DISORDERED SEX DEVELOPMENT

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INTRODUCTION:

- Ambiguous genitalia, currently *defined* as disorders of sex development (DSD), are not uncommon in our community. With our oriental traditions and believes, DSD constitute a complex, major social and medical emergency, as several forms of congenital adrenal hyperplasia can lead to significant *salt loss*, which may lead to shock *(if unrecognized and not appropriately treated).*
- To ensure that the affected individual has a high quality of life, medical practitioners must quickly and correctly assign the individual's gender and effectively relieve the family's concerns and anxiety.
- "**Intersex**" is a general term used for a variety of conditions in which a person is born with a reproductive or sexual anatomy that doesn't seem to fit the typical definitions of female or male.
- Recently, some doctors, scholars, and intersex activists have shifted to employing the term "Disorders of Sex Developments" (DSD) rather than "intersex," particularly in the medical context as the term intersex is imprecise.

NORMAL SEXUAL DEVELOPMENT:

Normal sexual development comprises of 3 main steps:

1. Effect of Sex Chromosomes on Gonadal Differentiation.
2. Proper Functioning of the Differentiated Testes.
3. Response of End-organs to Testicular activity.

Effect of Sex Chromosome on Gonadal Differentiation:

- Sex chromosome has only **one** function to perform in sexual development, *i.e. to determine the final morphology of the undifferentiated gonad;*
  - Presence of (Y) gonads are **testes**.
  - Absence of (Y) gonads are **ovaries**.
- A normal male must have 1-X & 1-Y while a normal female must have 1-X & 1-X.

Mechanism by Which the Y Chromosome Promotes Testicular Differentiation:

- This is done through a *single* determinant gene called Testicular Determinant Factor (TDF).
- TDF is present on *distal short arm of Y*-chromosome
- TDF begins its action at 6-7 weeks intrauterine.
- Loss of TDF leads to *gonadal dysgenesis*.
- If TDF transfer to X-chromosome leads to *XX-male*.

- TDF produces its actions via encoding & expressing 3 proteins: H-Y-antigen, ZFY-& SRY.

[NOTE: H-Y=histocompatibility antigen on Y, ZFY=zinc finger protein: SRY=sex determining region Y].

Proper Functioning of the Differentiated Testes:

The testes produce their intrauterine function by producing 2 substances:

a- Testosterone (T)

b- b- Antimullerian hormone (AMH)

Testosterone gives rise to development of:

1-External genitalia (T →(5a –reductase)→ DHT)

2- Internal genitalia (T) direct effect

- *AMH gives rise to:*

1- inhibition of the Mullerian structures.

2- descent of the testes into scrotum via contracting the gubernaculum.

3- extra-Mullerian function.

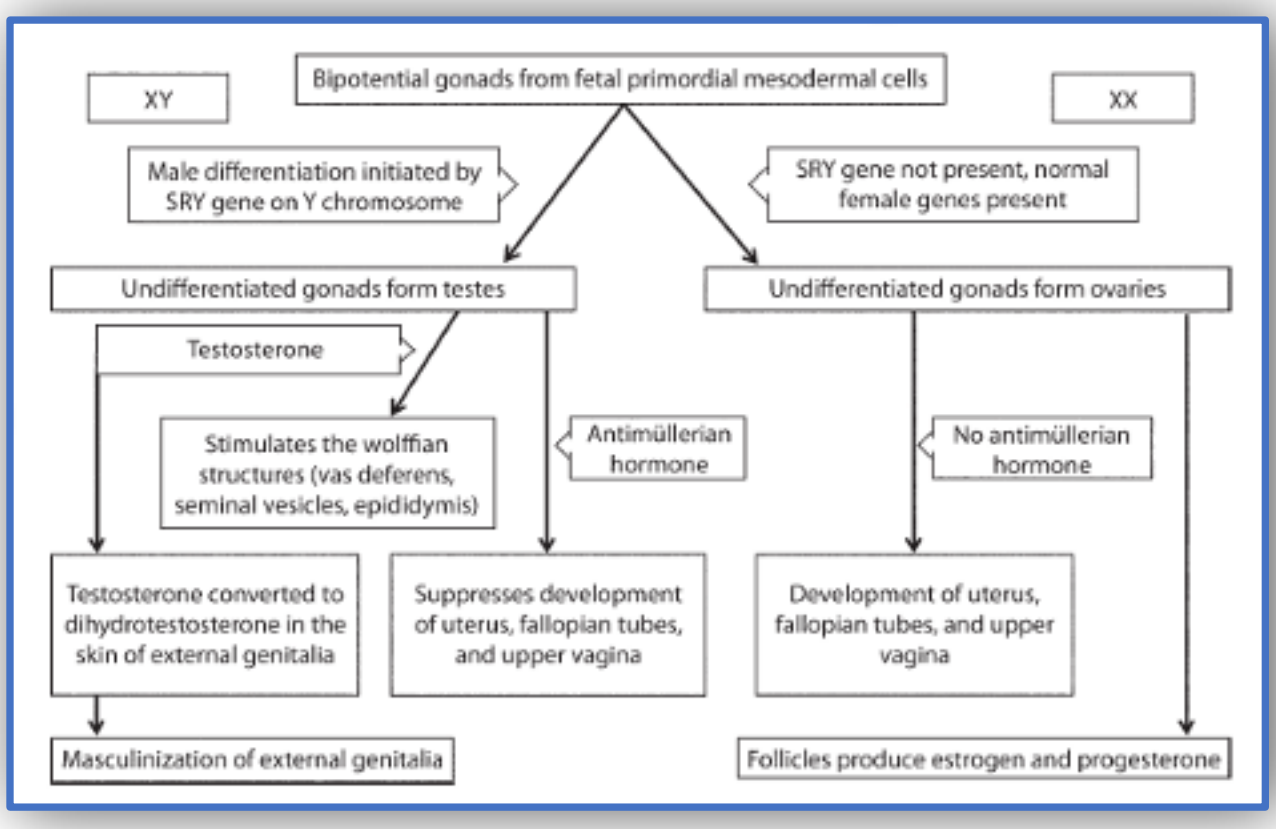


Figure (1): Flowchart showing hormone signaling pathways in normal sexual development

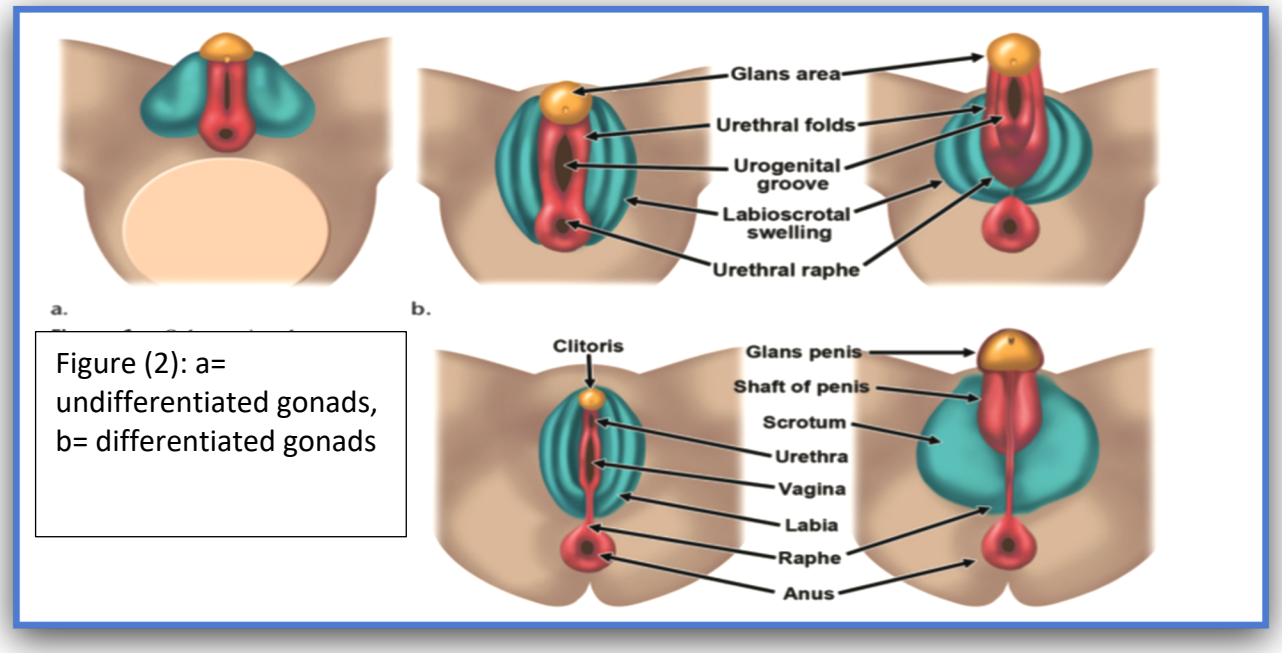


Figure (2): a= undifferentiated gonads, b= differentiated gonads

Figure (3): Schematic description of normal sex development.

