AMBIGUOUS GENITALIA

(DISORDERS OF SEXUAL DEVELOPMENT)

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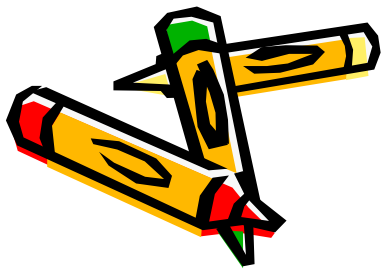
INTRODUCTION

- Normal sexual determination and differentiation
  → interaction of developmental factors (chromosomal, gonadal and hormonal)

- Intersex
  → Disagreement or inconsistency between chromosomal, gonadal and phenotypic sex
  → may or may not result in ambiguous genitalia

- Ambiguous genitalia
  → An atypical or confusing external genitalia appearance

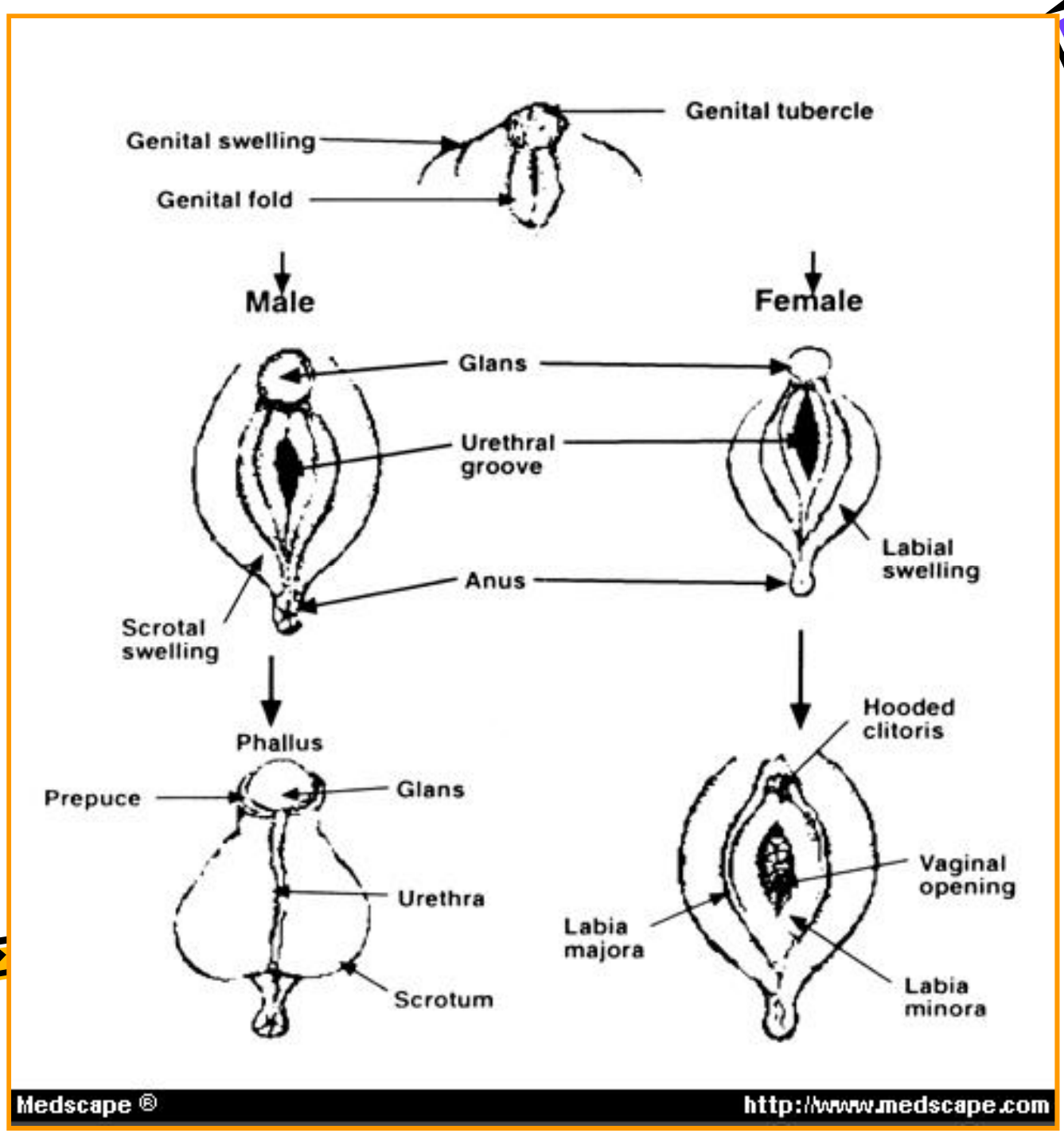


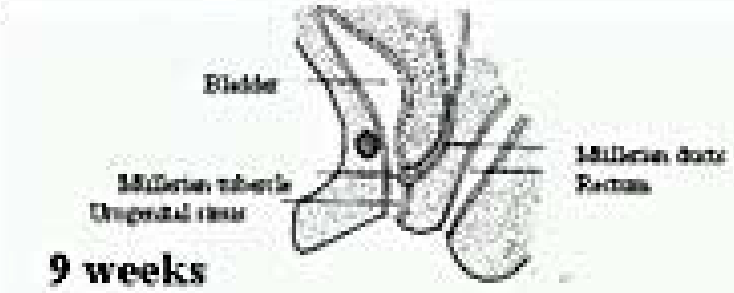
