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Embryology of the Female Genital Organ

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References: 436 doctor's slides and notes , Kaplan

Color code: Notes | Important | Extra | Kaplan

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Objectives:

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

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 • If exposed to androgens in-utero will be musculanized	Sexual development depends on the presence of functioning testes and responsive end organ

If XX exposed to androgen, the external genitalia will develop as male external genitalia, or she will have ambiguous genitalia (elongated clitoris & fused labia).

If the fetus is XY male but there is no androgen, he will develop female external genitalia.

External Genitalia

1. Undifferentiated stage (4-8 Weeks)

The neutral genitalia includes:

- Genital tubercle (phalus)
- Labioscrotal swellings
- Urogenital folds
- Urogenital sinus

2. Female and Male external genital development (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.

Testosterone $\xrightarrow{\text{5-alpha reductase}}$ DHT

No hormonal stimulation is needed for differentiation of the external genitalia into labia majora, labia minora, clitoris, and distal vagina

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Female Internal Genitalia

Gonads	• Undifferentiated gonads begin to develop on the 5th week. • Germ cells originate in yolk sac and 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 → primary sex cords grow into mesenchyme → outer cortex and inner medulla • The ovary develops from the cortex while the medulla regresses • The testes develop from the medulla while the cortex regresses • The development of the testes requires the presence of the SRY gene (Sex determining Region Y) found on Y chromosome • The ovary contains 2 million primary oocytes at birth (The number of primary oocyte will become less and less during life)
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, cx & F tubes (at 8-11 week) • 12-16 weeks → proliferation of the mesoderm around the fused lower part → muscular wall • In the male fetus the testes secrete the mullerian inhibiting factor → regression of the mullerian ducts • Mullerian ducts meet in midline, the mid portion develop to uterus, the outer parts develop to F tubes • Mullerian duct is present in all early embryos and is the primordium of the female internal reproductive system.No hormonal stimulation is required. **In females**, without MIF, development continues to form the fallopian tubes, corpus of the uterus, cervix, and proximal vagina. • **In males**, the Y chromosome induces gonadal secretion of müllerian inhibitory factor (MIF), which causes the müllerian duct to involute. Testosterone stimulation is required for development to continue to form the vas deferens, seminal vesicles, epididymis, and efferent ducts.
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

***slides (4-10) and (15-18) is not included as doctor said are not important**

Congenital Malformations of the Female Genital Tract

Uterine anomalies may result from 3 mechanisms:
Stage 1: failure of one or both of the 2 Müllerian ducts to form
Stage 2: failure of the 2 ducts to fuse completely
Stage 3: failure of the 2 fused Müllerian ducts to dissolve the septum that results from fusion

1. Mullerian Agenesis

- Mayer- Rokitansky-Kuster-Huser Syndrome
- **Etiology:** Failure of mullerian duct development → **absence** of the upper vagina, cervix and uterus (uterine remnants may be found) (fundus)
- The ovaries & fallopian tubes are **present** (They have ovaries because ovaries don't develop from Mullerian ducts)
- Normal 46XX female with normal external genitalia
- Pt presents with 1ry amenorrhea on Ultrasound there will be no uterus
- 47% have associated urinary tract anomalies so you have to do intravenous pyelogram (IVP), 12% skeletal anomalies.
- These anomalies are commonly associated with urinary tract anomalies because the structures that give rise to the urinary tract lie close to the Müllerian ducts and are affected by the same injurious insult.
- **Treatment**
  - Psychological counseling, they can have normal sexual life but can't have children
  - Surgical: Vaginoplasty, Vaginal dilators because they have short vagnia
  - Excision of uterine remnant (if it has functioning endometrium)