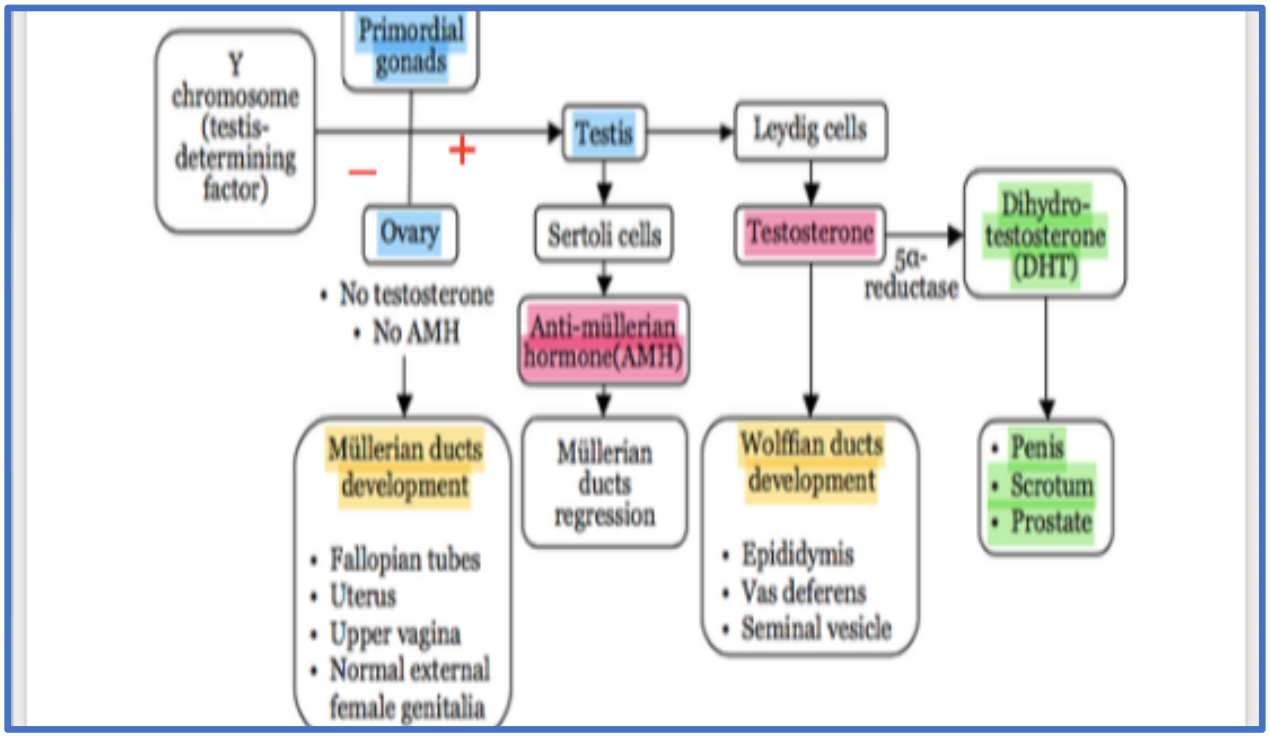


Table (1): Summary of normal gonadal development with gestational age:

Normal sexual differentiation

Osama warda	GONADS	INT. GENITALIA	EXT. GENITALIA
TIMING (IU)	7-9 Weeks	8-11 weeks	8-20 weeks
Embryonic Origin	Genital ridge	Wolffian (male) Mullerian (female)	1-Genital tubercle 2-Genital fold 3-Genital swelling
Determining Factor	TDF(encoded as SRY Gene on Yp)	-Testosterone - AMH	Dihydrotestosterone [Testosteroe—5a reductase-→ DHT]
Masculinization of the male external genitalia is completed by 14th week			
Feminization of the female external genitalia is completed by 20th week			

CLASSIFICATION OF DSD:

There are many classifications, summarized in the table (2).

Table (2) : Classification of DSD

	ACCEPTED (DSD)	PREVIOUS (INTERSEX)
1	46 XY DSD	• MALE PSEUDOHERMAPHRODITE • UNDERVIRILIZED XY MALE • UNDERMASCULINIZED XY MALE
2	46 XX DSD	• FEMALE PSEUDOHERMAPHRODITE • MASCULINIZED XX FEMALE • OVER VIRILIZED XX FEMALE
3	OVOTESTICULAR DSD	TRUE HERMAPHRODITE

A simple, etiologically based classification proceeds according to gonadal morphology proposed by (Speroff, 1999):

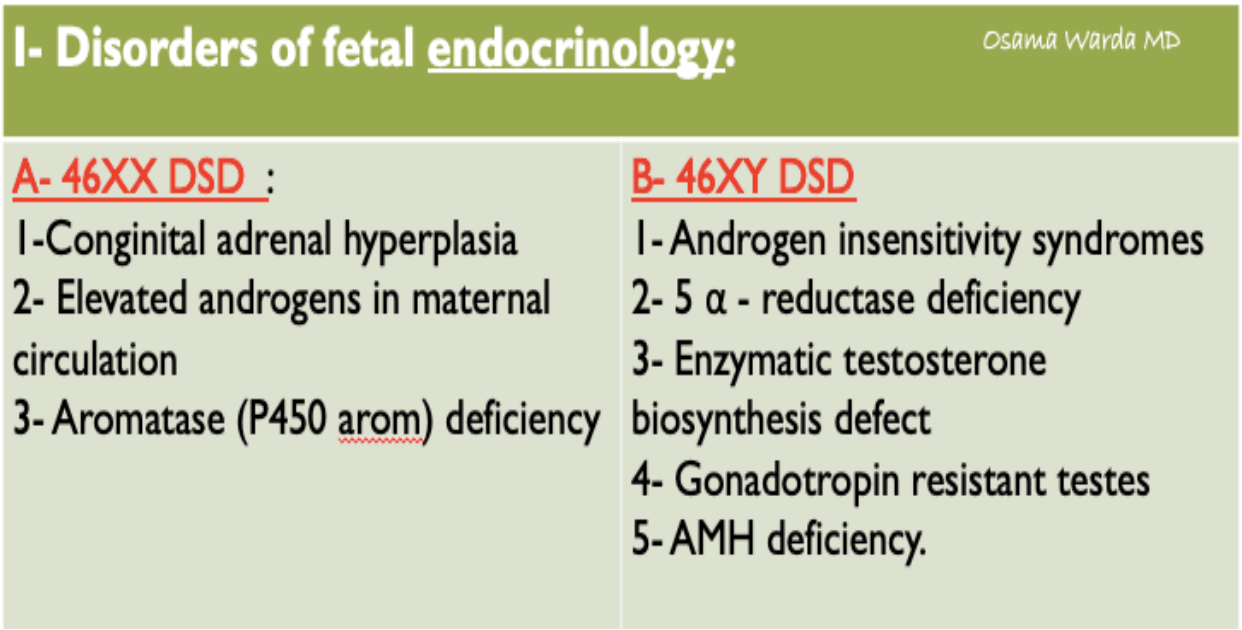
i. Female (46XX) DSD (previously female pseudo- hermaphroditism) = posses ovaries + masculine external genitalia
ii. Male (46XY) DSD (previously male pseudo- hermaphroditism) = posses testes + external (and sometimes internal) genitalia take on female phenotype.
iii. True (Mixed 46xx/46xy) DSD (previously true hermaphrodite) = posses both ovarian & testicular tissue

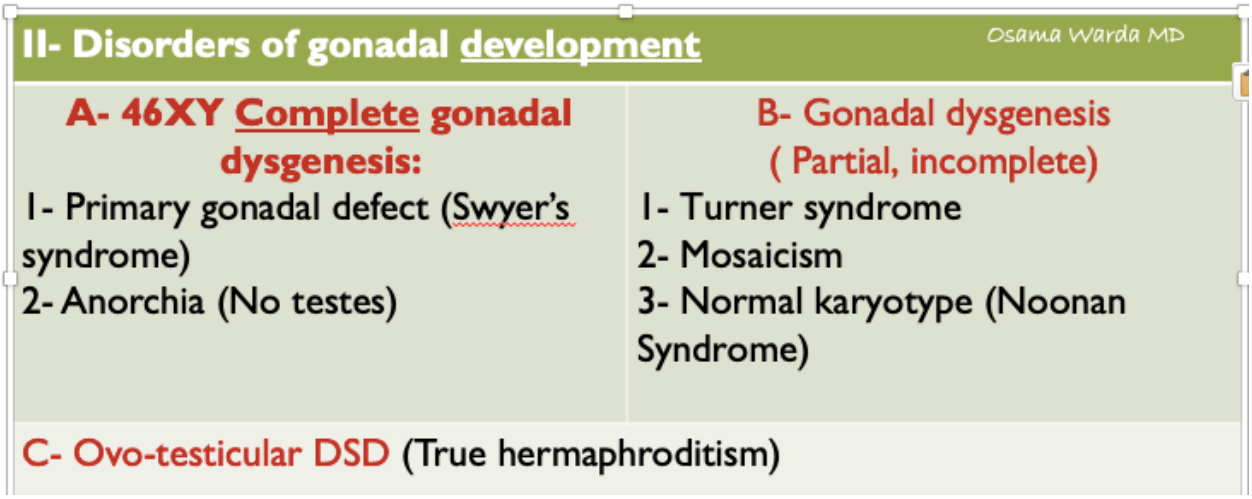
Etiological classification of DSD by Intersex Society of North America (ISNA- 2006):

1- *Congenital development of ambiguous genitalia* (e.g., 46,XX virilizing congenital adrenal hyperplasia; clitoromegaly; micropenis)
2- *Congenital disjunction of internal and external sex anatomy* (e.g., Complete Androgen Insensitivity Syndrome; 5-alpha reductase deficiency)
3-*Incomplete development of sex anatomy* (e.g., vaginal agenesis; gonadal agenesis)
4- *Sex chromosome anomalies* (e.g., Turner Syndrome; Klinefelter Syndrome; sex chromosome mosaicism)
5-*Disorders of gonadal development* (e.g., ovotestes)

ETIOLOGY OF DSD:

The etiology of DSD is either:
I- Disorder of fetal endocrinology or
II- Disorder in gonadal development.





