Paediatric Endocrinology

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DISORDERS OF SEX DIFFERENTIATION : PART I

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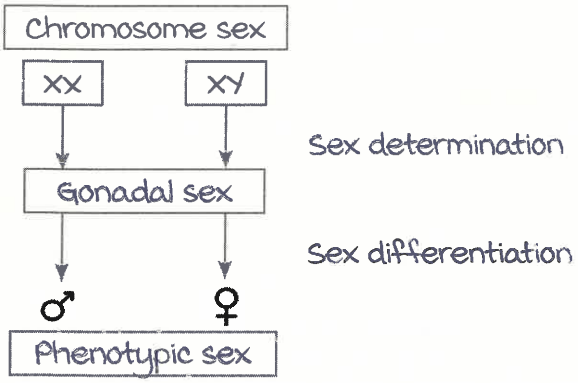
Sex determination and differentiation 00:00:17

Definition of DSD :

Congenital conditions in which the development of chromosomal, gonadal or anatomic (Phenotypic) sex is atypical.

3 levels of sex development :

- Chromosomal sex : Karyotype.
- Gonadal sex : Based on gonads (Testis/ovary).
- Phenotype sex : Based on external/internal genitalia.



Development of gonads :

- Sex determination : Chromosomal sex determines development of gonads.
- Sex differentiation : Gonads determine development of external/internal genitalia.

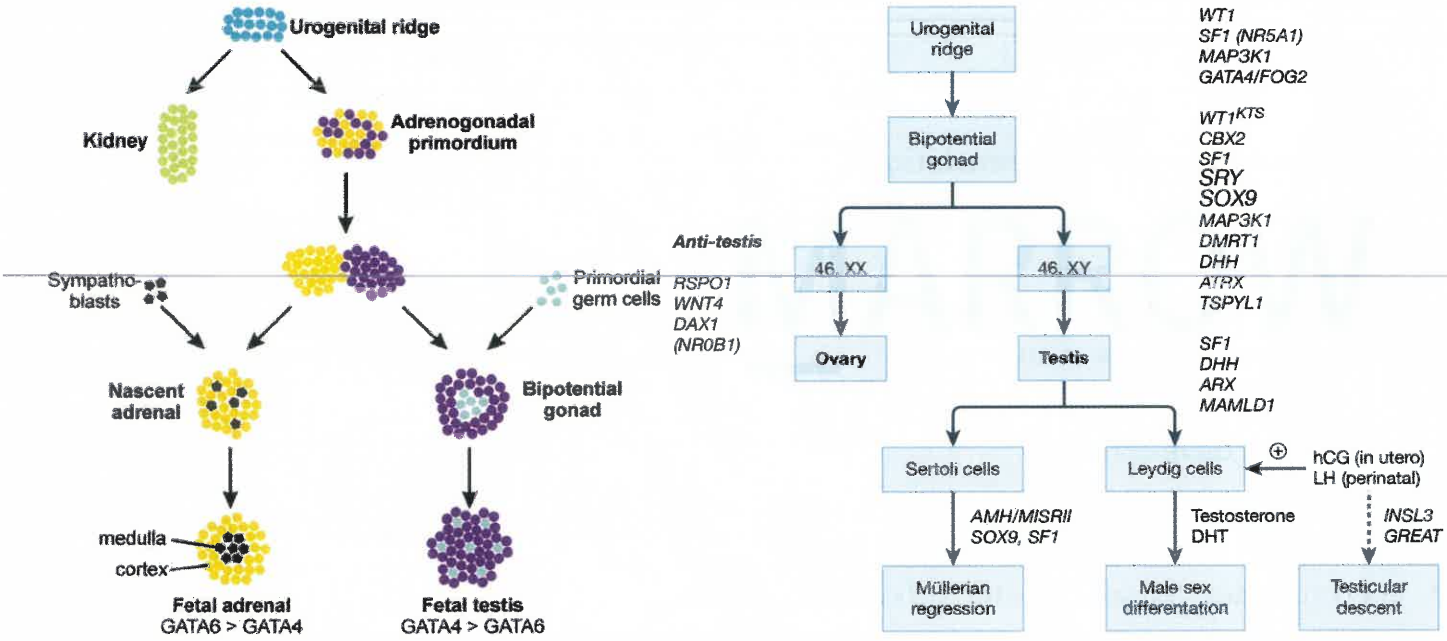
Origin of gonads : mesoderm (Urogenital ridge).

Adrenals & gonads have common origin :

- Defect of adrenal hormonogenesis is a/w ambiguous genitalia.
- Abnormal hormonogenesis in gonad (DSD) is a/w congenital adrenal hyperplasia.

Gonads are invaded by primordial germ cells from yolk sac.

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Development of gonads

Urogenital ridge : Bipotential gonad develops.

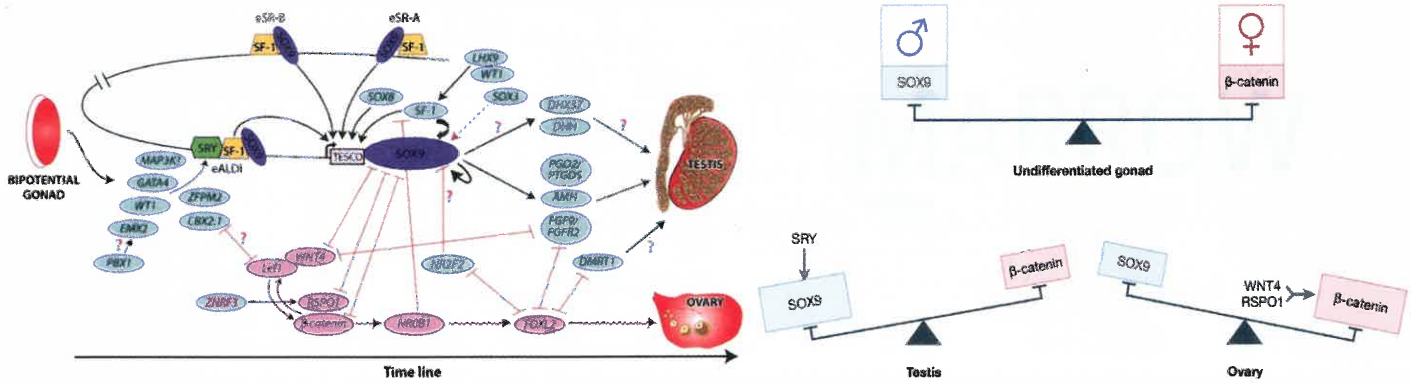
Sex determination :