2. Disorders of Lateral Fusion of the Mullerian Duct

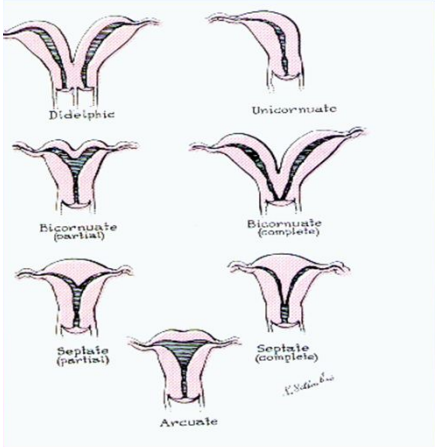
- Incidence 0.1-2% , 4% of infertile patients, 6-10% recurrent abortion patient
- Most patients can conceive without difficulty
- **Increased incidence of:**

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

[1] managed by Cervical cerclage during pregnancy to prevent abortions

- **Clinical Presentation**
  - shortly after menarche → if this is obstruction to uterine blood flow.
  - Difficulty in intercourse → Longitudinal vaginal septum
  - Dysmenorrhea or menorrhagia
  - Abnormality detected on D&C
  - U/S, Laparoscopy or laparotomy (as incidental finding)
  - Palpable mass
  - Complications of pregnancy like recurrent abortion and preterm delivery
  - HSG[2] → during infertility or RFL investigations
  - Presentation depends on:
    - If one part is patent & the other is obstructed they'll present with blood collection in one side, pain & mass.
    - If both parts are patent they'll present with menorrhagia

Non Obstructive Malformations of the Mullerian Ducts



Uterus didelphys (failure to fuse)	Bicornuate uterus (failure to fuse)
• Mullerian ducts didn't fuse, they're separate • Complete duplication of the uterus,cx & vagina (due to failure of fusion of the two mullerian ducts) • Increased pregnancy wastage (They will have late pre-term delivery) • Dx → HSG or at laparoscopy/ laparotomy • Rx → If affecting pregnancy outcome → surgical correction (Metroplasty) • These 2 uteri may each have a cervix or they may share a cervix.In 67% of cases, a didelphys uterus is associated with 2 vaginas separated by a thin wall.	• Most common congenital uterine anomaly (45%) • Incomplete fusion of the two mullerian ducts • Increased pregnancy wastage (The outside has dimple Results in preterm labor) • Dx→ HSG or at laparoscopy/ laparotomy • Rx→ If affecting pregnancy outcome → surgical correction (Metroplasty) Not always requiring surgery • Failure of fusion between the Müllerian ducts at the "top." This failure may be "complete," resulting in 2 separate single-horn uterine bodies sharing one cervix.

[2] HSG: hysterosalpingogram: put speculum, through vagina, inject dye in uterus, and then take x-ray

