Disorders of Sex Development (DSD)

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Presentation Objectives

- Normal sexual development.
- Disorder sex development (DSD).
- An approach to child with genital anomalies.
- Focus on various DSD conditions.
- Investigations.
- Management.

Basic concepts

Fetal sex differentiation:

- Occurs at 7-14 weeks' fetal age.
- As a male gender requires:
  - Sex-determining region of Y (SRY) gene.
  - Bilateral testes producing Mullerian inhibiting substance (MIS/MIF/AMH) & testosterone.
  - 5-α-reductase enzyme (external genitalia).
  - Testosterone and dihydrotestosterone. receptor (internal and external genitalia).
- As a female gender needs absence of the above needed factors of male sex.

Human sexual differentiation

- Differentiation of bipotential gonad into testis or ovary due to presence or absence of Y-chromosome genes especially SRY gene.
- Differentiation of the Wolffian ducts into epididymitis, vasa differentia & seminal vesicles due to effect of testosterone.
- Differentiation of the Mullerian ducts into uterus, fallopian tubes & upper vagina due to absence of AMH (anti-Mullerian hormone).
- Development of the external genitalia into penis, scrotum (due to DHT) or clitoris and labia majora & minora (in absence of DHT).

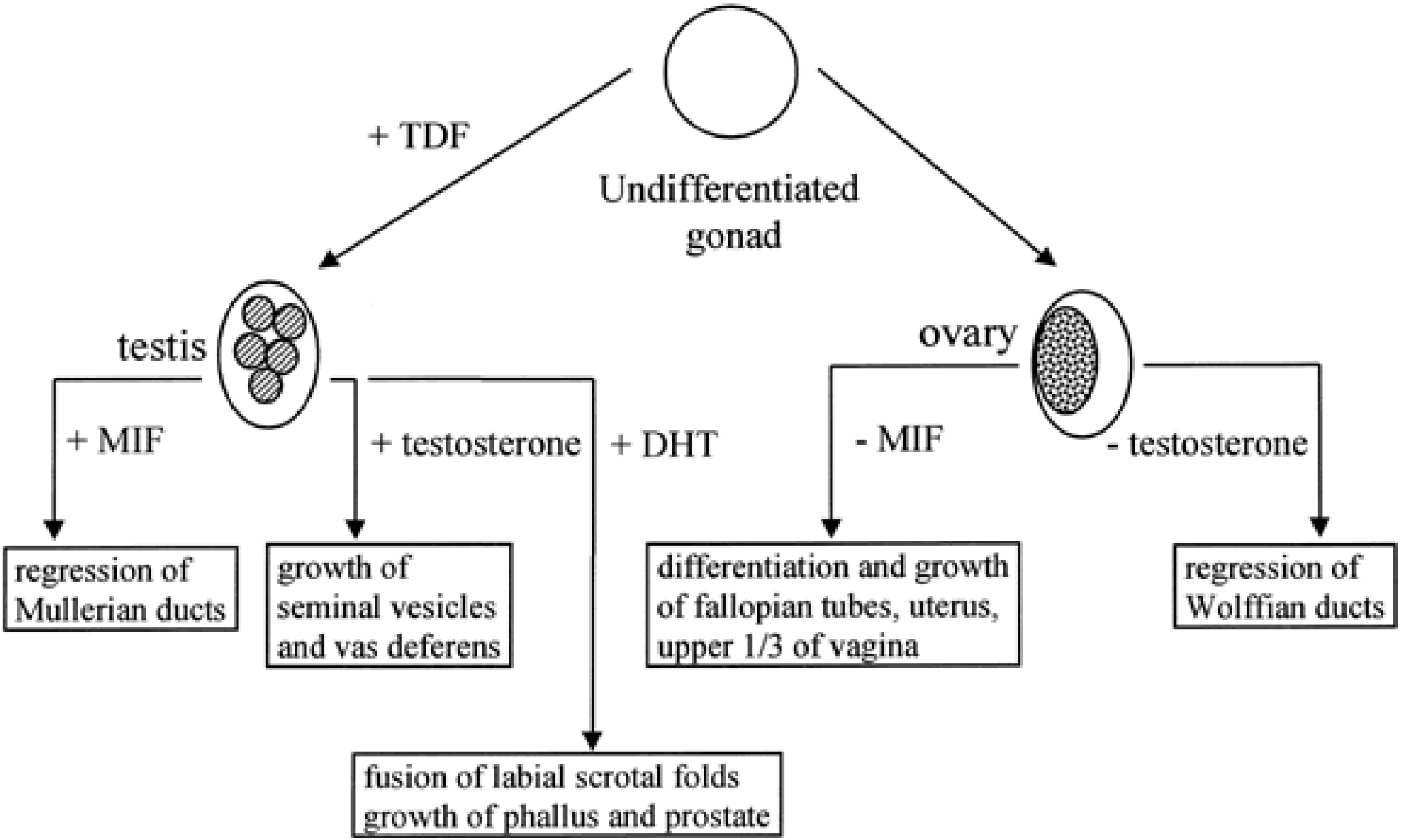
Mechanism by Which the Y Chromosome Promotes Testicular Differentiation

- Through “Testicular Determinant Factor (TDF)”.
- TDF locus is on distal short arm of Y -chromosome.
- TDF begins its action at 7 weeks of gestation.
- Loss of TDF leads to gonadal dysgenesis.
- TDF transfer to X-chromosome leads to XX-male.