Transcription factors responsible for development of testis (On Y chromosome) :

- SRY gene/sex determining region of Y chromosome.
- SOX9.
- WT1.

Transcription factors responsible for ovarian development/anti testis (On X chromosome) :

- RSPO1.
- WNT4
- DAX1.



Sex differentiation from bipotential gonad

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Sex differentiation :

Leydig cells in testis :

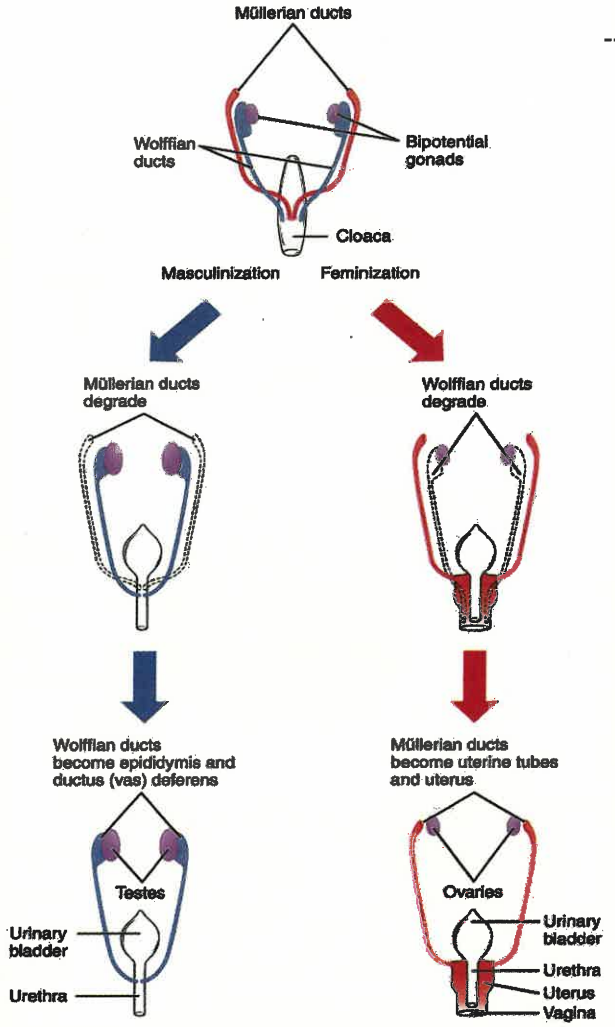
- Secrete testosterone : Development of internal genitalia/Wolffian structures.
- Testosterone → Dihydrotestosterone (DHT) (By 5α reductase) : Development of external genitalia.

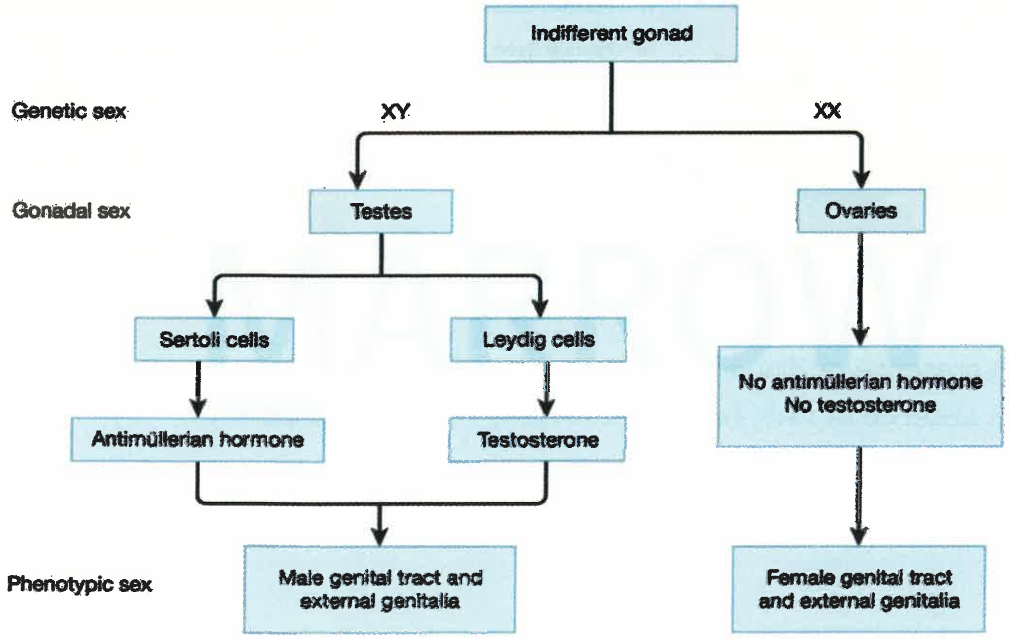
Sertoli cells in testis :

Secrete AMH (Antimullerian hormone) → Regression of mullerian structures.

Mullerian structures : Female internal genitalia.

Wolffian Structures : Male internal genitalia.