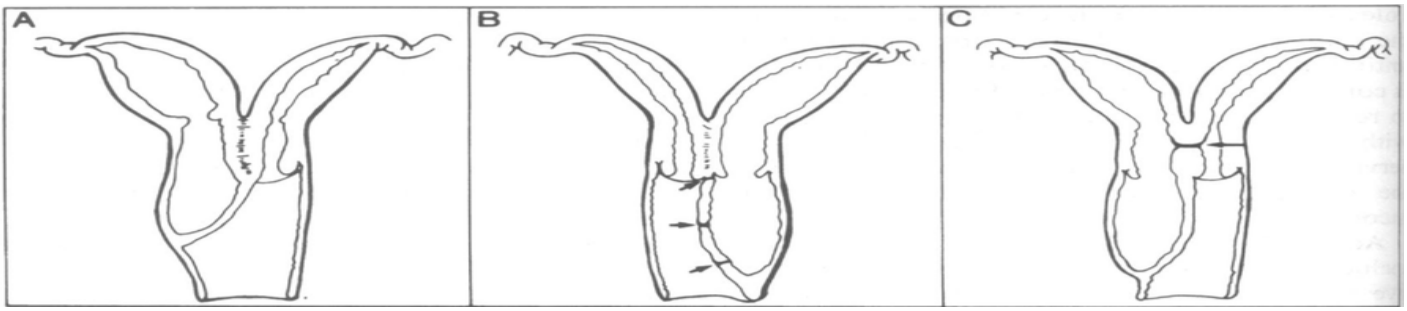
	Alternatively, in a "partial" bicornuate uterus, fusion between the Müllerian ducts occurs at the "bottom" but not the "top." Thus, there is a single uterine cavity at the bottom with a single cervix, but it branches into 2 distinct horns at the top. Because the ducts never fuse at the top, these 2 horns are separate structures when seen from the outside of the uterus.
Septate Uterus (failure to dissolve septum)	Unicornuate uterus (failure to form)
• The two Müllerian ducts fuse normally, but there is a failure in degeneration of the median septum. • External contour of the uterus is normal but there is intrauterine septum of varying length & thickness. • **Worst pregnancy outcome (Causes recurrent abortions)** • Dx → Both HSG & Laproscopy • RX → Hysteroscopic excision of the septum (You have to treat it, Remove septum through vagina with hysteroscope.) • If the failure is "complete," a median septum persists in the entire uterus, separating the uterine cavity into 2 single-horned uteri that share one cervix. • If the failure is "partial," resorption of the lower part of the median septum occurs in stage 2 but the top of the septum fails to dissolve in stage 3. Thus, there is a single cervix and uterine cavity at the bottom, but at the top that cavity divides into 2 distinct horns.	• Banana-shaped. • Due to the development of only one mullerian duct. • Almost all pts have associated single kidney • Pregnancy outcome→ similar to pts with didelphic uterus • Dx→ HSG or Surgery • Rx → **NO** corrective surgery ○ If the pt has associated cx incompetence→ cx cerclage • In 65% of women with a unicornuate uterus, the remaining Müllerian duct may form an incomplete (rudimentary) horn. • There may be no cavity in this rudimentary horn or it may have a small space within it, but there is no opening that communicates with the unicornuate uterus and vagina. • In some cases, the rudimentary horn contains a cavity that is continuous with the healthy single-horn uterus but is much smaller than the cavity within the healthy uterus. • There is a risk that a pregnancy will implant in this rudimentary horn, but because of space limitations 90% of such pregnancies rupture.
Unicornuate with rudimentary horn	
Non-communicating horn	Communicating horn
• Present with cyclic pelvic pain, mass, ectopic pregnancy in the rud horn or endometriosis & blood collection • Rx: Surgical excision	Present with ectopic pregnancy in the rud horn or increased pregnancy wastage.

3. Disorders of Vertical Fusion of the Mullerian Ducts[3]

Vaginal Septum	Cx Agenesis/ Dysgenesis
• Faults in the junction between the mullerian tubercle & the urogenital sinus → could be very thick or thin • 85% in upper two thirds the vagina which is more difficult to excise • Pt presents with 1ry amenorrhea, hematocolpos, mass or cyclic abdominal pain. • Increased incidence of endometriosis • Rx → Surgical excision	• Very rare • Difficult, unsuccessful surgical correction • Rx→ Hysterectomy Surgical correction is difficult, we can't create a cervix, we can create a hole for the menaustral flow, and when she gets pregnant she delivers by c-section. There is also difficulty in creating a hole for menstruation so the other choice is to give her treatment to suppress menstruation, and when she completes her family she undergo 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



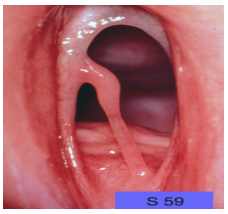
Complete Vaginal Obstruction	Incomplete Vaginal Obstruction	Comp Obstruction with Common Double uterus
This is a uterus didelphys but one side is blocked, so we remove the blockage	There are fenestrations, she might get infected	