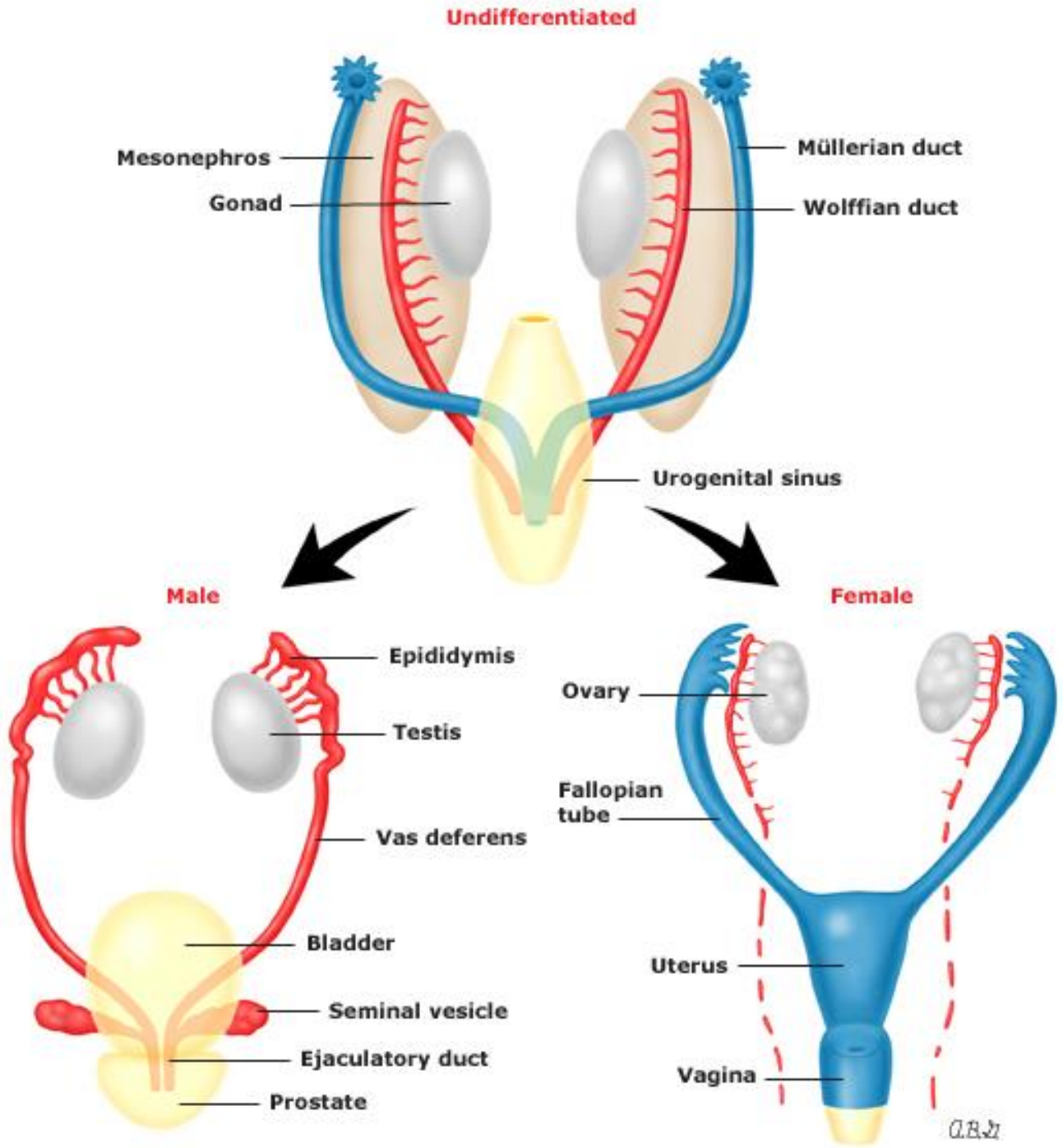
Differentiation of external genitalia

- The external genitalia of both sexes are identical during the first 7 weeks of gestation.
- Without the hormonal action of the testosterone & dihydrotestosterone (DHT), external genitalia appear phenotypically female.
- In the gonadal male, differentiation toward the male phenotype actively occurs over the next 8 weeks.
- This differentiation is moderated by testosterone, which is converted to DHT by 5-α reductase enzyme.
- DHT is bound to androgen receptors within the cytoplasm and subsequently is transported to the nucleus, where it leads to translation and transcription of genetic material.