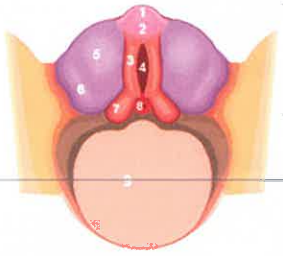
Phenotypic sex differentiation

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Development of external genitalia :

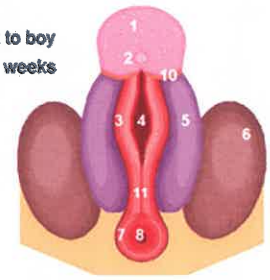
Homologies in the anatomy of the external human genitalia

1 = Glans
2 = Epithelial tag
3 = Urethral fold
4 = Urethral groove
5 = Lateral butress
6 = Labio-scrotal swelling
7 = Anal tubercle
8 = Anal pit
9 = Coccyx, tail
10 = Coronal sulcus
(future origin of prepuce)



Early foetal stage:
The embryonic precursors of the organs are identical in males and females.

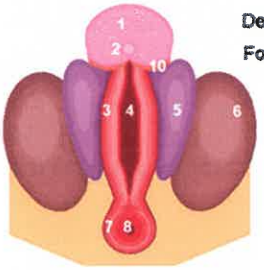
Development to boy
Foetus about 10 weeks



5 = Lateral tubercle becomes shaft of penis / of clitoris

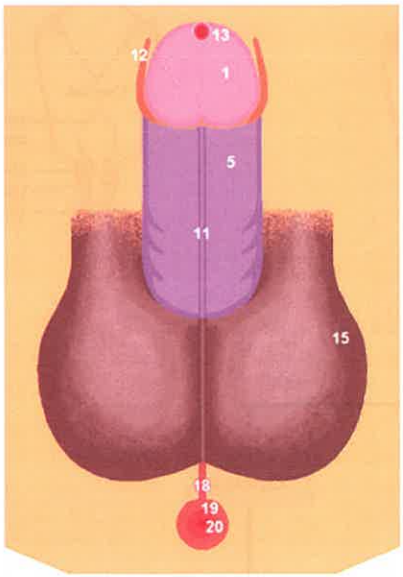
6 = Labioscrotal swelling becomes Scrotum / Labia majora

11 = Raphe



Development to girl
Foetus about 10 weeks

Time of birth



12 = Prepuce

13 = External urethral orifice

14 = Labia minora (inner Lips)

