagina & urethra
  3. Thickening & rugosity of the labia majora resembling the scrotum



- A dangerous salt losing syndrome due to deficiency of aldosterone may occur in some pts
- Delayed menarche & menstrual irregularities
- Note that when there is blockage in 21 hydroxylase enzyme (most common) there will be increase in the precursor (17 hydroxy pregnenolone) which will shunt synthesis towards DHEA and increased androstenedione(increased androgens)
- Another important deficiency occurs in 11- hydroxylase which also leads to increased androgen synthesis
- **Investigations:**
  1. Karyotyping (to know the true gender) **2.** 17-α-hydroxyprogesterone ↑
  3.17-ketosteroids (androgens) in urine **4.** Electrolytes **5.** U/S
- **Rx:**
  1. Cortisol or its synthetic derivatives (+sometimes we give aldosterone) → suppress the adrenals → ↓androgen production
  2. Corrective surgery : - Neonatal period → Clitroplasty
     - Delayed till puberty → Division of the fused labial folds (to form the vaginal opening)

- CAH must be taken seriously because these patients may have electrolyte disturbances due to aldosterone deficiency --> these electrolyte disturbances may be life threatening
- This is only seen in the salt wasting type
- Note that if the mother has a previously affected child we give the mother cortisone during pregnancy to prevent the development of CAH in the current fetus(start early and if the fetus turned out to be a female then you have to continue throughout pregnancy)
- But if the fetus was identified to be male then you have to stop the cortisone (NO NEED TO CONTINUE)



B. Exposure of the mother to androgens:

- Rare
- Androgen secreting tumors e.g. luteoma, arrhenoblastoma
- Drugs
- Picture showing Masculinization of female child (enlarged clitoris and a blocked vagina)→ mother exposed to methyl testosterone.

2. Undermasculanized Pseudohermaphroditism (male♂)

A. Anatomical Testicular Failure:

1. Pure gonadal dysgenesis

- Normal chromosomes 46XY
- Variable features of ambiguous genitalia - mild-severe (normal female (♀) , ♀ with mild musculanization)
- uterus present

Because the testes didn't develop thus no MIF --> uterus is formed

2. Mosaicism 45X/46XY

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

B. Enzymatic Testicular Failure:

- Enzymatic defects in the biosynthesis of testosterone
- These defects are usually incomplete → varying degrees of masculinization of the external genitalia
- Uterus & tubes → absent (MIF produced by the testes)

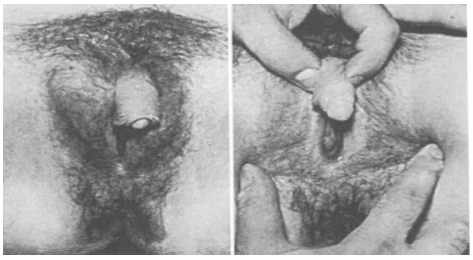
C. Andorgan Insensitivity:

1. 5α reductase deficiency

- Autosomal recessive
- Formation of the male external genitalia requires **5α reductase.**

  5α reductase

  Testosterone → → → → → → Dihydrotestosterone



- Formation of the internal wolffian structures respond directly to testosterone.
- Male external genitalia depends upon the presence of **DHT**
- Depending on the degree of enzyme blockage or deficiency , the fetus will form the external genatalia • Mild : male but ambiguous • Severe blockage : female external genitalia

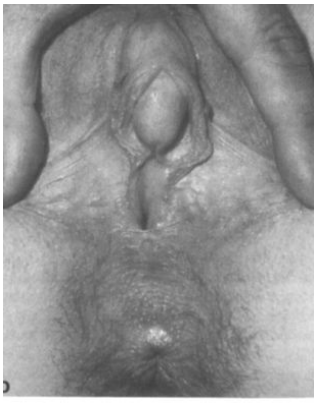
- External genitalia ♀ with mild masculinization
- Absent uterus
- At puberty → ↑ testosterone secretion → virilization

2. Androgen Insensitivity (Testicular Feminization)

Androgen Sensitivity	Etiology	Clinical feature	Treatment
Complete (classical TF)	Lack of androgen receptors	- Normal ♀ external genitalia with blind vagina - Absent uterus, Present with 1ry amenorrhea - Breast development - Testes found in abdomen or inguinal canal - Normal ♂ testosterone level	- Gonadectomy after puberty due to ↑ incidence of malignant change (5%) - Estrogen replacement (because when we remove the testes ,we are indirectly removing the estrogen from the body by removing the testosterone formed in the testes) -remember that testosterone is converted into estrogen in adipose tissue
Incomplete	Receptors are present but low in number or inactive	- Ambiguous genitalia with varying degrees - Breast development	- Musculanization at puberty

-How do we differentiate between androgen insensitivity and mullerian agenesis?
-By karyotyping because mullerian is XX while androgen insensitivity is XY, but they look alike externally!
-Patients often look like attractive females with normal secondary characteristics (because of the high levels of estrogen in the body due to the peripheral conversion of testosterone to estrogen by aromatase enzyme) • No or little adult pubic hair because of the lack of androgenic activity

3. True Hermaphrodites



- Have both ovarian & testicular tissue
- Ovotestes 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 (mosaic pattern)
- 46XY
- 46XY/47XXY

Klinefelter Syndrome:

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

★Q1: Which of the following makes the the uterus and Fallopian tube during female genital organs development.

A. Mullerian duct.
B. Wolffian duct.
C. Mesonephric duct.
D. Genital ridge.

The answer is: A

★Q2: A baby was born with ambiguous genitalia. Karyotyping showed 46XX. What is the most likely diagnosis?

A. Androgen insensitivity syndrome.
B. Congenital adrenal hyperplasia.
C. Mullerian agenesis.
D. Turner syndrome.

The answer is: B