DETAILED CASES OF DSD

CONGENITAL ADRENAL HYPERPLASIA (CAH)

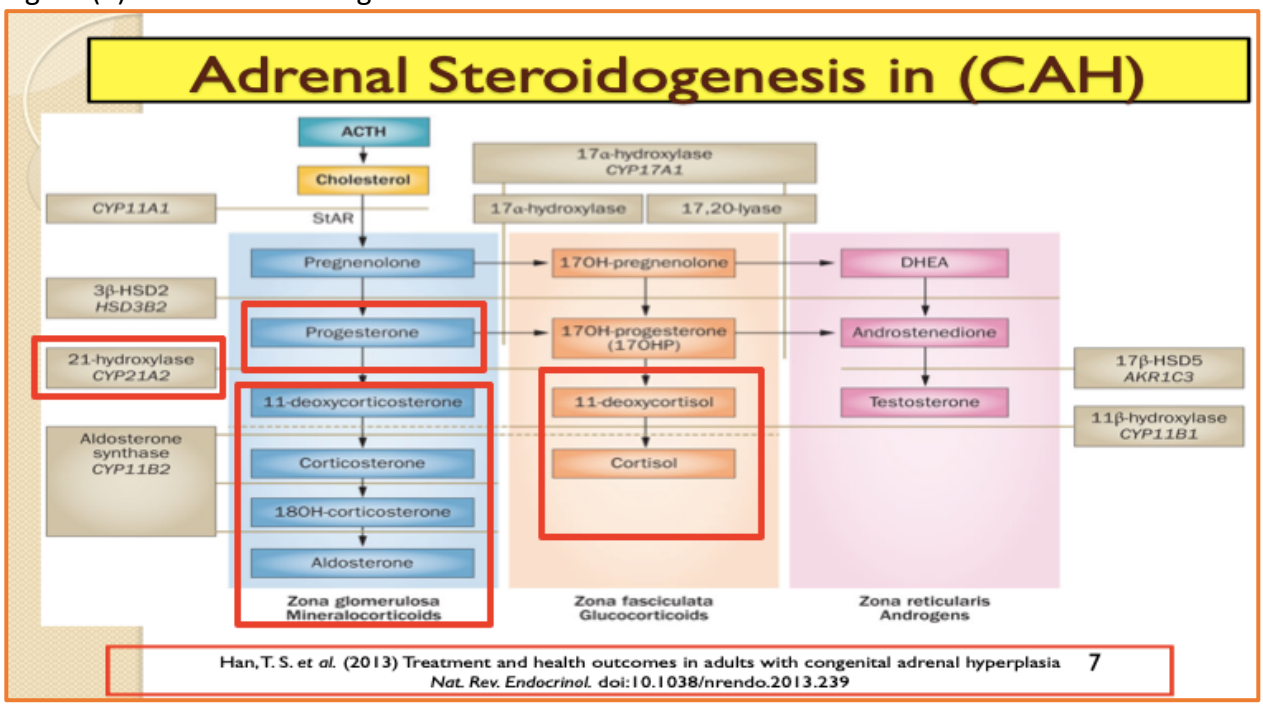
Definition: Congenital adrenal hyperplasia (CAH) are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of *mineralocorticoids, glucocorticoids or sex steroids from cholesterol* by the adrenal glands (steroidogenesis)*
Incidence: the most common, 45%
Sub-types:
1- 21 hyroxylase deficiency (classic CAH- commonest)
2- 11 β hyroxylase deficiency
3- β hydroxy-steriod dehydrogenase deficiency
4- 17 α hyroxylase deficiency
5- PORD (P450 oxido-reductase deficiency)

PATHOPHYSIOLOGY

- The most common cause of 46XX DSD, congenital adrenal hyperplasia (CAH), leads to virilization of a female fetus.
- It is due to an enzyme deficiency in the corticosteroid production pathway in the adrenal gland, with over 90% being a deficiency in *21-hydroxylase, which converts progesterone to deoxycorticosterone and 17-hydroxyprogesterone (17-OHP) to deoxycortisol.*
- The reduced levels of cortisol being produced drive the negative-feedback loop, resulting in hyperplasia of the adrenal glands.
- This leads to an excess of androgen precursors and then to elevated testosterone production.
- Raised androgen levels in a female fetus will lead to virilization of the external genitalia. The clitoris is enlarged and the labia are fused and scrotal in appearance.

- The upper vagina joins the urethra and opens as one common channel onto the perineum.
- In addition, two-thirds of children with 21-hydroxylase CAH will have a 'salt-losing' variety, which also affects the ability to produce aldosterone.
- This represents a life- threatening situation, and those children who are salt-losing often become dangerously unwell within a few days of birth.
- Affected individuals require life-long steroid replacement, such as hydrocortisone, along with fludrocortisone for salt losers.
- Once the infant is well and stabilized on their steroid regime, surgical treatment of the genitalia is considered.
- Traditionally, all female infants with CAH underwent feminizing genital surgery within the first year of life.

Figure (4): adrenal steroidogenesis



CLINICAL MANIFESTATIONS OF CAH:

[I]. 21hydroxylase deficiency (75%-Classic type):

[*Males are not affected by the classic type of CAH*]

1- simple virilizing type (classic-CAH) 2- salt losing type 3- hypertensive type

Common clinical manifestation

A- Masculinization of external genitalia.

1- Clitoris 2- Labioscrotal 3- Labia major 4-Vagina 5- Progressive virilization post-natal→(*heterosexual precocious puberty*)

B- Metabolic disorders:

1- salt losing type (aldosterone deficiency) 2- hypertensive type 3- hypoglycemia.

[II]. 11-β hydroxylase deficiency patients are protected from the symptoms associated with adrenal crisis, although they are subject to others such as hypertension due to salt retention and ambiguous genitalia in females.

[III]. 17α-hydroxylase deficiency results in ambiguous external genitalia in males and lack of pubertal development or menstrual cycles (amenorrhea) in females.

[IV]. 3-β-hydroxysteroid dehydrogenase deficiency leads to ambiguous genitalia in males and females. In both genders it can lead to salt- wasting.

[V]. Congenital lipoid adrenal hyperplasia may cause early death due to adrenal crisis. Males have ambiguous genitalia. Both males and females, if they survive, would likely be infertile.

[VI]. PORD (P450 oxidoreductase deficiency) presents with signs and symptoms that may resemble 21-hydroxylase deficiency, 17- hydroxylase deficiency, or a combination of the two enzyme deficiencies. Some cases have been associated with a skeletal disorder known as Antley-Bixler syndrome.

SUMMARY OF CLINICAL MANIFESTATION OF DIFFERENT SUBTYPES OF CAH	Osama Warda MD
21hydroxylase deficiency (75%-Classic type):	1- simple virilizing type (classic-CAH) 2- salt losing type 3- hypertensive type *Males are not affected by the classic type of CAH*
11-β hydroxylase deficiency patients	-No crisis- but hypertension. -Ambiguous genitalia in FEMALES
17α-hydroxylase deficiency	Ambiguous external genitalia in males - Lack of pubertal development or menstrual cycles (amenorrhea) in females.
3-β-hydroxysteroid dehydrogenase deficiency	-Ambiguous genitalia in males and females. -In both genders it can lead to salt- wasting.
Congenital lipoid adrenal hyperplasia	-Early death due to adrenal crisis . -Ambiguous genitalia in MALES -Both males and females, if they survive, would likely be infertile.
PORD (P450 oxidoreductase deficiency)	- May resemble 21-hydroxylase deficiency, 17- hydroxylase deficiency, or a combination of the two enzyme deficiencies. -Some cases have been associated with a skeletal disorder known as Antley-Bixler syndrome.