15 = Labia majora (outer Lips) or Scrotum

16 = Vaginal orifice

17 = Posterior labial commisure

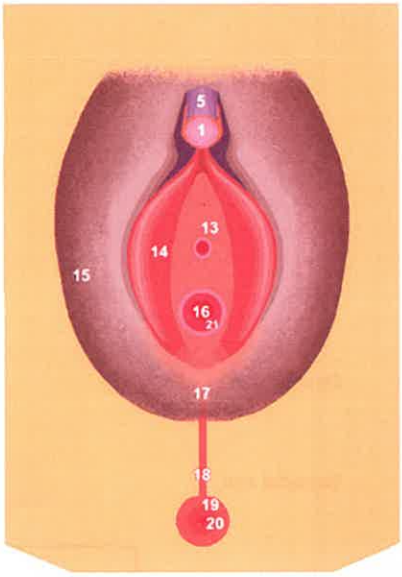
18 = Perineal raphe

19 = Perianal tissues including external anal sphincter muscle

20 = Anus

21 = Hymen

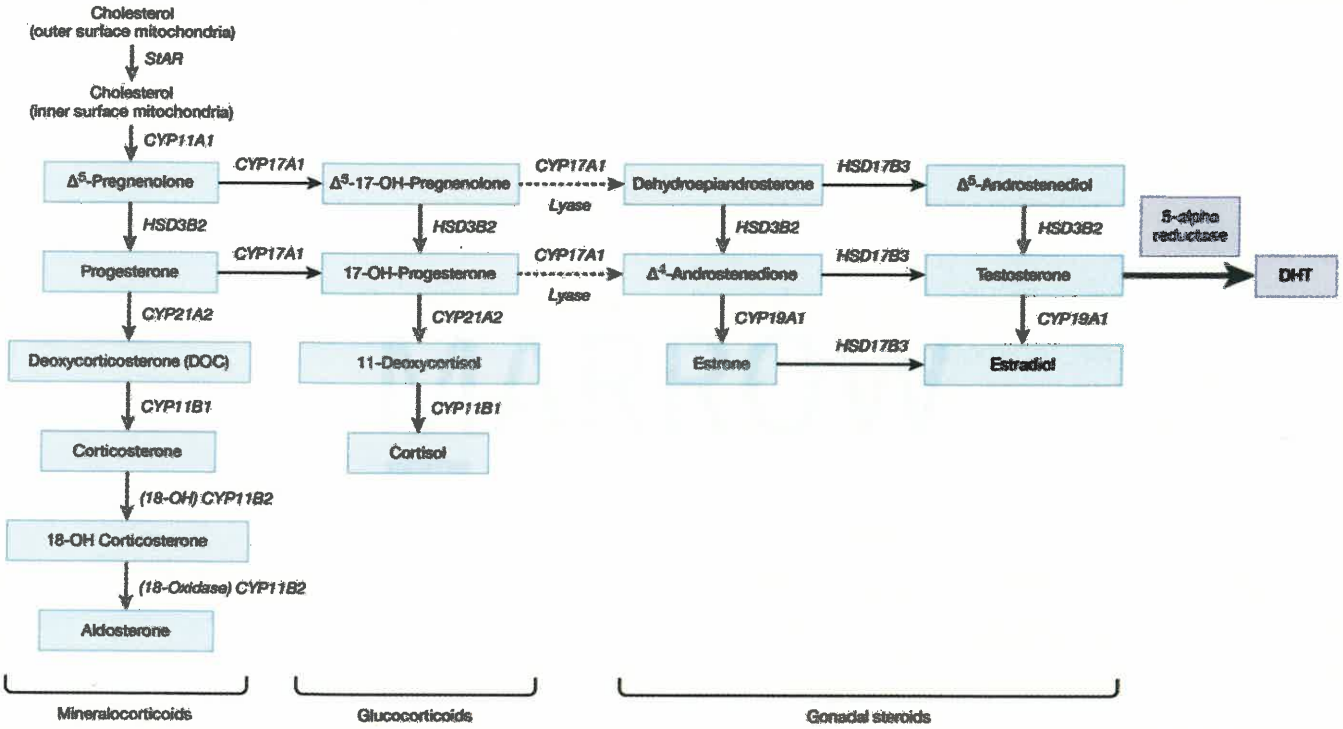
Time of birth



- In presence of dihydrotestosterone, male external genitalia develops.
- In absence of DHT, female external genitalia develops.

Androgen synthesis in testes :

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Androgen synthesis in testis :

- In fetal life (5th–12th week of IUL) : Stimulated by hCG (Placenta).
- In post pubertal period : Stimulated by LH.
- Initial steps in androgen synthesis in both adrenals and testes are same.
- 17 hydroxylase enzyme has intrinsic 17, 20 lyase activity : 17 hydroxylase-17, 20 lyase.
- 17 β hydroxy steroid dehydrogenase Type 3/17βHSD3 : Converts androstenedione to testosterone.
- Aromatase : Converts androgen precursors to estrogen precursors.

Note :

Pituitary starts secreting LH, FSH by 12 weeks of IUL.

Psychological sex (Brain sex) :

Term	Explanation
Gender identity	Self identification of gender as male, female or other
Gender expression/role	Expression of gender stereotypical behavior Aggression Parenting rehearsal Peer & group interactions Labeling (Eg : tomboy) Grooming behavior
Sexual orientation	Pattern of sexual & romantic attraction

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Ambiguous genitalia

00:24:04

Causes :

1. Undervirilized male.
2. Virilized female.

Virilisation : Exposure to androgens/male hormones.

Classification of disorders of sex differentiation (DSD) :

Sex chromosome DSD :

- 47,XXY (Klinefelter syn- drome) and variants.
- 45,X (Turner syndrome) and variants.
- 45,X/46,XY (mosaicism) and variants.
- 46,XX/46,XY (Chimerism).

46, XY DSD :

Disorders of gonadal (testis) development :

- Complete or partial gonadal dysgenesis (e.g., SF1/NR5A1, WT1, GATA4, FOG2/ZFPm2, CBX2, SRY, SOX9, SOX8, MAP3K1, ESR2/NR3A2, DMRT1, TSPYL1, DHH, SAMD9, ARX, MAMLD1/CXorf6).
- Ovotesticular DSD.
- Testis regression.

Disorders in androgen synthesis or action.

- Disorders of androgen synthesis.
  - Luteinizing hormone (LH) receptor mutations.
  - Smith-Lemli-Opitz syndrome.
  - STAR protein mutations.
  - Cholesterol side-chain cleavage (CYP11A1).
  - 3B-hydroxysteroid dehydrogenase 2 (HSD3B2).
  - 17a-hydroxylase/17,20-lyase (CYP17).
  - P450 oxidoreductase (POR).
  - Cytochrome b5 (CYB5A).
  - Aldo-keto reductase 1C2 (AKR1C2).
  - 17 beta-hydroxysteroid dehydrogenase (HSD17B3).
  - 5a-reductase 2 (SRD5A2).
- Disorders of androgen action :
  - Androgen insensitivity syndrome.
- Drugs and environmental modulators.

Other

----- Active space -----

- Syndromic associations of male genital development (E.g. cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium).
- Persistent müllerian duct syndrome.
- Vanishing testis syndrome.
- Isolated hypospadias.
- Cryptorchidism (INSL3, GREAT).
- Environmental influences.

46, XX DSD :

Disorders of gonadal (Ovary) development :

- Gonadal dysgenesis.
- Ovotesticular DSD (E.g. NR5A1, NR2F2, RSPO1).
- Testicular DSD (E.g., SRY, dup SOX9, dup SOX3, NR5A1, NR2F2, RSPO1, WNT4).

Androgen excess :

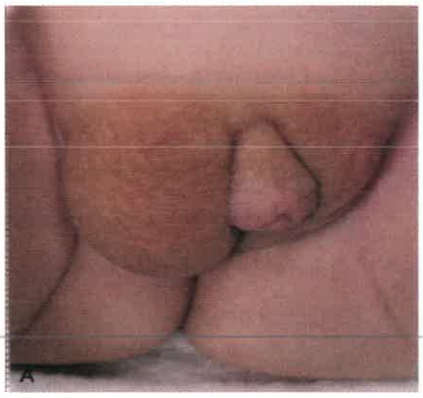
- Fetal :
  - 3B-hydroxysteroid dehydrogenase 2 (HSD3B2).
  - 21-hydroxylase (CYP21A2).
  - P450 oxidoreductase (POR).
  - 11 beta-hydroxylase (CYP11B1).
  - Glucocorticoid receptor mutations.
- Fetoplacental :
  - Aromatase (CYP19) deficiency.
  - Oxidoreductase (POR) deficiency.
- Maternal :
  - Maternal virilizing tumors (E.g., luteomas).
  - androgenic drugs.

Other :

- Syndromic associations (E.g., cloacal anomalies).
- müllerian agenesis/hypoplasia (e.g., MKRH).
- Uterine abnormalities (E.g., MODY5).
- Vaginal atresias (E.g., McKusick-Kaufman).
- Labial adhesions.