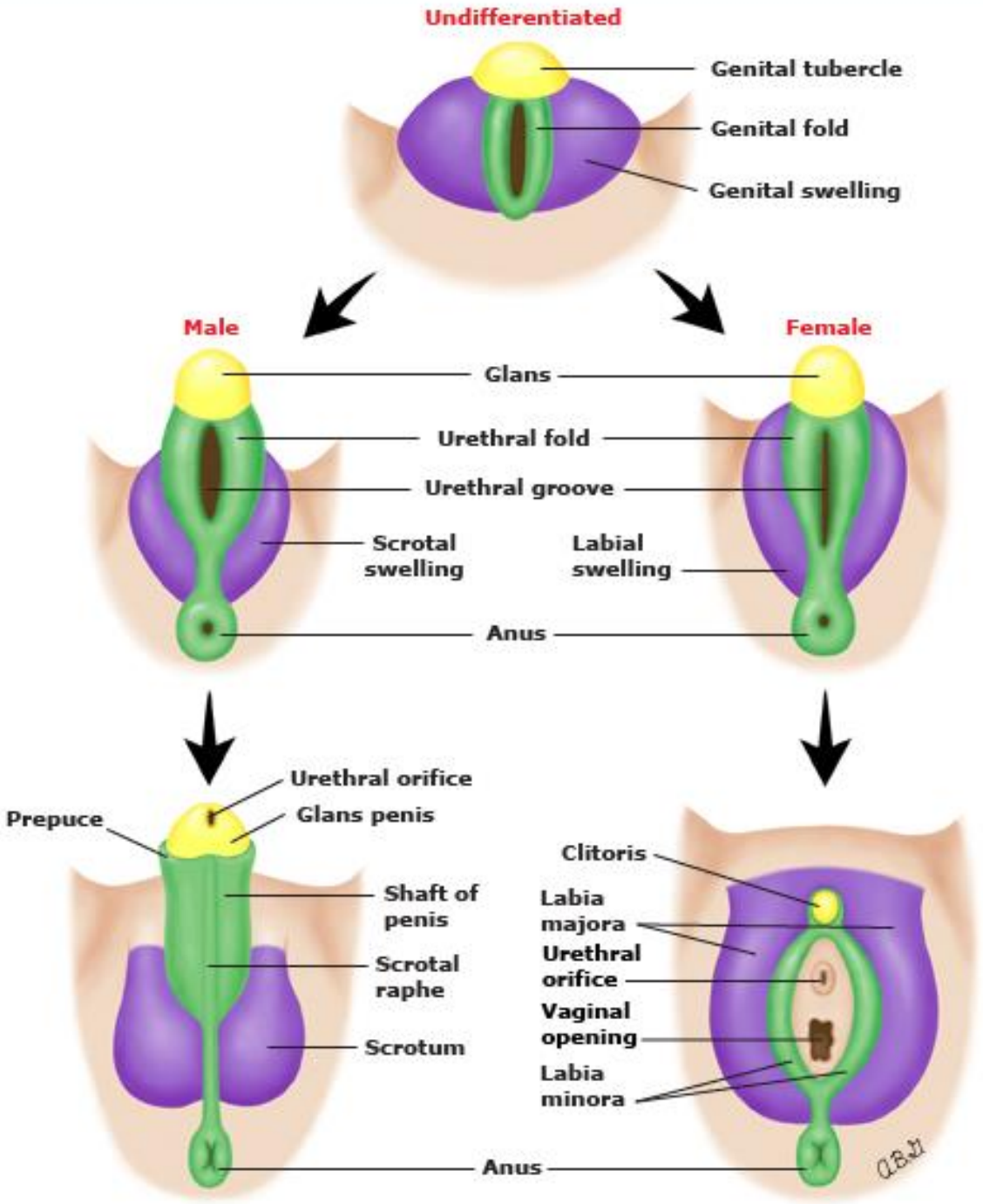
Human sexual differentiation

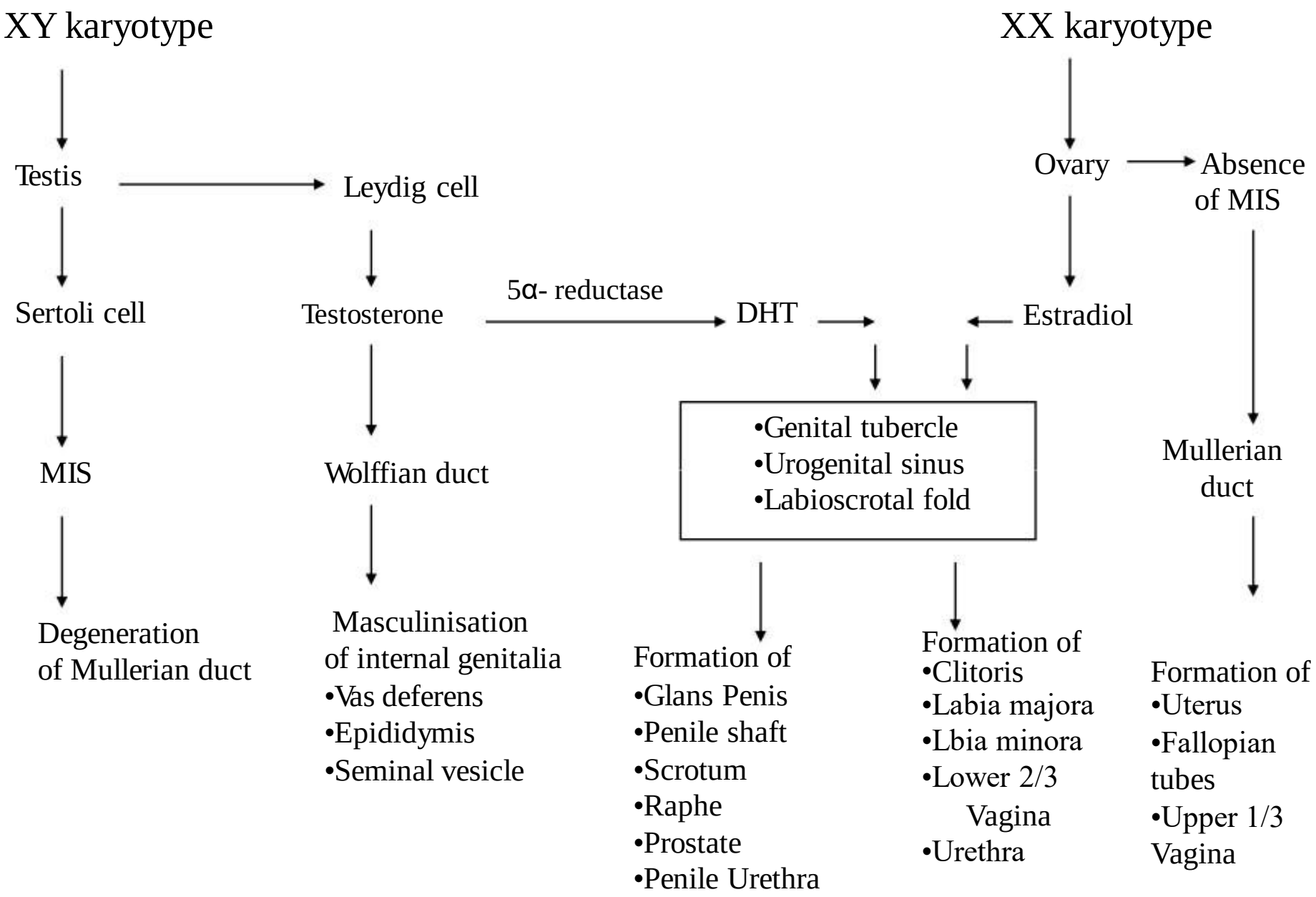


Phenotypic differentiation of the male and female urogenital tracts



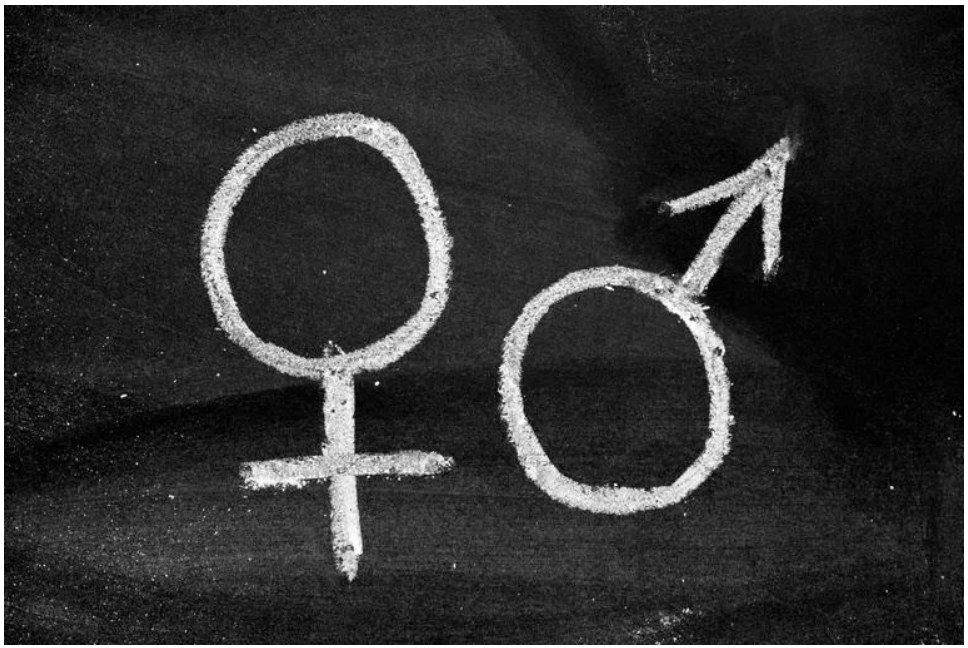
Phenotypic differentiation of the external genitalia in male and female embryos




XY karyotype
XX karyotype
Testis
Leydig cell
Ovary
Absence of MIS
Sertoli cell
Testosterone
5α- reductase
DHT
Estradiol
•Genital tubercle
•Urogenital sinus
•Labioscrotal fold
MIS
Wolffian duct
Mullerian duct
Degeneration of Mullerian duct
Masculinisation of internal genitalia
•Vas deferens
•Epididymis
•Seminal vesicle
Formation of
•Glans Penis
•Penile shaft
•Scrotum
•Raphe
•Prostate
•Penile Urethra
Formation of
•Clitoris
•Labia majora
•Lbia minora
•Lower 2/3 Vagina
•Urethra
Formation of
•Uterus
•Fallopian tubes
•Upper 1/3 Vagina