5. Defects of the External Genitalia

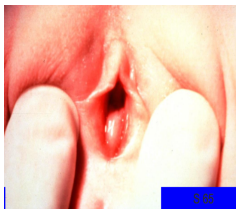
- Ambiguous genitalia → congenital adrenal hyperplasia hermaphrodites
- Defects of the clitoris → Uncommon → bifid clitoris
- Hypertrophied→ androgen effect
- **Imperforate Hymen**
  - Hymen is formed at the junction of the urogenital sinus & sinovaginal bulbs

[3] The fusion of mullerian tubercle with the urogenital sinus

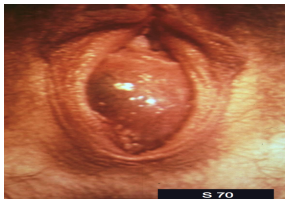
- Pt presents with 1ry amenorrhea with cyclic abdominal pain or hematocolpos / hematometra
- When examining the patient, you find a bulging bluish membrane that has blood behind it, you can feel a uterine mass if they present late
- Rx → Cruciate incision We excise part of it, because if you just incise it and leave it open it'll close again



vaginal tag



imperforate hymen

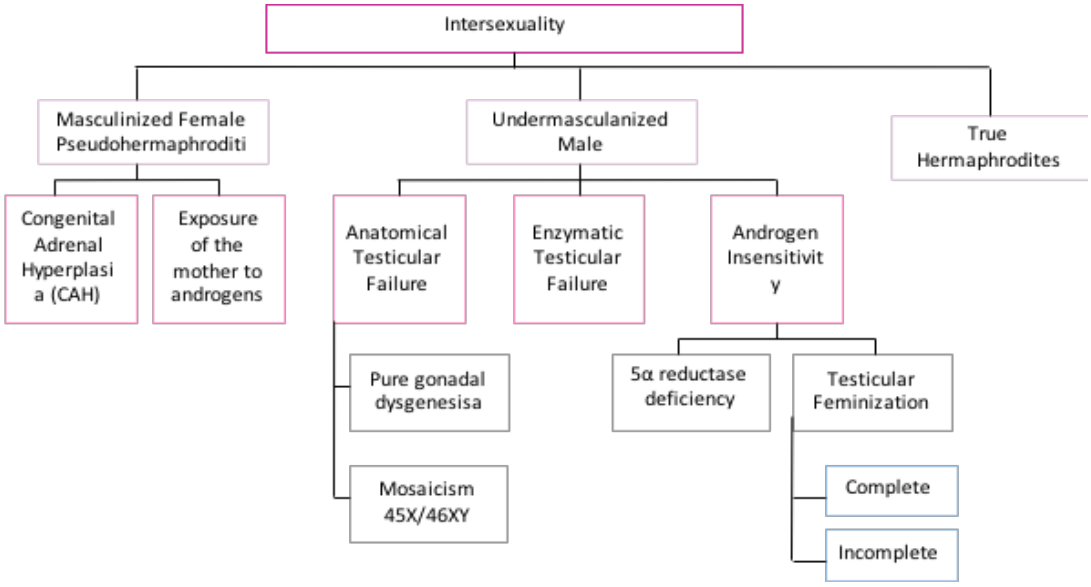


Imperforate hymen+Bulging membrane

Intersexuality

General causes of abnormal Sexual Development

I. Sex chromosome abnormality Mosaicism associated with gonadal dysgenesis → 45X/46XY half of the human cells has 45X chromosomes and the other half has 46XY chromosomes
II. Testis incapable of producing testosterone, he will have female external genitalia, but there is no internal organs, because the testis is able to produce Mullerian Inhibiting Factor MIF, but if the testes destroid very early during embryonic development, then he will have female internal organs.
III. End organs incapable of utilizing testosterone e.g. 5α reductase deficiency or failure of testosterone binding to receptors (androgen insensitivity), he will develop as a female
IV. Deficient production of MIF → female internal genital organs in otherwise normal males
V. Masculinization of the female external genitalia due to increased androgen e.g. congenital adrenal hyperplasia the genitalia will have different degrees of virilization depending on how severe is the case
VI. Rarely 46XX male due to the presence of a gene the SRY gene (Sex Determining Region Y)
VII. True hermaphroditism → the presence of testicular & gonadal tissue in the same individual there are testis and ovaries in the same person