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45 X/46 XY mosaicism and variants :


Ambiguous genitalia

- Mixed gonadal dysgenesis.
- D/t anaphase lag during mitosis in the zygote.
- 45 X/46 XY, 45 X/47 XYY or 45 X/46 XY/ 47 XYY.
- Asymmetric gonadal differentiation.
- Streak gonads (Intra abdominal) and well formed testes (Inguinoscrotal region).
- 40% cases have Turner phenotype : Short stature, nuchal folds, low set hair line, cardiac and renal abnormalities.

Ovotesticular DSD :

- Chimerism.
- 2 sets of cells from 2 different lineage.
- Lateral cases (20%) : Testis on one side and an ovary on the other side. Ovary (Or ovotestis) is more frequently found on the left side, whereas the testis (Or ovotestis) is found more often on the right.
- Bilateral cases (30%) : Testicular and ovarian tissue bilaterally as ovotestis.
- Unilateral cases (50%) : Ovotestis on one side and an ovary/testis on the other side.

Note :

Chromosmal DSD have remnants of mullerian structures (Dysplastic gonads do not produce AMH) and asymmetry of gonads.

46 XY DSD :

1. Disorders of gonadal development.
2. Disorders of androgen biosynthesis.
3. Disorders of androgen action.

Disorders of testicular development :

Mutation	Features
WT1	Denys Drash syndrome, Fraisier syndrome, WAGR
SF1	Adrenal hypoplasia congenita Mothers : Premature ovarian insufficiency
SRY	Dysgenetic testes or ovotestes

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SOX9	Dysgenetic testes or ovotestes Campomelic dysplasia
GATA4, FOG2	Cardiac defects (Septal defects, tetralogy of Fallot)
NR3A2 (ESR2)	Anal atresia, blepharophimosis, dysmorphic features
DHH	Minifascicular neuropathy
TSPYL	Sudden infant death
SAMD9	MIRAGE syndrome (myelodysplasia, infections, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy)
ARX	X-linked lissencephaly, epilepsy, temperature instability
ATRX	α Thalassemia, mental retardation
DMRT1	mental retardation
WNT4	mental retardation
DAX1	Dysgenetic testes or ovary Hypogonadotropic hypogonadism

Denys Drash syndrome :

- Complete/partial dysgenesis.
- Risk of Wilm's tumour.
- Early onset nephropathy.

Fraisier syndrome :

- Complete/partial dysgenesis.
- Renal abnormality.
- Wilm's tumour.
- Late onset nephropathy.

WAGR syndrome :

- Wilm's tumour.
- Aniridia.
- Genital abnormalities.
- Retardation.

Campomelic dysplasia :

- Bowing of long bones.
- Thoracic cage abnormalities.
- Craniosynostosis.
- Hypertelorism.

----- Active space -----

Phenotype of disorders of testicular development :

Complete gonadal dysgenesis :

- Swyer syndrome, 46 XY.
- Complete gonadal dysgenesis → Female genitalia.
- Remnants of mullerian structures present.
- Female with delayed puberty.

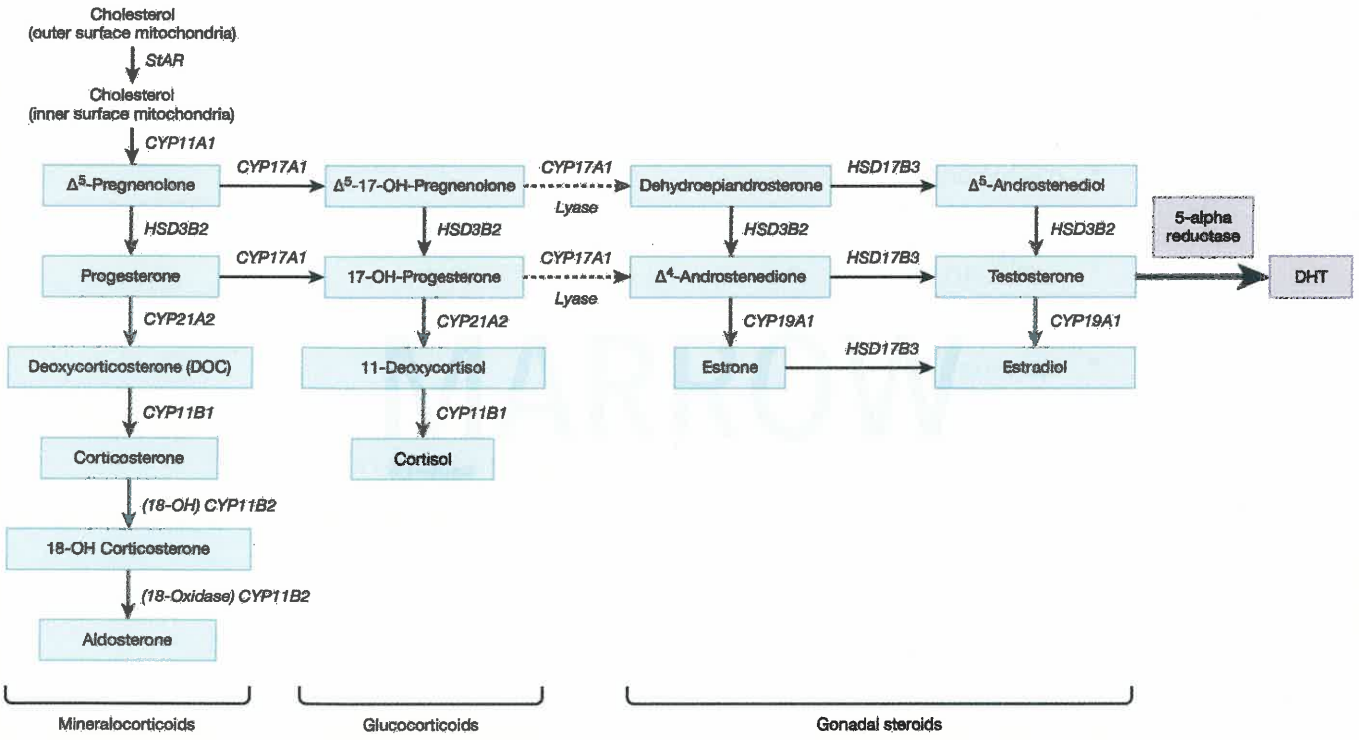
Partial gonadal dysgenesis :

- Ambiguous genitalia.
- Cryptorchidism.