DIAGNOSIS OF CAH:

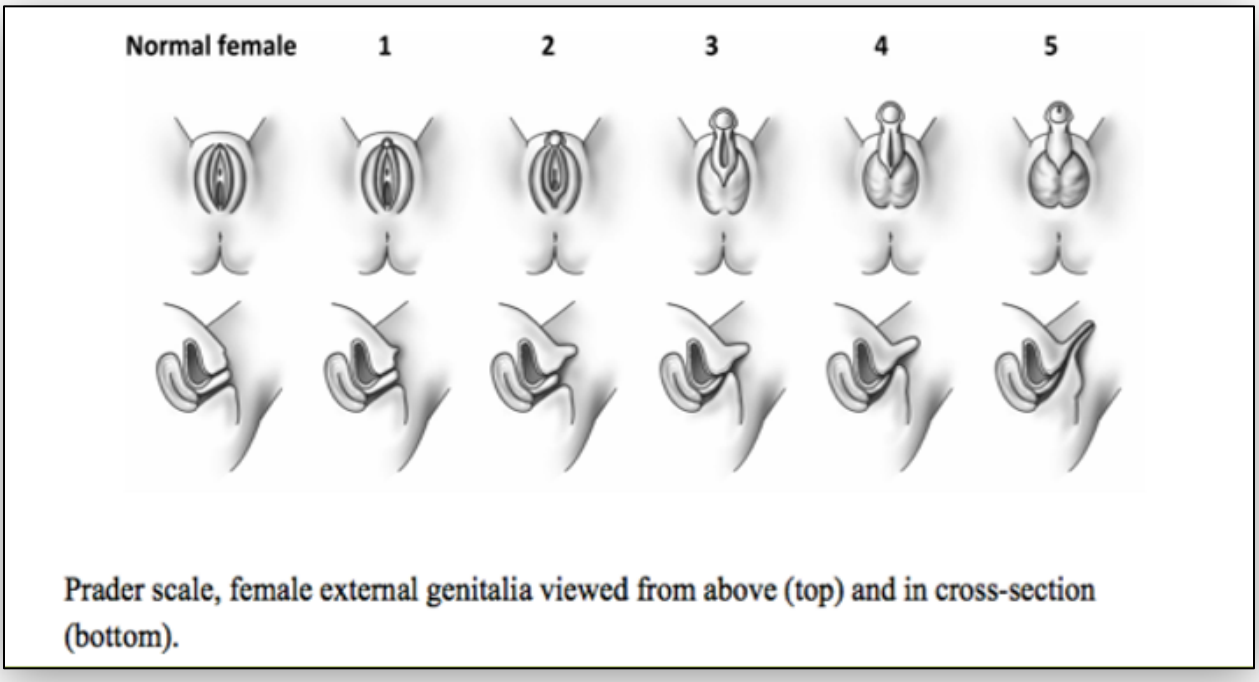
Summarized in the following table

A- Prenatal:	B- Postnatal: Osama Warda MD
1- CAH is autosomal recessive 2- detection of elevated amniotic fluid levels of (17 OHP , 21 deoxycortisol & androstendione) 3- molecular genetic diagnosis (CVS)→ most accurate.	1- Clinical: ambiguous genitalia: no palpable testes 2- 17 OHP in blood 3- plasma renin activity 4- Urinary 17- ketosteriod 5- others (karyotype, USS)

Table (.):

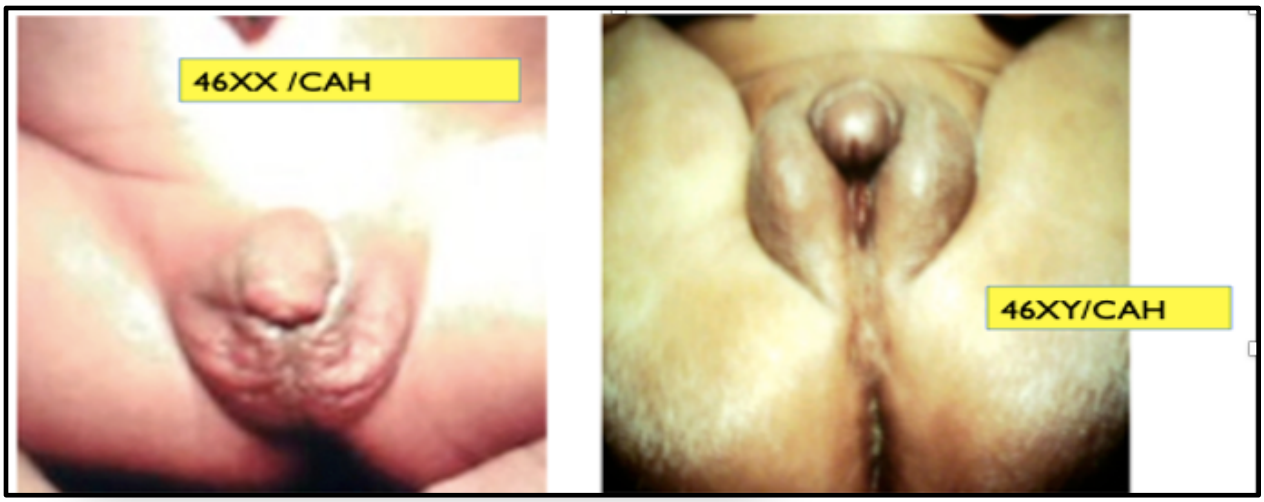
Degree of virilisation of the external genitalia according to Prader's classification (23)

Classification	Characteristics
Type 1 (P-1)	Clitoral hypertrophy
Type 2 (P-2)	Clitoral hypertrophy, urethral and vaginal orifices present, but very near
Type 3 (P-3)	Clitoral hypertrophy, single urogenital orifice, posterior fusion of the labia majora
Type 4 (P-4)	Penile clitoris, perioneoscrotal hypospadias, complete fusion of the labia majora
Type 5 (P-5)	Complete masculinisation (normal-looking male genitalia) but no palpable testes



Prader scale, female external genitalia viewed from above (top) and in cross-section (bottom).

Figure (.) : Prader's classification of degree of virilization of external genitalia



TREATMENT OF CAH:

Prenatal Treatment:

- The rationale for prenatal treatment *is to treat the fetus with a glucocorticoid (dexamethasone DEX) via the mother*, to suppress the fetal adrenal androgen production that is increased in fetuses with severe forms of CAH (the salt-wasting and simple virilizing variants).
- Indicated *in mother that has previously given birth to a child with severe CAH at 6-7th week of next pregnancy*.
- **The dose** given is 20µg/kg body weight/day, based on pre-pregnancy weight and maximum 1.5 mg/day, in three divided doses.
- A few weeks later, around week 12, prenatal diagnosis is performed on fetal DNA obtained from a chorionic villous biopsy (CVS).
- In healthy fetuses and in CAH affected boys' treatment will be stopped while affected girls will be treated until term.

Post-natal treatment

A- Medical:

- 1- hydrocortisone (10 mg/day) OR
- 2- prednisone (3.5-5 mg/m2 surface area] monitoring of treatment by 17 OHP (range 500 – 4000 ng/dl)

B- Surgical:

- 1- general consideration; Patient is genetically female and potentially fertile. Surgical correction *must be after* medical control. Parents must be counseled about the procedure
- 2-Surgical procedures: Reduction of clitoris size (amputation, clitoral recession). Division of labio-scrotal folds (introito-plasty).

ANDROGEN INSENSITIVITY SYNDROME (AIS)

1- Complete androgen insensitivity (CAIS); testicular feminization=TFS= [Morris syndrome]*.
2- Incomplete androgen insensitivity (PAIS =Reifenstein syndrome]
3- 5 α reductase deficiency **

*Note that the complete androgen insensitivity does not present as ambiguous genitalia but presents at puberty as primary amenorrhea as the phenotype and genitalia are like normal females
** 5 α reductase deficiency is not androgen receptor insensitivity as the AIS, but added here because it is an androgen production defect. A special is gue

Complete Androgen Insensitivity Syndrome:

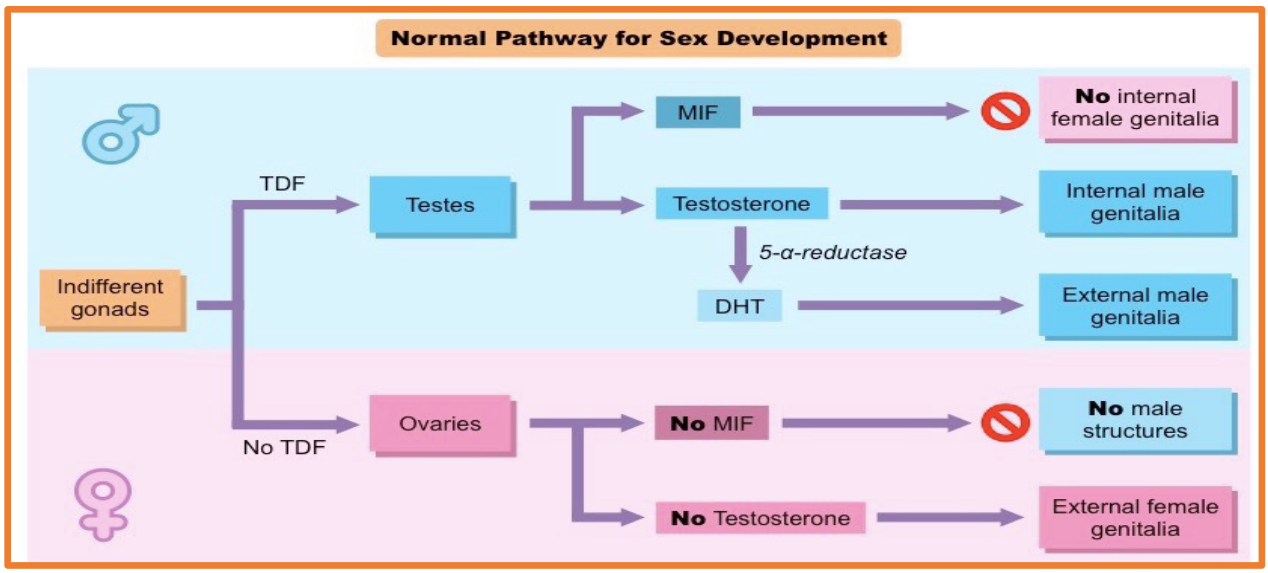
- Individuals with androgen insensitivity syndrome do **not** respond to the production of testosterone.
- Testosterone is responsible for the development of male sex characteristics (female sex characteristics develop in its absence)
- Males who suffer from androgen insensitivity do **not** therefore develop external male genitalia (despite having internal testes)
- Because they do not respond to testosterone, they develop **female sex characteristics** (such as enlarged breasts)
- Despite being genetically male (XY), these individuals physically resemble females and will associate with that gender.
- For genetic background see below under PAIS.

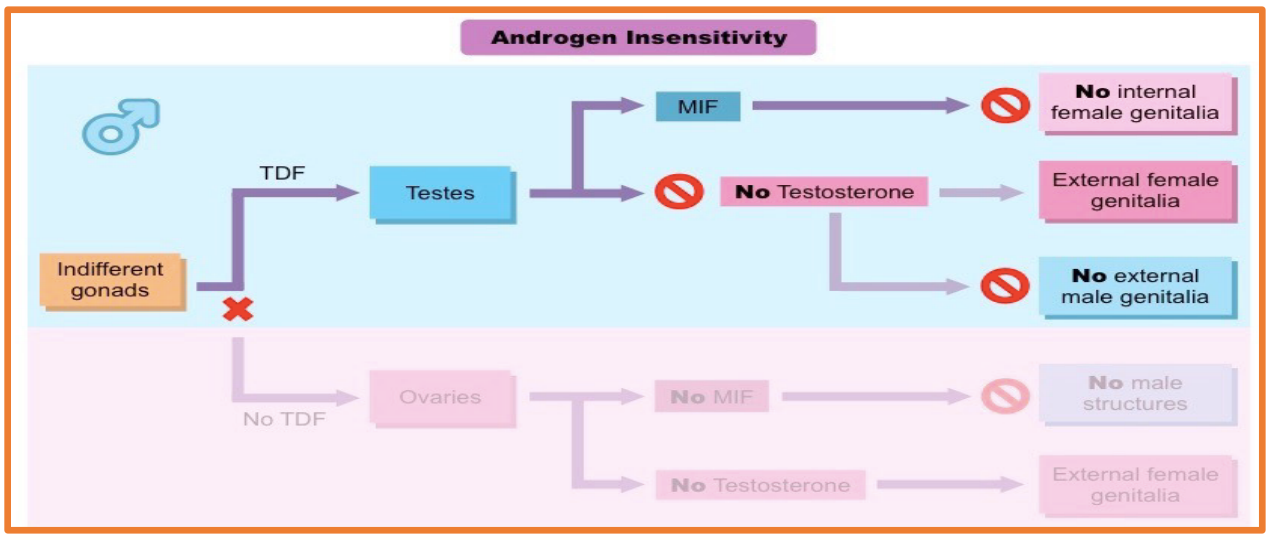
Partial androgen insensitivity syndrome:

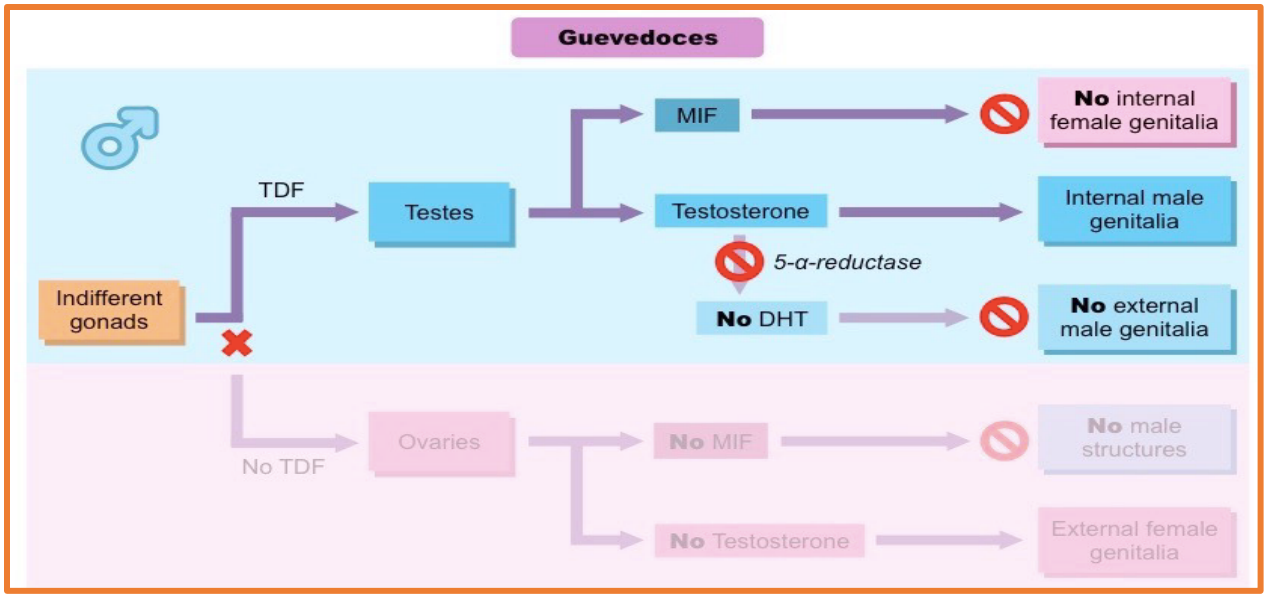
- Partial androgen insensitivity syndrome (PAIS) is a genetic (inherited) condition that occurs when the body can't respond to androgens due to abnormality of androgen receptors.
- There is a change in *the gene on the X chromosome that helps the body recognize and use male hormones properly*. This leads to problems with the development of the male sex organs. At birth, the baby may have ambiguous genitalia.
- The syndrome is passed down genetically (X-linked recessive inheritance). People with two X chromosomes are not affected if only one copy of the X chromosome carries the genetic mutation. Males who inherit the gene from their mothers will have the condition. There is a 50% chance that a male child of a mother with the gene will be affected. Every female child has a 50% chance of carrying the gene. Family history is important in determining risk factors of PAIS.

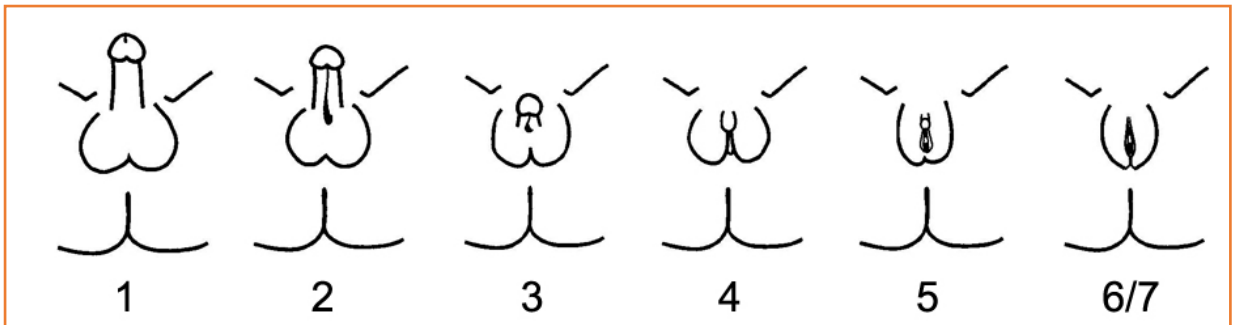
5 ∝ Reductase deficiency [Guevedoces]:

- Guevedoces are girls who turn into boys at puberty.
- Guevedoces possess a rare genetic mutation which prevents the synthesis of the enzyme 5-α-reductase.
- This enzyme converts testosterone into dihydrotestosterone (DHT), triggering a hormone surge that develops male genitalia.
- Without this enzyme, genetic males (XY) do **not** initially develop male genitals and instead develop as females.
- A second hormone surge occurs with the onset of puberty, and it is at this point that the male genitals develop.