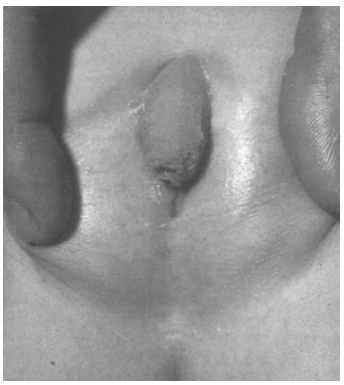


1. Masculinized Female Pseudohermaphroditism

- 46 XX
- Family history may be positive.
- Late-onset CAH is one of the most common autosomal recessive genetic disorders.
- 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 biosynthesis (**21-hydroxylase**, 11β-hydroxylase, 3β hydroxysteroid dehydrogenase)
- 21-hydroxylase deficiency is the commonest defect 90%
- Affected female 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

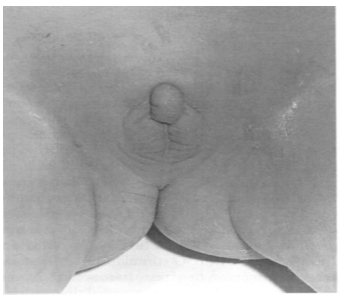


- A dangerous salt losing syndrome due to deficiency of aldosterone may occur in some pts
- Delayed menarche & menstrual irregularities
- **Investigations:**
  - Karyotyping
  - 17-α-hydroxyprogesterone ↑
  - 17-ketosteroids (androgens) in urine
  - Electrolytes & U/S

- **Rx:**
  - Cortisol or its synthetic derivatives → suppress the adrenals → ↓androgen production[4]
  - Corrective surgery
    - Neonatal period → Clitroplasty
    - Delayed till puberty → Division of the fused labial
    - Vaginoplasty, better delayed till puberty, because if done in childhood it become stenotic

B. Exposure of the mother to androgens

- Rare
- Androgen secreting tumors e.g. luteoma, arrhenoblastoma
- Drugs
- Picture showing Masculinization of female child → mother exposed to methyl testosterone.



2. Undermasculanized Male Pseudohermaphroditism (male♂)

A) Anatomical Testicular Failure	B) Enzymatic Testicular Failure	C) Androgen Insensitivity
• **Pure gonadal dysgenesis** ○ Normal chromosomes 46XY ○ Variable features of ambiguous genitalia - mild-severe ○ (normal female (♀) , with mild musculanization ○ uterus present • **Mosaicism 45X/46XY** ○ variable features (normal female, ambiguous genitalia, nearly normal male)	• 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)	1. **5α reductase deficiency** • Autosomal recessive • Formation of the male external genitalia requires **5α reductase.** • Testosterone → → → → → → Dihydrotestosterone • Formation of the internal wolffian structures respond directly to testosterone. • External genitalia female with mild masculinization • Absent uterus • At puberty → ↑ testosterone secretion → virilization 2. **Androgen Insensitivity (Testicular Feminization)** Discussed below

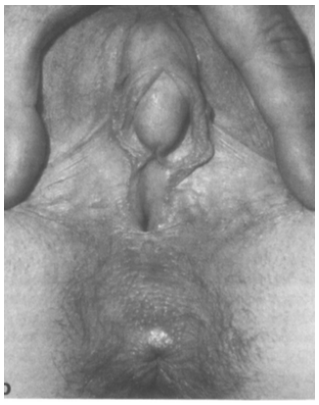
[4] Continuous corticosteroid replacement to arrest the signs of androgenicity and restore ovulatory cycles.