DISORDERS OF SEX DIFFERENTIATION : PART II

----- Active space -----

Androgen synthesis in testes :



Disorders of androgen biosynthesis

00:00:35

Cholesterol synthesis defect :

Smith Lemli Opitz syndrome :

- 7 dehydrocholesterol reductase deficiency.
- Coarse facies, second third toe syndactyly, failure to thrive.
- Developmental delay, cardiac and visceral abnormalities.
- Adrenal insufficiency, salt wasting crisis.

Luteinising hormone receptor mutations :

- Female genitalia.
- Hypospadias or micropenis.
- Wolffian duct derivatives : Hypoplastic.
- Mullerian duct derivatives : Absent.
- Gonads : Testes.
- Biochemical and physiological features : Underandrogenisation with variable insufficiency of sex hormone production at puberty.

----- Active space -----

- Hormone profile :
  a. Low testosterone, dihydrotestosterone.
  b. Elevated LH, exaggerated LH response to LHRH stimulation.
  c. Poor response to testosterone, dihydrotestosterone response to hCG stimulation.

Lipoid congenital adrenal hyperplasia :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in STAR gene.
- Genitalia : Female, sometimes ambioguous, hypospadias or male.
- Wolffian duct derivatives : Hypoplastic/normal.
- Mullerian duct derivatives : Absent.
- Gonads : Testes.
- Biochemical and physiological features : Severe adrenal insufficiency in infancy with salt loss, lack of pubertal development.
- Hormone profile : Usually deficiency of glucocorticoids, mineralocorticoids, sex steroids.

P450 side chain cleavage enzyme deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive, mutations in CYP11A1 gene.
- Genitalia : Female, rarely ambiguous or hypospadias.
- Wolffian duct derivatives : Hypoplastic or normal.
- Mullerian duct derivatives : Absent.
- Gonads : Testes (Or absent).
- Biochemical and physiological features : Severe adrenal insufficiency.
- Hormone : Deficiency of glucocorticoids, mineralocorticoids, sex steroids.

3 β hydroxysteroid dehydrogenase type 2 deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in HSD3B2 gene.
- Genitalia : Ambiguous, hypospadias.
- Wolffian duct derivatives : Normal.
- Mullerian duct derivatives : Absent.
- Gonads : Testes.

----- Active space -----

- Biochemical and physiological features : Severe adrenal insufficiency in infancy, poor virilisation at puberty with gynaecomastia.
- Hormone : Increased concentrations of Δ5C21 and C19 steroids (17 hydroxypregnenolone/cortisol ratio).

17 α hydroxylase/17, 20 lyase deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in CYP17 gene.
- Genitalia : Female, ambiguous or hypospadias.
- Wolffian duct derivatives : Absent or hypoplastic.
- Mullerian duct derivatives : Absent.
- Gonads : Testes.
- Physiological features :
  a. Absent or poor virilisation at puberty, gynaecomastia, hypertension.
  b. At puberty : Primary amenorrhoea, absence of 2° sexual characters.
- Hormone profile :
  a. Decreased testosterone, increased LH and FSH.
  b. Increased plasma deoxycorticosterone, corticosterone, progesterone.
  c. Decreased plasma renin activity.
  d. Low renin hypertension with hypokalemic alkalosis.

P450 oxidoreductase deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in POR gene.
- Genitalia : Ambiguous, hypospadias or male.
- Wolffian duct derivatives : Absent or hypoplastic.
- Mullerian duct derivatives : Absent.
- Gonads : Testes.

Biochemical and physiological features :

- Variable androgenisation at birth.
- Variable virilisation at puberty, especially in girls.
- Glucocorticoid deficiency.
- No severe mineralocorticoid deficiency.
- Antley Bixler syndrome : Skeletal abnormality.

----- Active space -----

Hormone profile :

- Evidence of combined CYP17 and CYP21 insufficiency.
- Normal or low cortisol with poor response to ACTH stimulation.
- Elevated 17-OHP, low testosterone.

17 β hydroxysteroid dehydrogenase type 3 deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in HSD17B3 gene.
- Genitalia : Female, ambiguous, blind vaginal pouch.
- Wolffian duct derivatives : Present.
- Mullerian duct derivatives : Absent.
- Gonads : Testes (usually undescended).

Physiological features :

- Virilisation at puberty : Phallus enlargement, deepening of voice, development of facial and body hair.
- Gynaecomastia : Aromatase converts androgenic precursors to estrogen.

Hormone profile :

- Increased plasma estrone and androstenedione.
- Decreased ratio of plasma testosterone/androstenedione after hCG stimulation test.
- Increased plasma FSH and LH levels.

5 α reductase type 2 deficiency :

- Karyotype : 46, XY.
- Inheritance : Autosomal recessive.
- Mutations in SRD5A2 gene.
- Genitalia : Usually ambiguous with small, hypoplastic phallus, blind vaginal pouch.
- Wolffian duct derivatives : Normal.
- Mullerian duct derivatives : Absent.
- Gonads : Normal testes.

Physiological features :

- Decreased facial and body hair, no temporal hair recession.
- Prostate not palpable.
- Pubertal virilisation (Penis at 12 syndrome).
- No gynaecomastia.

----- Active space -----

Hormone profile :

- Decreased ratio of 5 α/5 βCal and C19 steroids in urine.
- Increased testosterone/dihydrotestosterone ratio before and after hCG stimulation.
- Modest increase in plasma LH.
- Decreased conversion of testosterone to dihydrotestosterone in vitro.