- The term intersex and others → controversial and confusing to practitioners and patients alike.

New term "Disorders of Sex Development (DSD)"

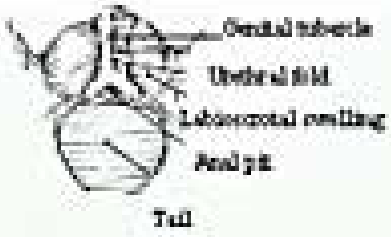
DSD : a congenital conditions in which development of chromosomal, gonadal and anatomic sex is atypical

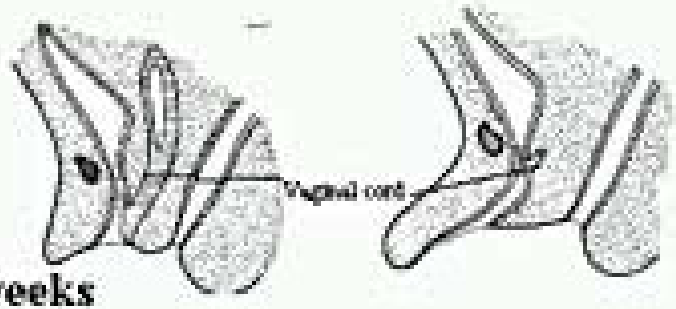
- Management DSD : multidisciplinary approach → hormonal, surgical and gender reassignment


Genital swelling
Genital tubercle
Genital fold
Male
Female
Glans
Urethral groove
Anus
Scrotal swelling
Labial swelling
Phallus
Prepuce
Glans
Urethra
Scrotum
Hooded clitoris
Vaginal opening
Labia majora
Labia minora
Medscape ®
http://www.medscape.com