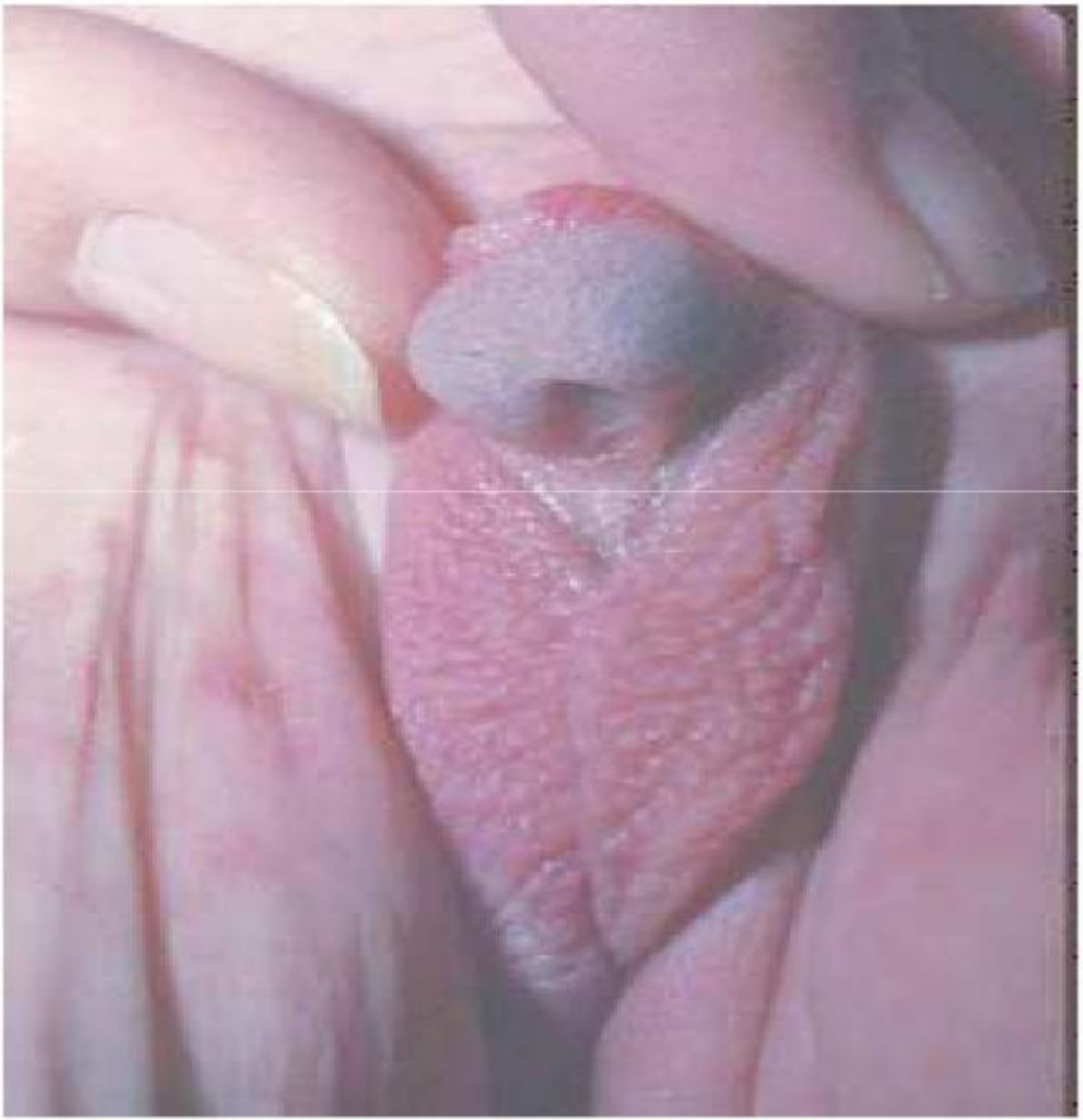
Disorders of Sexual Differentiation

- Incidence 1:4500 live births.
- Human sexual differentiation is a highly complex process under the control of multiple genes & hormones.



“ Is it a boy or a girl ?”

Is it a boy or a girl ?