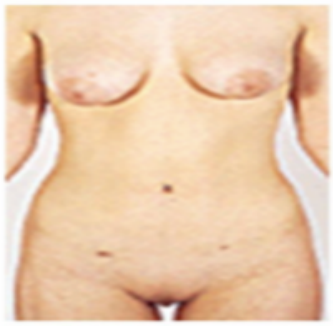




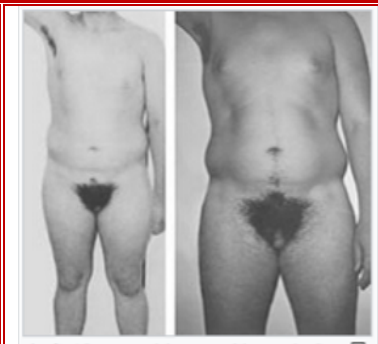




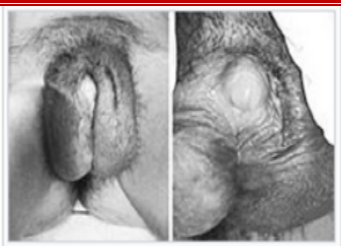
QUIGLY SCALE FOR ANDROGEN INSENSITIVITY SYNDROME (UNDERVIRILIZATION)



COMPLETE ANDROGEN INSINSITIVITY SYNDROME

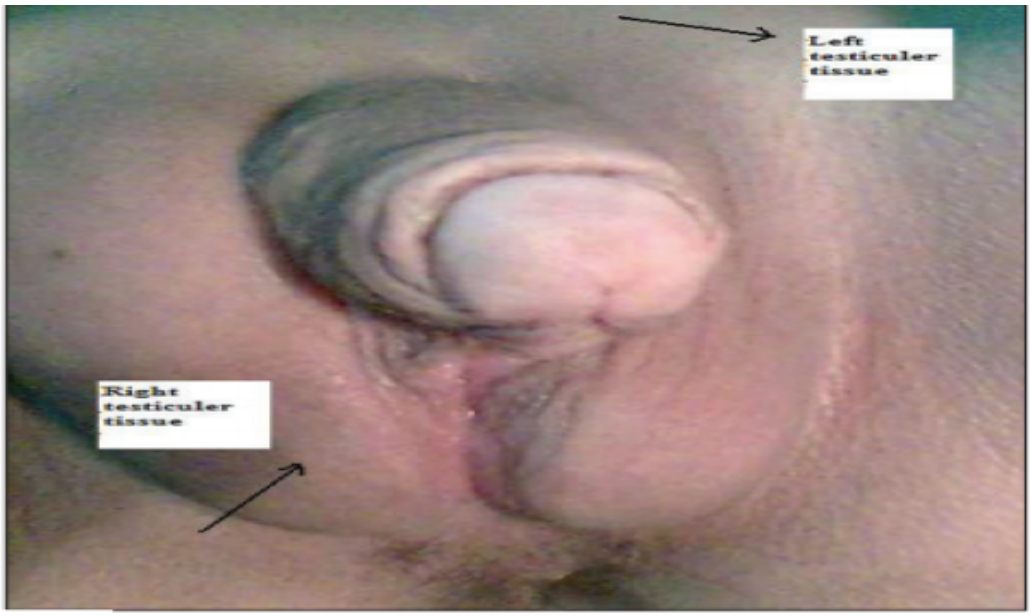


Left, 19-year-old man with grade 3 PAIS before initiation of androgen therapy. *Right*, Habitus after 3.5 years of androgen treatment.[14]

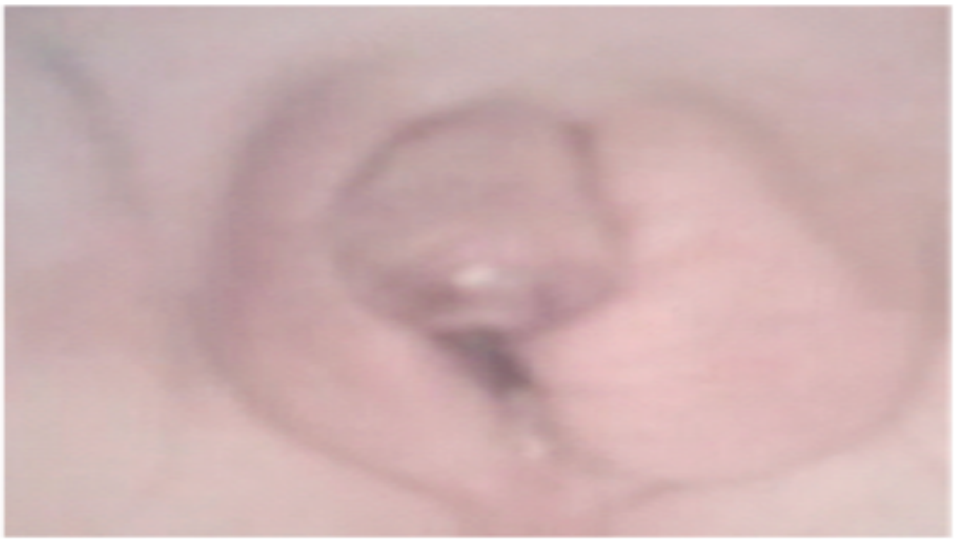


Grade 4 PAIS with bifid scrotum, microphallus-like clitoris, and urethral orifice with terminal sinus urogenitalis[35]

PARTIAL ANDROGEN INSENSITIVITY SYNDROMES

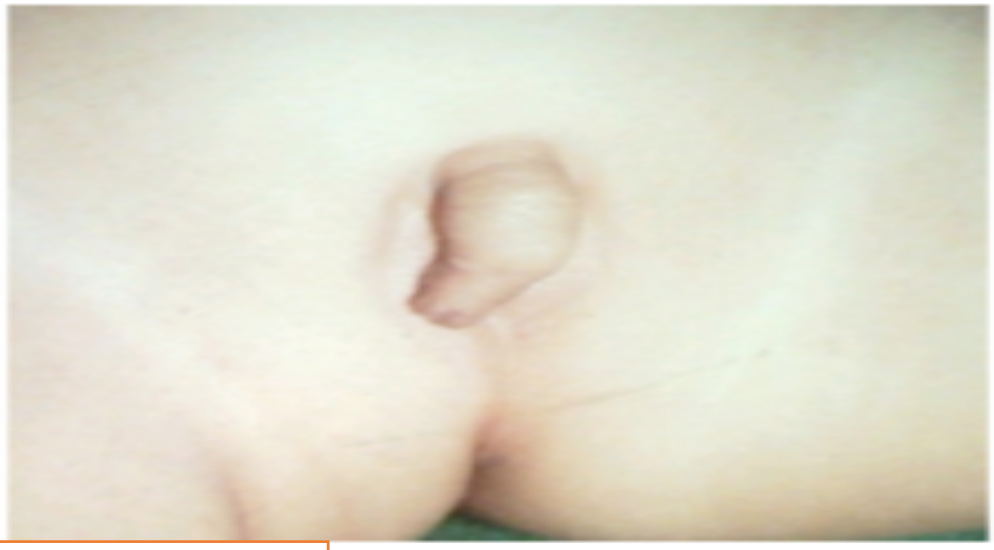


PAIS ; note the site of palpable testes: the right in the scrotum while the left at the external inguinal ring.



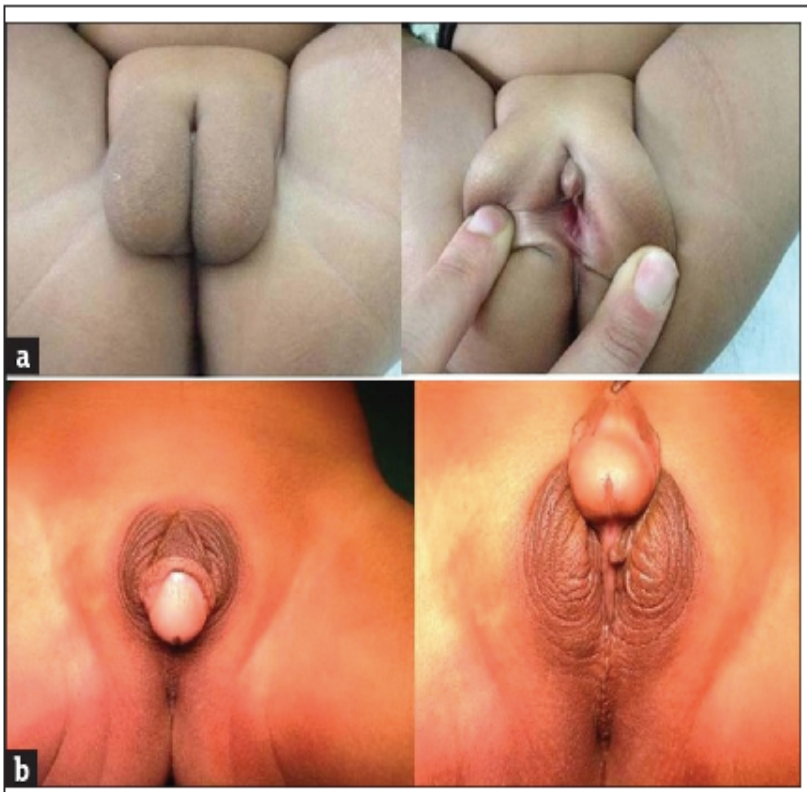
PAIS:
Note →

: Ambiguous genitalia in a 46,XY patient known to have partial androgen insensitivity. Note the micropenis, urogenital sinus, and labioscrotal folds (the left fold contains a palpable gonad).