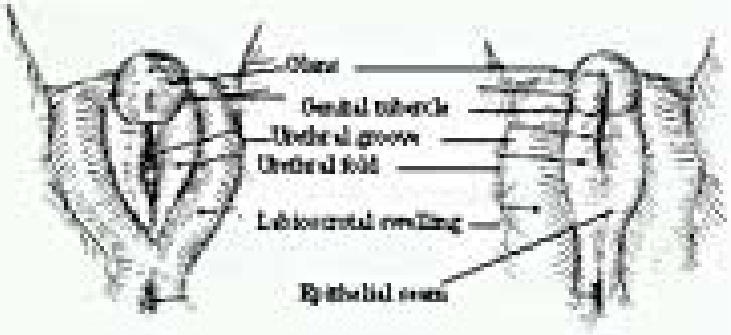


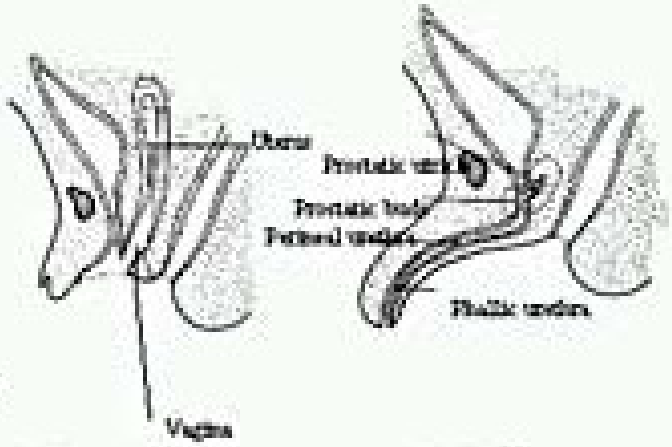
9 weeks



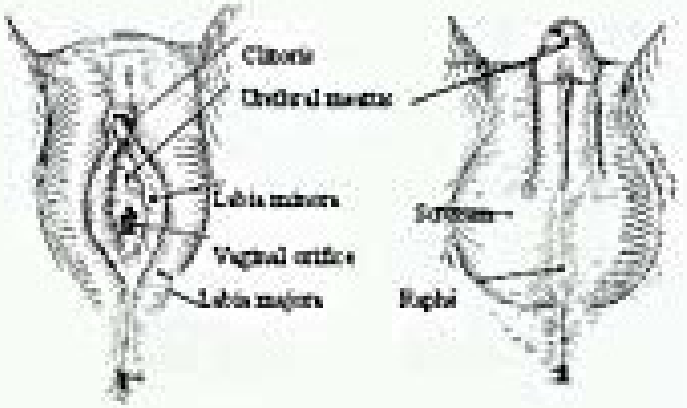


12 weeks

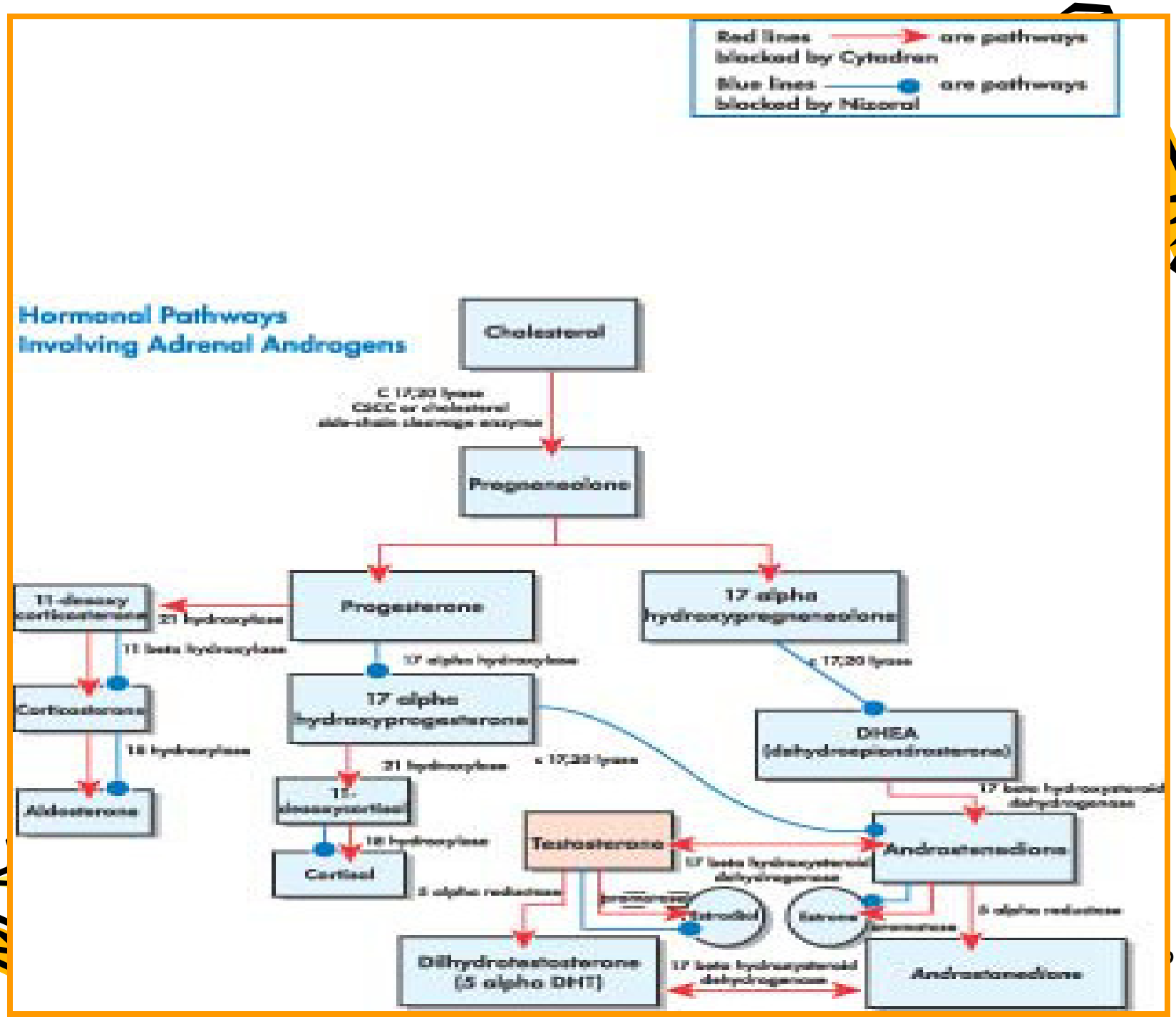




Birth



Female Male Female Male


Red lines are pathways blocked by Cytadren
Blue lines are pathways blocked by Nizoral
Hormonal Pathways
Involving Adrenal Androgens
Cholesterol
C 17,20 lyase
CSCC or cholesterol
side-chain cleavage enzyme
Pregnenealone
Progesterone
17 alpha hydroxypregnenealone
11-deoxy corticosterone
21 hydroxylase
11 beta hydroxylase
17 alpha hydroxylase
c 17,20 lyase
Corticosterone
17 alpha hydroxyprogesterone
DHEA (dehydroepiandrosterone)
18 hydroxylase
21 hydroxylase
c 17,20 lyase
Aldosterone
11-deoxycortisol
17 beta hydroxysteroid dehydrogenase
18 hydroxylase
Testosterone
Androstenedione
Cortisol
17 beta hydroxysteroid dehydrogenase
5 alpha reductase
5 alpha reductase
Dihydrotestosterone (5 alpha DHT)
17 beta hydroxysteroid dehydrogenase
Androstanedione

CLASSIFICATION

- Basically intersex disorders were classified into:
  - Male Pseudohermaphroditism (MPH)
  - Female Pseudohermaphroditism (FPH)