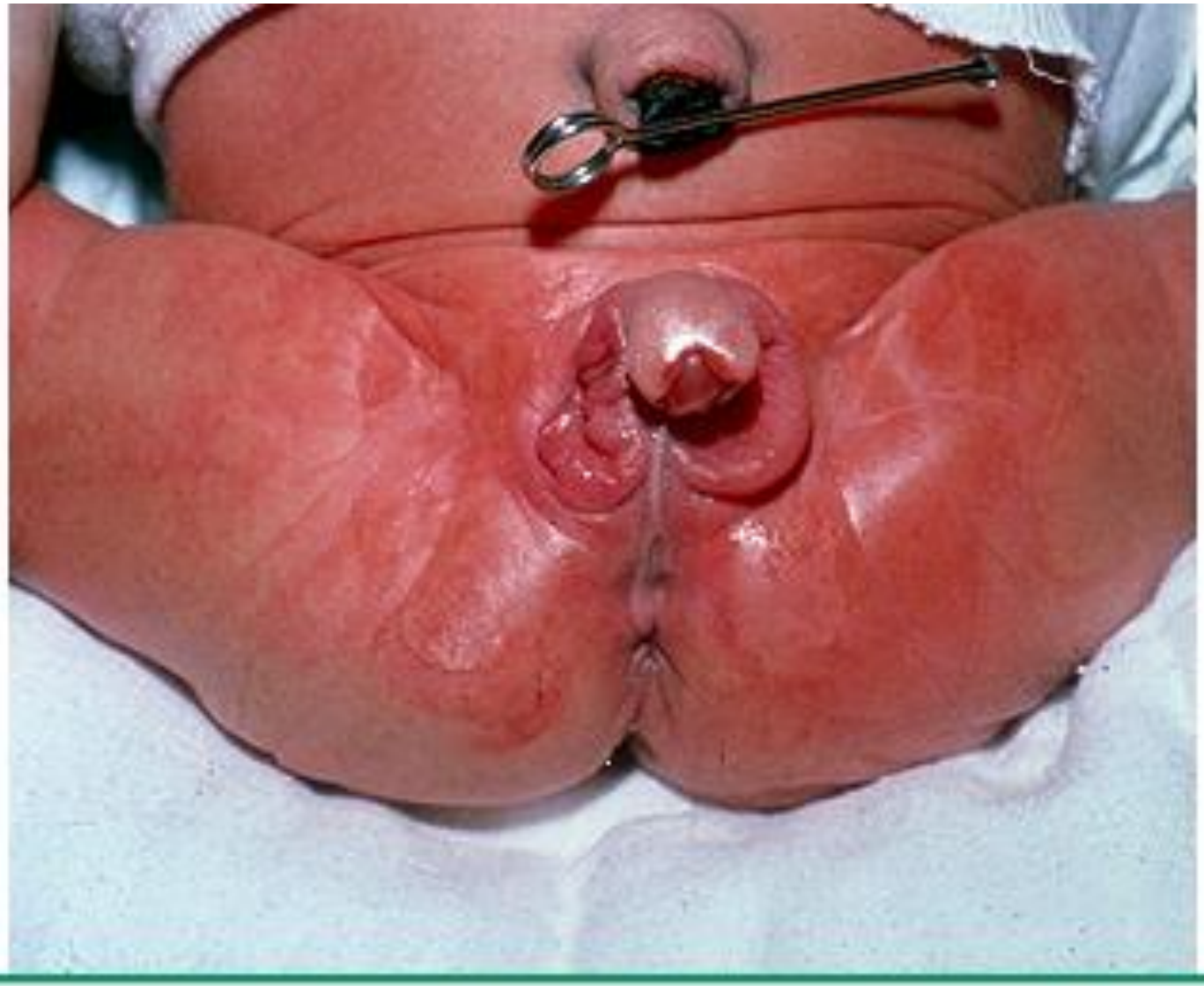
Disorder of sexual differentiation can be subdivided into four main steps: genetic, Gonadal, ductal, & genital differentiation.

- Chromosomal sex (46 XY or 46 XX).
- Gonadal sex (testis or ovary).
- Internal duct sex (male or female internal genital organs).
- External duct sex (male or female external genitalia).

Old term	New term
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite: Undervirilization of an XY male Undermasculanization of an XY male	46 XY DSD
Female pseudohermaphrodite Overvirilization of an XX female Masculanization of an XX female	46 XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46 XX testicular DSD
XY sex reversal	46 XY complete gonadal dysgenesis

46 XX DSD

The commonest type in 30-50 % of all cases of DSD



This patient with male phenotypic appearance had a 46,XX karyotype and ambiguous genitalia. The labioscrotal folds are empty, but rugated and at least partially fused; the phallus is intermediate sized.

46 XX DSD

Indications for evaluation for female phenotype with any of the following features:

- Clitoromegaly: Clitoral width >6 mm or clitoral length >9 mm).
- Posterior labial fusion: Anogenital ratio > 0.5.
- Single opening (common urogenital sinus) instead of a separate opening for the urethra & vagina.
- Gonads palpable in the labioscrotal folds or the inguinal region.
- Genital appearance discordant with the sex chromosomes.

46,XX DSD

- Typically have female internal genitalia (Mullerian-derived structures).
- External genitalia is virilized as a result of in utero androgen exposure.
- The two major etiologies are either, exposure to fetal or maternal excessive androgens.
- The main cause of excessive fetal androgens is congenital adrenal hyperplasia (CAH).

46,XX DSD

- Excessive maternal androgens are usually consequence of adrenal or ovarian tumors.
- Administration of exogenous androgenic medications is a potential & preventable cause of ambiguous genitalia.
- Placental aromatase enzyme deficiency is another cause of excess androgens in-utero.

46 XY DSD

The second common type of DSD

46 XY DSD

Indications for evaluation for male phenotype with any of the following features:

- Bilaterally nonpalpable gonads.
- Severe hypospadias (scrotal or perineal ectopic meatus, severe penile curvature, fusion of the foreskin with the scrotum, and/or a small glans size (< 14 mm before one year of age).
- Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism (nonpalpable gonad) and/or micropenis (stretched penile length less than 2.5 cm in a full-term infant).
- Genital appearance discordant with the sex chromosomes.

46,XY DSD

- The main etiologic causes that lead to under virilized genitalia in 46XY neonate are:
  - abnormal testis determination factor.
  - defects in androgen biosynthesis & metabolism.
  - resistance to androgens.
  - malformation syndromes.
- It is important to note that a definitive diagnosis/etiology for a newborn with 46,XY genotype is often difficult to establish, and there are many times, when nothing conclusive is discovered.