Androgen Insensitivity (Testicular Feminization)

Androgen Sensitivity	Etiology	Clinical feature	Treatment
Complete (classical TF)	Lack of androgen receptors and high levels of androgens present.	• Normal female external genitalia with blind vagina Absent uterus, Present with 1ry amenorrhea • Breast development (Breast is present because the testosterone in converted to estrogen in the periphery) • Testes found in abdomen or inguinal canal • Normal male testosterone level	• Gonadectomy after puberty due to ↑ incidence of malignant change (5%) Testes removal at age 20 because the higher temperatures associated with the intra-abdominal position of the testes may lead to testicular cancer. Estrogen replacement is then needed. • Estrogen replacement so She can have normal sexual life, but can't have children
Incomplete	Receptors are present but low in number or inactive	• Ambiguous genitalia with varying degrees • Breast development • Musculanization at puberty	

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
  - 46XY
  - 46XY/47XXY



Klinefelter Syndrome

- 47XXY
- testicular atrophy
- Normal male external genitalia
- Tall stature
- Gynecomastia

- Azoospermia (infertility)
- Truncal obesity.
- Learning disorders, autoimmune diseases, and low IQ are common.

Summary

- Sexual Differentiation: The first step in sexual differentiation is the determination of genetic sex (XX or XY).
- **External Genitalia:**
  - Undifferentiated Stage: **4-8 Weeks**
  - Male & Female Genital Development: **9-12 Weeks**

- **Internal Genitalia:**
  1. Gonads: Undifferentiated gonads begin to develop on the **5th wk**
  2. Uterus & Fallopian Tubes: Fusion of the two Mullerian ducts → uterus, cervix, fallopian tubes at 8-11 wk, upper ⅔ of vagina.
  3. Vagina:
     - The upper ⅔ of the vagina → formed by Mullerian tubercle.
     - The lower ⅓ → urogenital sinus.

- **Congenital Malformations of the Female Genital Tract:**
  1. Mullerian Agenesis**:** Failure of Mullerian duct development (Mayer- Rokitansky-Kuster-Huser Syndrome).

  2. Disorders of **Lateral Fusion** of the Mullerian Duct
     A- Uterus didelphys **B-** Bicornuate Uterus **C-** Septate Uterus **D-** Unicornuate Uterus **E-** Unicornuate with rudimentary horn.

  3. Disorders of **Vertical Fusion** of the Mullerian Ducts:
     A- Vaginal Septum **B-** Cervix Agenesis/ Dysgenesis.

  4. Unusual Configuration of **Vertical/ Lateral Fusion** Defects:
     Combined lateral & vertical defects.

  5. Defects of the **External Genitalia**
     Ambiguous genitalia - Defects of the clitoris - Imperforate Hymen.

- **Intersexuality:**
  1. Masculinized **Female** Pseudohermaphrodites:
     A- CAH **B-** Exposure of the mother to androgens

  2. Undermasculanized **Male** Pseudohermaphrodites:
     A- Anatomical Testicular Failure **B-** Enzymatic Testicular Failure

     C- Androgen Insensitivity (5α reductase deficiency, Testicular Feminization).

3. True Hermaphrodites: Have both ovarian & testicular tissue

MCQs

1- Development of testes requires presence which of the following:

A- SRY gene

B- testosterone

C- Mullerian inhibiting factor

D- Mullerian duct

2- Which of following occurs at (8-11) weeks:

A- Fusion of the two mullerian duct

B- Proliferation of the mesoderm

C- Obliteration of Mullerian tubercle

3- Which of the following is the most common cause of female intersexuality?

A- Drugs

B- Congenital adrenal hyperplasia

C- Androgen secreting tumours

D- 5α reductase deficiency

4- Normal 46XX female with normal external genitalia and absence of upper part of the vagina, cervix and uterus; indicates which of the following:

A- Lateral fusion defect

B- Vertical fusion defect

C- combined lateral and vertical defect

D- Mullerian Agenesis

Answers: 1- A. 2- A. 3- B. 4- D.