46 XY : GONADOTROPIN DEFICIENCY MALE HYPOGONADISM

Ambiguous genitalia in a 46,XY patient known to have gonadotrophin hormone deficiency. Note the micropenis, underdeveloped scrotum, and bilateral undescended testes



(a) Complete androgen insensitivity syndrome: 4-months baby, reared as girl, small clitoris, well-developed labial folds, but both gonads descended and 46,XY karyotype.

(b) 5-alpha-reductase deficiency: Small phallus, bifid scrotum, cryptorchidism, and perineal hypospadias

From Kashish et al. 2019

MANAGEMENT OF ANDROGEN SENSITIVITY SYNDROMES:

-Management of AIS is currently limited to *symptomatic management*.
-Methods to correct a malfunctioning androgen receptor protein that result from an AR gene mutation are not currently available.
-Areas of management include:
1- Sex assignment.
2- Genito-plasty.
3-Gonadectomy in relation to tumor risk,
3-Hormone replacement therapy, and
5-Genetic and psychological counseling.

Complete AIS (CAIS):

A- Diagnosis: Clinical, hormonal profiles, Karyotype
B- General consideration (TFS-Complete form)
1- Rearing as female (complete form only)
2- Other members of the family must be investigated (x-linked diseases)
3- Patients are sterile female
C- Treatment options:
1-Gonadectomy (malignancy is a risk after 25 ys) 2- Neo-vagina (when needed)
3- Psychotherapy

Partial androgen insensitivity (PAIS)

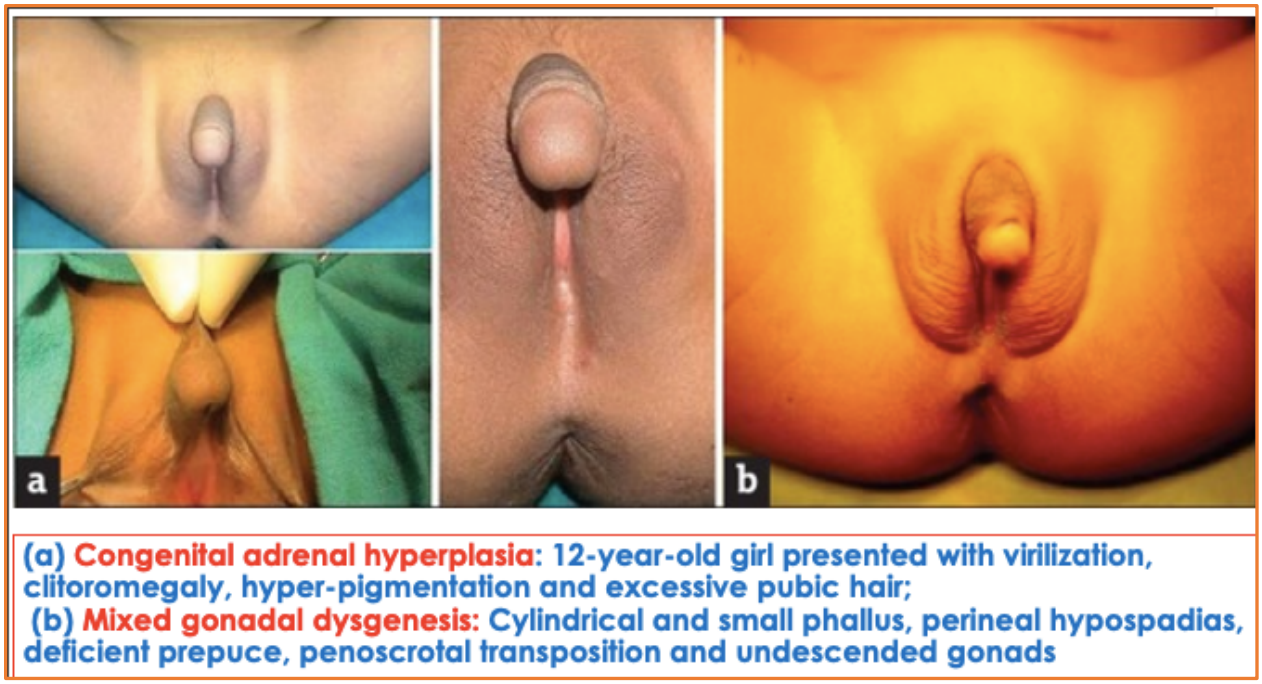
-Treatment with testosterone may improve the chance that a boy will be able to have children when he grows up.
-Other common measures are followed: *Sex assignment*, *Genito-plasty, Gonadectomy in relation to tumor risk, Hormone replacement therapy, and Genetic and psychological counseling.*

Disorders of Gonadal Development

- Abnormal gonadogenesis may occur because of structural defect or disease related catastrophes leading to *loss of fetal gonadal function*.
- Abnormal gonadal development is classified in the following table:

Disorders of gonadal development (Osama Warda MD)

A- 46XY Complete gonadal dysgenesis:	B- Gonadal dysgenesis (Partial, incomplete)
1- Primary gonadal defect (Swyer's syndrome) 2- Anorchia (No testes)	1- Turner syndrome 2- Mosaicism 3- Normal karyotype (Noonan Syndrome)
C- Ovo-testicular DSD (True hermaphroditism)	

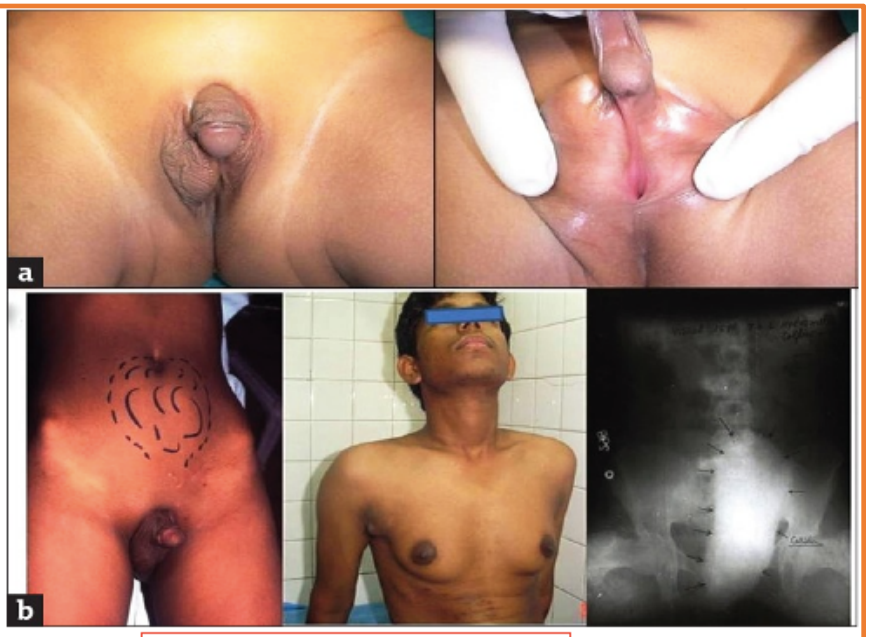


(a) Congenital adrenal hyperplasia: 12-year-old girl presented with virilization, clitoromegaly, hyper-pigmentation and excessive pubic hair;
(b) Mixed gonadal dysgenesis: Cylindrical and small phallus, perineal hypospadias, deficient prepuce, penoscrotal transposition and undescended gonads

SWYER'S SYNDROME:

- Swyer's syndrome occurs in approximately 1 in 80,000 people.
- Mutations in the SRY gene have been identified in about 15 percent of cases.
- Most cases of Swyer's syndrome are not inherited; they occur in people with no history of the condition in their family
- In Swyer's syndrome, individuals with 46xy karyotype but have female reproductive structures; typical female external genitalia. The uterus and fallopian tubes are normally formed, but the gonads are not functional (streak gonads).
- Because of the lack of development of the gonads, Swyer's syndrome is also called 46,XY *complete gonadal dysgenesis*.
- The residual gonadal tissue often becomes cancerous, so it is usually removed surgically.
- People with Swyer's syndrome are typically raised as girls and have a female gender identity.
- Swyer's syndrome may be identified before birth, at birth, or later when a child does not go through puberty as usual.
- Because they do not have functional ovaries, affected individuals often begin hormone replacement therapy during adolescence to start puberty, causing the breasts and uterus to grow, and eventually leading to menstruation.
- Hormone replacement therapy also stimulates bone development and helps reduce the risk of abnormally low bone density (osteopenia and osteoporosis).
- Women with Swyer syndrome do not produce eggs, but they may be able to become pregnant with a donated egg or embryo.

a) True hermaphrodite: triangular phallus, right descended gonad with dual consistency, severe hypospadias, and wide urethral meatus with mucosa lining the urethral plate.
(b) A 16-year-old patient postrepair of hypospadias and undescended testes, presented with pain and lump per abdomen, cyclic hematuria, and postpubertal breast development; Retrograde genitogram showed the presence of uterus.