Causes of 46 XY DSD

- Testicular Hypoplasia.
- Gonadotrophin deficiency/ resistance.
- Bilateral Testicular Dysgenesis (Sawyer syndrome).
- Anti- Mullerian hormone deficiency.
- Testosterone biosynthesis defects.
- 5 α - reductase deficiency.
- Androgen Insensitivity syndrome (partial & complete forms).

Androgen Insensitivity Syndrome

- X-linked recessive disorder.
- AR gene is localized to Xq11-Xq12.
- Two forms of androgen insensitivity syndrome have been described:
  - complete (CAIS) & partial (PAIS).
- The defect often lies in the sensitivity of target receptors to the androgens.
- Wide range of presentations.

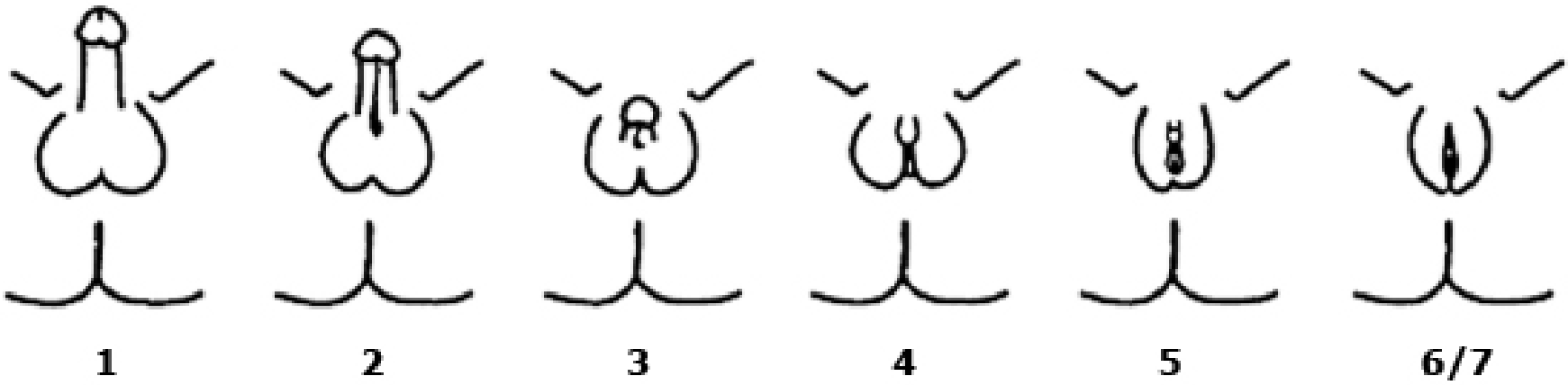
Complete Androgen Insensitivity (CAIS)

- Must be suspected in normal female with palpable gonad (s) at the inguinal region.
- 1-2% of phenotypic females with inguinal hernias have CAIS.
- Testes are normal prepubertal.
- After puberty, the somniferous tubules become atrophic, with no spermatogenesis.
- Risk of malignancy is low < 25 years of age.

Partial Androgen Insensitivity (PAIS)

- The external genitalia are predominantly male or ambiguous.
- Wide range of presentations.
- Pubic & axillary hair develops.
- Gynecomastia.
- Poorly developed male sex characters.

Schematic representation of grading scheme for clinical classification of androgen insensitivity syndromes (AIS)



Grades are numbered 1-7 in order of increasing severity (more defective masculinization).

- Grade 1: Normal masculinization in utero
- Grade 2: Male phenotype with mild undervirilization, eg, isolated hypospadias
- Grade 3: Male phenotype with severe undervirilization, eg, small penis, perineoscrotal hypospadias, bifid scrotum and/or cryptorchidism
- Grade 4: Severe genital ambiguity, with intermediate phallic size, separated labioscrotal folds, and single perineal orifice
- Grade 5: Minimally virilized phenotype, with posterior labial fusion and clitoromegaly
- Grade 6/7: Female phenotype (grade 6 if pubic hair present in adulthood, grade 7 if no pubic hair in adulthood).

5-α - reductase enzyme deficiency

- Autosomal recessive disorder.
- Mapped to 2p23 chromosome.
- Typically, this enzyme converts testosterone to dihydrotestosterone (DHT), which, in turn, acts on the genital tubercle and swellings, & the urogenital sinus to promote external genitalia formation & the formation of the prostate.

Gonadal Disorders

The term Gonadal disorders encompasses both Ovotesticular DSD (ODSD) & Gonadal dysgenesis

Ovotesticular DSD

- Newborn has both ovarian & testicular tissues.
- There are various combinations of these two types of tissues:
  - one ovary & one testis
  - 2 ovotestes
  - one ovotestis partnered with either an ovary or a testis.
- The external genitalia could be male or female, but most often it is ambiguous in nature.
- The most common genotype (over 50% patients) is 46,XX, 30% are mosaic (46,XY/46,XX) or (46,XY/47,XXY or 45,X/46,XY), while small minority have a 46,XY genotype.