  - Gonadal Dysgenesis (GD)
  - True Hermaphroditism (TH)

- Proposed nomenclature has simplify into 3 categories :
  - 46, XX DSD
  - Sex chromosome DSD
  - 46, XY DSD

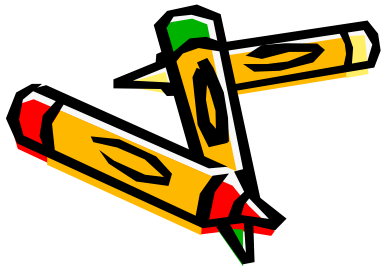
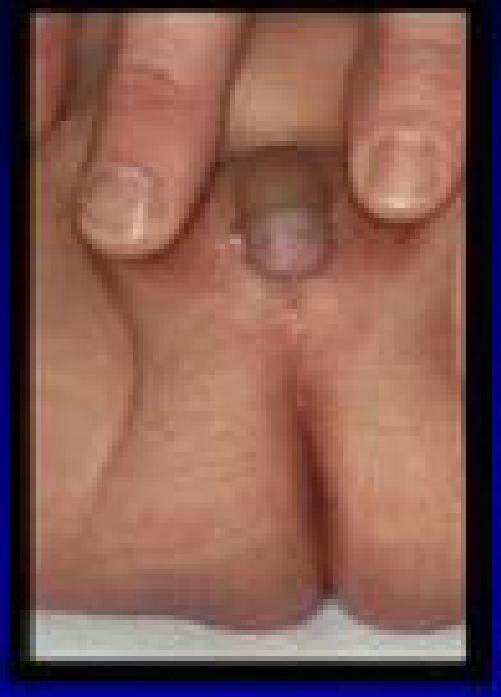


Table 1. Proposed Revised Nomenclature

Previous	Proposed
•Intersex	•DSD
•Male Pseudohermaphroditism, undervirilization of an XY male, and undermasculinization of an XY male	•46, XY DSD
•Female Pseudohermaphroditism, overvirilization of an XX female, and masculinization of an XX female	•46, XX DSD
• True Hermaphroditism	•Ovotesticular DSD
•XX male or XX sex reversal	•46, XX testicular DSD
•XY sex reversal	•46, XY complete gonadal dysgenesis

Ambiguous genitalia



46, XX DSD

- Most common cause of DSD
- Occur in 60-70% of Ambiguous genitalia

- Ovotesticular DSD
  - 10% of children with ambiguous genitalia
  - Children have both ovarian and testicular tissue
    - Testis in 1 side and ovary on contralateral
    - Ovo-testis on 1 side and normal gonad on contralateral
    - Bilateral ovo-testes
  - Appearance : from extremely virilized to extremely feminized