Disorders of androgen action 00:19:35

Complete androgen insensitivity syndrome :

- Karyotype : 46, XY.
- Inheritance : X linked recessive.
- Mutations in AR gene.
- Genitalia : Female with blind vaginal pouch.
- Wolffian duct derivatives : Often present.
- Mullerian duct derivatives : Absent or vestigial.
- Gonads : Testes.

Physiological findings :

- Scant/absent pubic and axillary hair.
- Breast development at puberty d/t increased aromatase activity.
- Primary amenorrhea.

Partial androgen insensitivity syndrome (Reifenstein syndrome) :

- Ambiguous genitalia at birth.
- Partially/completely descended testis.
- Pubertal virilisation.

Hormone and metabolic profile :

- Increased LH and testosterone levels.
- Normal or increased estradiol.
- FSH levels often normal or slightly increased.
- Resistance to androgenic and metabolic effects of testosterone.

----- Active space -----

46 XX DSD

00:22:58

Disorders of ovarian development :

- SRY gene : Male or ambiguous genitalia.
- SOX9 : Male or ambiguous.
- RSPO1 : Palmar plantar hyperkeratosis, squamous cell carcinoma.
- WNT4 : SERKAL (Sex reversal kidney, adrenal & lung dysgenesis) syndrome.

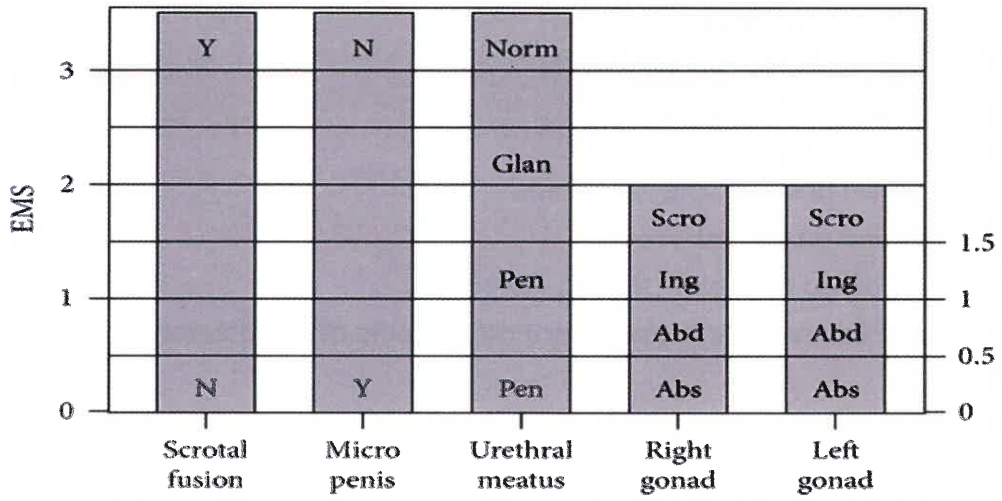
Androgen excess :

- 3 β hdroxysteroid dehydrogenase type 2 deficiency.
- 21 hydroxylase deficiency.
- P450 oxidoreductase deficiency.
- 11 β hydroxylase deficiency.
- Familial glucocorticoid resistance : Resistance of cortisol receptor, excess ACTH.
- Placental aromatase deficiency : Intrauterine exposure to excessive androgens.
- Maternal androgen excess : Primary malignancy and benign lesions such as luteoma and hyperreactio luteinalis.

Examination of ambiguous genitalia :