Ovotesticular DSD

- 46,XX patients may have translocation of the SRY gene; however, in most cases the genes responsible have yet to be identified.
- The degree of virilization of the external genitalia depends heavily on the ability of the testicular tissue to secrete testosterone, and whether or not the Mullerian ducts have matured into female structures.
- Often, the differentiation of internal & external genitalia will coincide with the gonad on the ipsilateral side.
- For example, if a testis is present on the left side, the Wolffian duct on the left side will remain & differentiate into the appropriate structures and the left side of the Mullerian system will regress (ipsilateral Mullerian inhibiting substance).

Mixed Gonadal Dysgenesis

- Subnormal production of testosterone.
- Insufficient production of MIS.
- Presence of both structures internally.
- Gonadal tumors occur in 30%.
- Early removal of dysgenetic gonads to prevent risk of gonadoblastoma or germinoma.
- 90% of 45X / 46XY have normal male genitalia, remaining 10% have ambiguity.

46,XY gonadal dysgenesis

- The estimated prevalence is 1:100,000 births.
- In complete 46,XY gonadal dysgenesis (Swyer syndrome), the fibrous streak gonad cannot secrete anti-müllerian hormone (AMH).
- This results in persistent Mullerian structures and a female phenotype.
- The phenotype of partial gonadal dysgenesis can range from genital ambiguity to an under virilized male.
- In partial form, because of the phenotypic variability, some patients are diagnosed in infancy with DSD, while others are not diagnosed until puberty when they present with primary amenorrhea.

46 XY Gonadal dysgenesis

- Bilateral dysgenetic gonad development.
- Ranging from Gonadal streaks, dysgenetic testis to normal testis.
- 30% risk of malignancy > age of 30.
- Normal amount of SRY gene.
- The degree of masculinization depends on the extent of testicular differentiation.

46 XY Gonadal dysgenesis

- Testosterone level low – normal.
- HCG test is blunted (dysgenetic gonad).
- Presence of both mullerian & Wolffian structures.
- The diagnosis is made by Gonadal histology.
- Preferred sex of rearing is female (presence of uterus).
- Dysgenetic testes have to be removed.

DSD associated Syndromes

- Trisomy 13
- Trisomy 18
- Aniridia-Wilms
- Aarskog
- Camptomelic dwarfism
- Carpenter
- CHARGE
- VACTERL

Smith-Lemli-Opitz

Meckle-Gruber

Ellis-Van Creveld

Triploidy

4P -

13q-

Laboratory evaluation

- Chromosomal analysis (essential for all cases)
- To rule out congenital adrenal hyperplasia:
  - 17α- hydroxyprogestrone.
  - Fasting glucose.
  - Serum electrolytes & renal function.
  - Plasma ACTH & Cortisol.
  - Plasma Renin activity & Aldosterone.
  - Urinary steroid profiles.

In cases of 46 XY DSD:

- HCG stimulation test to evaluate testosterone / DHT ratio (pre & post HCG stimulation test).

Imaging studies & Laparoscopy

- Abdomen & Pelvic U/S is essential to evaluate the presence / Absence internal male or female internal organs.
- Adrenal U/s (size of Adrenal gland /hyperplasia or tumor.
- Genitogram (presence / absence of vaginal tract & urogenital fistula).
- MRI of the pelvis (if U/S not conclusive).
- Laparoscopy / Laparotomy.
- Gonadal biopsy & histology (pure ovarian /testicular / ovotestis/ mature or dysgenetic structures).

To ensure that the affected individual has a high quality of life , medical practitioners must quickly and correctly assign the individual’s gender & effectively relieve the family’s concerns and anxiety.

Management consideration

Gender assignment depends on:

- Potential for future sexual & reproductive functions.
- Anatomical abnormalities.
- Capabilities of reconstructive surgery.
- In micropenis, if penile size doesn't reach 2.5 cm (after 3 injections of 25 mg testosterone), male assignment is not advisable.
- Religious consideration is important.

Management

- Management of CAH if present.
- Female surgical correction of ambiguous genitalia (procedure depending on age).
- Males:
  - Testosterone injections for micropenis.
  - HCG course followed by orchiopexy if necessary for cryptorchidism.
  - No circumcision if hypospadias.
  - Do not remove Mullerian structures.
  - Gonadectomy if streak or dysgenetic gonads with Y chromosome (risk of malignancy high from infancy).

Islamic view of DSD management : Fatwa From Saudi Arabia (2011)

1) Sex change operation (in non-DSD individual) is totally prohibited & considered to be criminal in accordance with the Holy Quran & the Prophet's sayings.
2) Those who have both male & 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 (i.e., with hormones or surgery)in order to eliminate the ambiguity and to raise him as a male and vice versa.
3) Physicians are required to explain to the child's guardians the results of the medical investigations and whether the evidence indicates that the child is male or female in order to keep the guardians well informed.

Parental counseling

- Parents should see the genitalia.
- Clear statement that it will be possible to decide whether the child is either male or female.
- Investigations are needed to determine the sex identity.
- Postpone naming of the baby & birth certificate till tests results are ready.
- When results back, the diagnosis, prognosis & treatment options are fully discussed
- Parent’s should be involved in taking the decision of “gender assignment.

- When results back, the diagnosis, prognosis and treatment options are fully discussed

- Parent’s should be involved in taking the decision of “gender assignment "and how the child will develop sexually as an adult?


THANKS