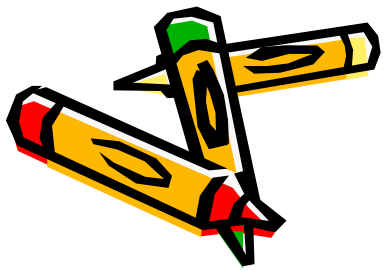


Table 2. Classification of 46,XX DSD (Hughes et al, 2006)

Sub classification	Clinical condition
A. Disorders of gonad (ovary) development	1. Gonad dysgenesis 2. Ovotesticular DSD 3. Testicular DSD (e.g SRY+, dup SOX9, RSPO1)
B. Androgen excess	1. Fetal 3 beta-hydroxysteroid dehydrogenase II deficiency 21 hydroxylase deficiency P450 oxoreductase deficiency (POR) 11 beta-hydroxylase deficiency Glucucorticoid receptor mutations 2. Fetoplacental Aromatase deficiency Oxoreductase deficiency 3. Maternal Maternal virilizing tumor (e.g luteoma) Androgenic drugs
C. Other	1. Syndromic association (e.g cloacal anomalies) 2. Mullerian agenesis / hypoplasia (e.g MURCS) 3. Uterine abnomalities (e.g MODY5) 4. Vaginal atresia (e.g McKusick-Kaufman) 5. Labial adhesion

- The common cause : Congenital Adrenal Hyperplasia (CAH)

- 95% of CAH
  - Hypocortisolism
  - Enzyme 21-hydroxylase deficiency
  - Increased 17-hydroxy progesterone or 17-OHP
  - Manifest as virilization (clitoromegaly, acne, etc)
  - Cortisol substitution → less masculine and potentially fertile
  - May cause Addison's Crisis
  - Newborn female CAH → presence of ambiguous genitalia
  - Newborn male CAH → similar symptoms with Hyperthropic Pyloric Stenosis (HPS), to differentiate it :
    - CAH : hyperkalemia, metabolic acidosis
    - HPS : hypokalemia, matabolic alkalosis

46, XY DSD

- Common cause : Androgen Insensitivity Syndrome (AIS)

- AIS : Testosterone synthesis and secretions normal
  Defect in androgen receptor
  Classified as partial and complete AIS

- PAIS : Presence of ambiguous genitalia
- CAIS : Presence of femoral hernia or amenorrhea in a phenotypic female

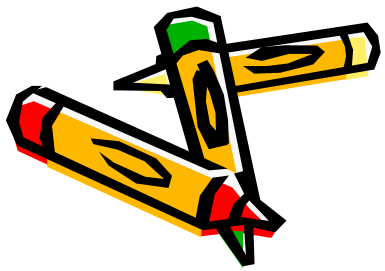


Table 3. Classification of 46,XY DSD

Sub classification	Clinical condition
A. Disorders of gonad (testis) development	1. Complete or partial gonadal dysgenesis (e.g SRY, SOX9, SF1, WT1, DHH, XH-2, duplication of DAX-1 genes, 9p &10p depletion) 2. Ovotesticular DSD 3. Testis regression
B. Disorders in androgen synthesis or action	1. Disorder in androgen synthesis LH receptor mutations Smith-lemli-Opitz syndrome STAR mutation Cholesterol side chain cleavage 3 beta-hydroxysteroid dehydrogenase II P450 oxoreductase 17 beta-hydroxysteroid dehydrogenase II 5 alfa reductase II 2. Disorders of androgen action Androgen Insensitivity Syndrome Drugs and environmental modulations
C. Other	1. Syndromic association of male genital development 2. Persistent Mullerian Duct Syndrome 3. Vanishing Testis Syndrome 4. Isolated Hypospadias (e.g CXorf6) 5. Congenital hypogonadotrophic hypogonadism 6. Cryptorchidism 7. Environmental influences

SEX CHROMOSOME DSD

- Turner & Klinifelter Syndrome → no ambiguous genitalia
- Mixed gonadal dysgenesis → External genitalia varies from ambiguous to normal appearance
- Chromosomal Y should be removed because of the high risk of gonadoblastoma