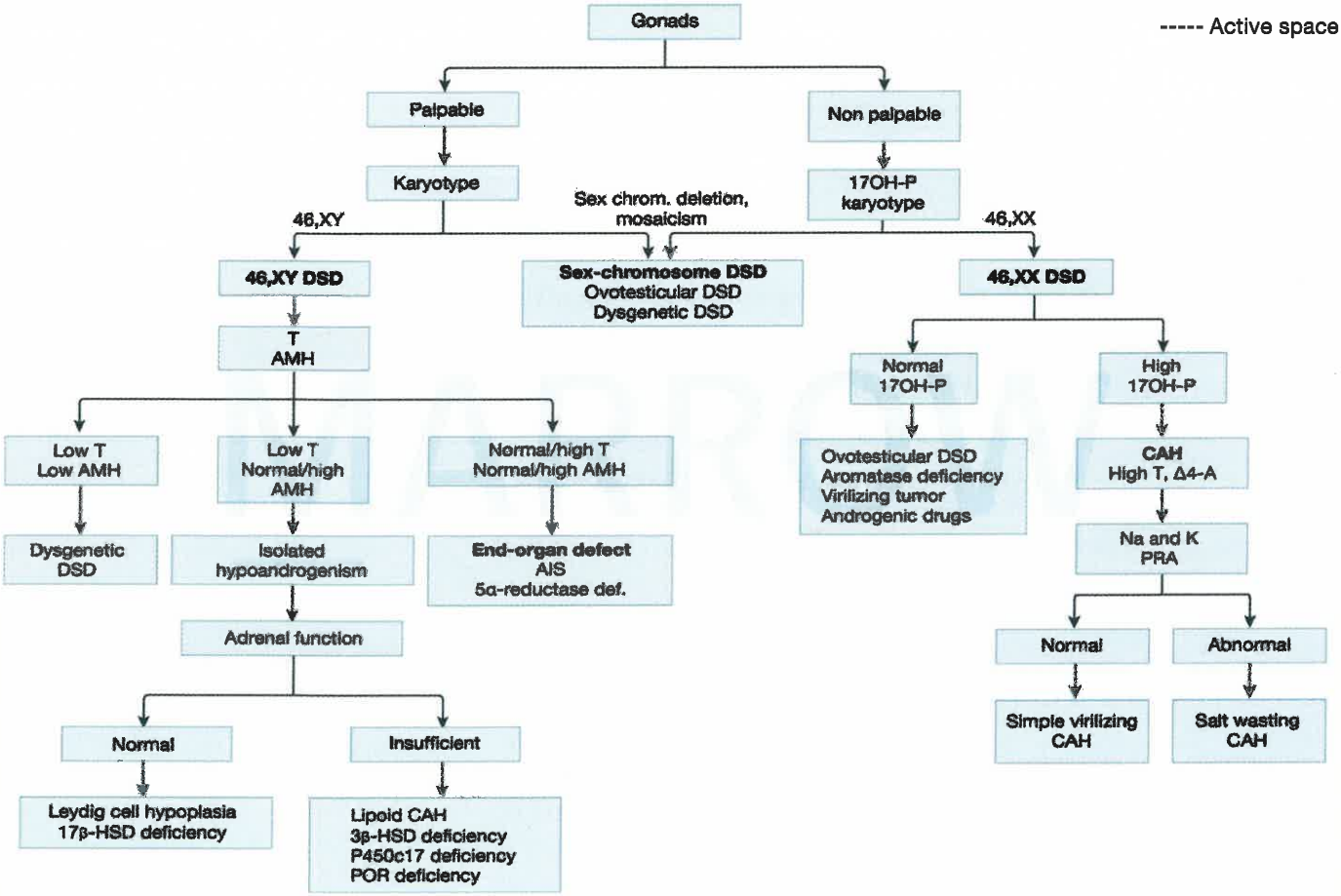


Prader score : To assess virilisation



External masculinisation score (EMS) : To assess undervirilisation

----- Active space -----



Approach to a case with DSD

Investigations :

Hormonal evaluation :

- Testosterone.
- Anti mullerian hormone (MAH).
- Gonadotropins, dihydrotestosterone, 17 hydroxy progesterone.
- Plasma renin activity.
- Random blood sugar.
- Serum sodium, potassium, cortisol.
- hCG stimulation test :
  - Testosterone : Androstenedione <0.8 is → 17 β HSD3 deficiency.
  - Testosterone : DHT >10-20 is suggestive of 5 α reductase deficiency.

Imaging :

- USG pelvis : Mullerian remnants.
- Cystourethroscopy, sinogram.
- MRI pelvis : Gonads, mullerian structures, associated anomalies, anatomy.
- Exploratory laparotomy.

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Treatment :

- Sex of rearing : Collective decision by caregiver/parents/child.
- Hormonal supplementation.
- Corrective surgeries.

Note :

m/c/c of ambiguous genitalia in newborn : 21 hydroxylase deficiency.

Causes of pubertal virilisation :

- 17 β HSD3 deficiency.
- 5 α reductase deficiency.
- Partial androgen insensitivity syndrome.

PRECOCIOUS PUBERTY : PART I

----- Active space -----

Physiology of puberty

00:00:39

Puberty is the sexual maturation of an organism for reproduction.

Gonadal hormones :

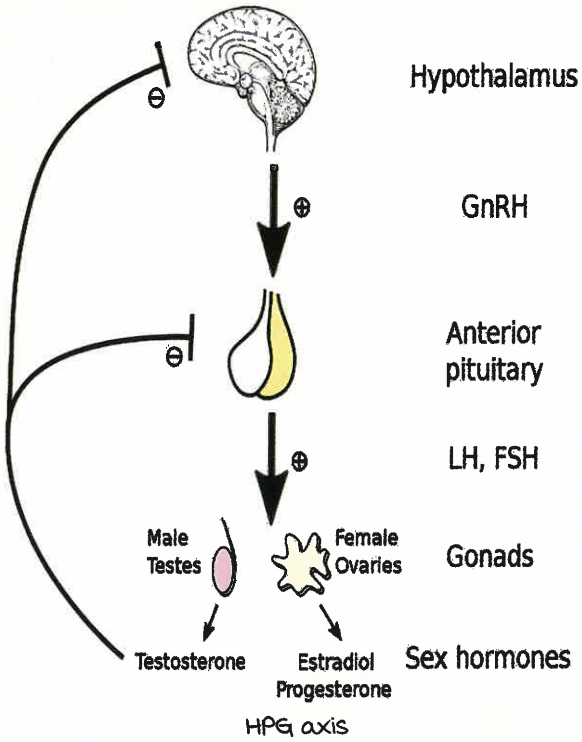
- Testosterone : Males.
- Estrogen, progesterone : Females.

These hormones are required at 2 stages in life :

- 14 weeks gestation (Phenotype sex differentiation).
- At puberty.

HPG axis :

- Hypothalamo pitutary gonadal (HPG) axis is active immediately after birth (mini puberty) → Lasts for 6 months after birth in boys and for about 1-2 years in girls.
- HPG axis goes dormant after minipuberty uptil 8 to 9 years of age (Childhood suppression of HPG axis).
- GnRH hormone releasing neurons are present in hypothalamus.
- Stimulatory input of GnRH neurons are :
  i. KISS peptin & KISS peptin receptor.
  ii. Glutamate.
- Inhibitory input of GnRH neurons are :
  i. MKRN3.
  ii. GABA.



HPG axis

- During childhood, the inhibitory inputs are stronger and stimulatory inputs are weak → Leading to suppression during childhood.
- After skeletal maturation → Stimulatory inputs like KISS peptin are activated → GnRH is released from GnRH releasing neurons in a pulsatile manner → GnRH reaches the anterior pituitary through hypophyseal total circulation.
- If GnRH pulsation frequency is less → Favours secretion of FSH (Follicle stimulating hormone) from anterior pituitary.
- If GnRH pulsation frequency is more → Favours secretion of LH (Luteinising hormone).