From Kashish et al. 2019

NOONAN'S SYNDROME:

- Noonan syndrome is a condition that affects many areas of the body.
- It is characterized by *mildly unusual facial features, short stature, heart defects, bleeding problems, skeletal malformations, and many other signs and symptoms.*
- People with Noonan syndrome *have distinctive facial features such as a deep groove in the area between the nose and mouth (philtrum), widely spaced eyes that are usually pale blue or blue-green in color, and low-set ears that are rotated backward, high-arched palate, poor teeth alignment, and a small lower jaw (micro-gnathia). Webbed neck and a low hairline at the back of the neck.*

Individuals with Noonan's syndrome

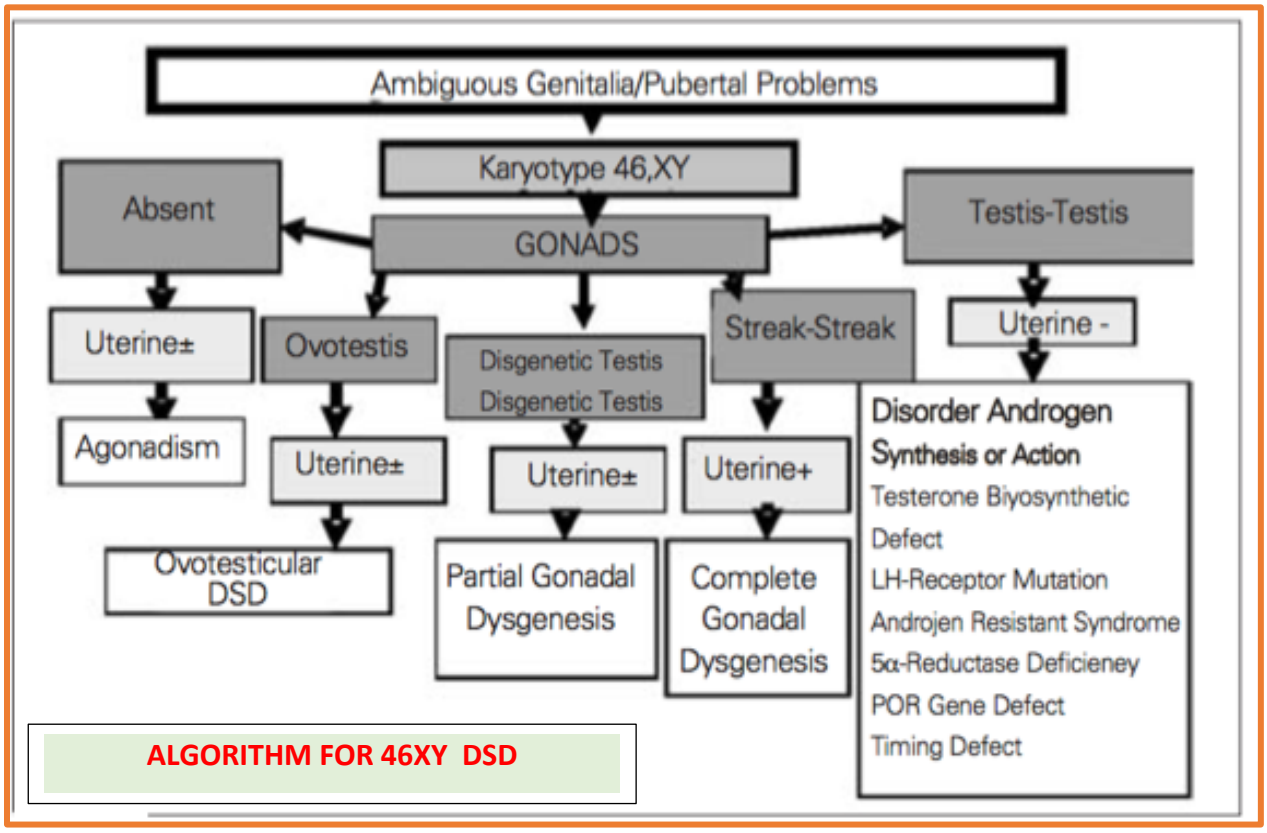
Islamic guidelines for management of DSD

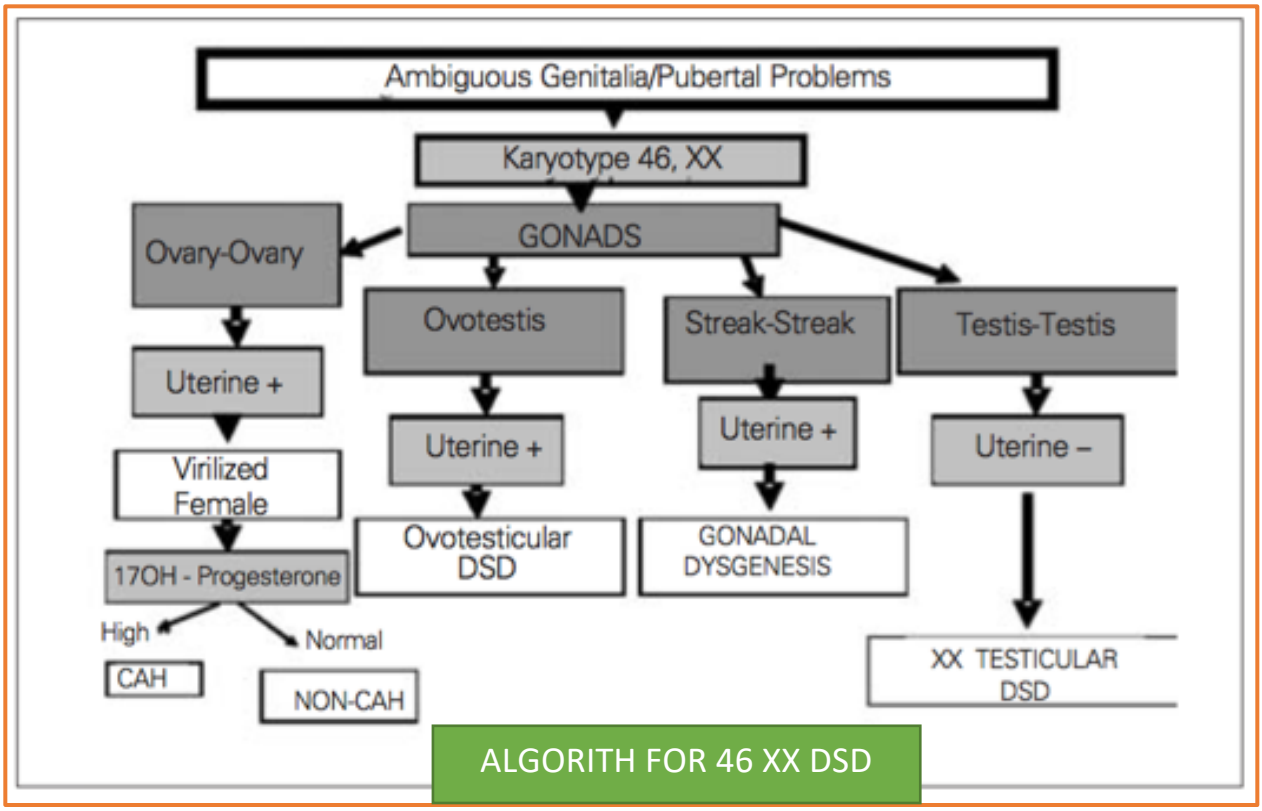
The current Islamic recommendations put forward by the senior Ulama Council in Saudi Arabia as well as the experiences of local medical practitioners yield a set of very useful general guidelines. These recommendations are translated as follows:
1.A sex-change operation (i.e., converting someone with a completely developed gender to the opposite sex) is totally prohibited, and it is even considered criminal in accordance with the Holy Quran and the Prophet's sayings.

2. Those who have both male and female organs require further investigation, and if the evidence is more suggestive of a male gender, then it is permissible to treat the individual medically (by hormones or surgery) to eliminate his ambiguity and to raise him as a male. If the evidence is suggestive of a female gender, then it is permissible to treat her medically (by hormones or surgery) to eliminate her ambiguity and to raise her as a female.

3 Physicians must explain the results of medical investigations to the child's guardians and whether the evidence indicates that the child is male or female so that guardians are well-informed.

ALGORITH FOR DIAGNOSIS OF A CASE OF AMBIGUOUS GENITALIA (DSD)





ALGORITH FOR 46 XX DSD

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