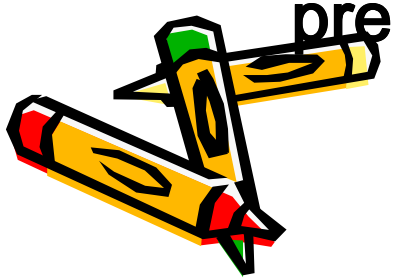
Table 4. Classification of Sex Chromosome DSD

A. 46, XXY (Klinifelter Syndrome and Variants)
B. 45, X (Turner Syndrome and Variants)
C. 45, X / 46, XY (Mixed gonadal dysgenesis, ovotesticular DSD)
D. 46, XX / 46, XY (Chimerism, ovotesticular DSD)

DIAGNOSTIC

- Diagnostic based on :History, Physical examination and Investigations

- Criteria that suggest DSD:
  1. Over genital ambiguity (e.g cloacal extrophy)
  2. Apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal / labial mass
  3. Apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias or mild hypospadias with undescended testis
  4. A family history of DSD such as CAIS
  5. A discordance between genital appearance and prenatal karyotype

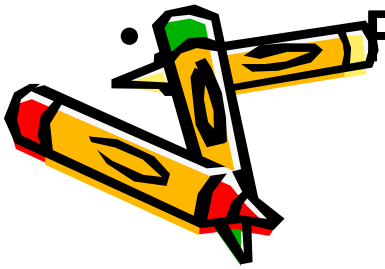


HISTORY

- Pregnancy history
  → progressive androgenization (e.g aromatase deficiency) or miscarriage (e.g CYP11A1 deficiency), or that ended in early infant deaths (e.g salt losing CAH)
- Maternal hormonal or drug ingestion (e.g androgenic drug)
- Family history of ambiguity or infertility
- Gender reassignment at puberty
- Absent puberty
- Accelarated linear growth
- Skeletal abnormalities
- Learning difficulties
- Syndactily
- Fits
- Developmental delay

PHYSICAL EXAMINATION

- No pathognomonic physical feature
- Dysmorphic feature
- Failure to thrive
- Hyperpigmentation
- Acne in prepubertal
- Hypertension → CAH
- Presence or absence of palpable gonads in scrotum or inguinal canal
- Genital examination : phallus size, shape, location of urethral meatus
- Hyperthrophy clitoris
- Examination of scrotum or labia
- Rectal examination → presence or absence of uterus



INVESTIGATION

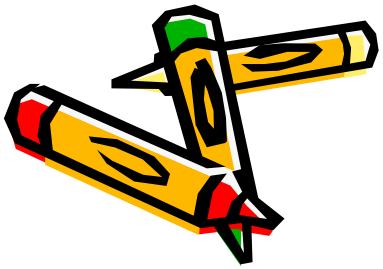
- Laboratory examination
  - Chromosomal analysis or genetic evaluation
  - FISH and karyotyping
  - Serum electrolyte →CAH
  - Serum 17 alfa-hydroxyprogesterone
  - Urinary level of 17-ketosteroid

- Imaging
  - Abdominal and pelvic ultrasound
  - Genitogram
  - Laparotomies, laparoscopy or gonadal biopsy
  - Bone age

MANAGEMENT

- General concept of clinical mangement of DSD:
  - Avoid gender assignment in newborn
  - Evaluation and long term management with multidisciplinary team
  - Gender assigment
  - Communication with patient and families
  - Respect with patient and family concerns

- Multidisciplinary approach → pediatric endocrinology, surgery, urology, pscychology/psychiatry, gynaecology, genetics, neonatology, social working, nursing and medical ethics



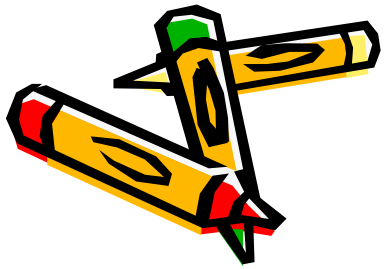
- Management
  - Gender assignment and surgical
  - Hormone replacement and psychosocial therapy → not always indicated in DSD
  - Sex steroid therapy → hypogonadism
  - Cortisol → avoid adrenal crisis

- Factors that influence gender assignment :
  - Diagnosis, surgical options, need for life long replacement therapy, fertility, etc

- Surgery : vaginoplasty, testis removal, clitoroplasty → decision involved family

CONCLUSION

- Etiologies of DSD many and complex
- Evaluation should be expeditiously and multidisciplinary approach → involved endocrinologist, geneticist, radiologist, urologist, pediatric surgeon and psychiatrist



THANK YOU