MARROW

2024 NEET-SS

UPDATED PEDIATRICS NOTES

ENDOCRINE

Active space

DISORDERS OF SEX DIFFERENTIATION PART 1

Sex determination and differentiation 00:00:17

Definition of DSD :

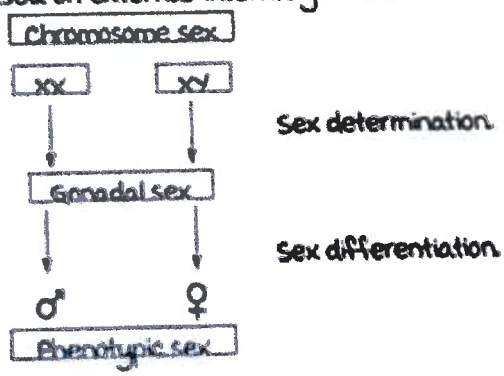
Congenital conditions in which the development of chromosomal, gonadal or anatomic (Phenotypic) sex is atypical.

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 : 00:03:03

Sex determination : Chromosomal sex etermines development of gonads.

Sex differentiation : Gonads determine development of external/internal genitalia.

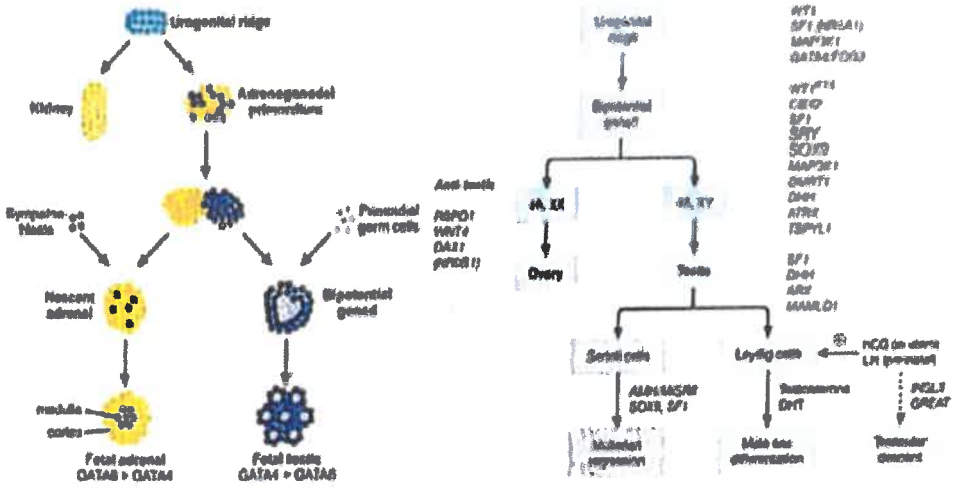
Origin of gonads : mesoderm (urogenital ridge).

Adrenals and gonads have common origin :

- Defect of adrenal hormonogenesis is associated with ambiguous genitalia.
- Abnormal hormonogenesis in gonad (DSD) is associated with congenital adrenal hyperplasia.

Gonads are invaded by primordial germ cells from yolk sac.

Feedback



Development of gonads.

Urogenital ridge : Bipotential gonad develops.

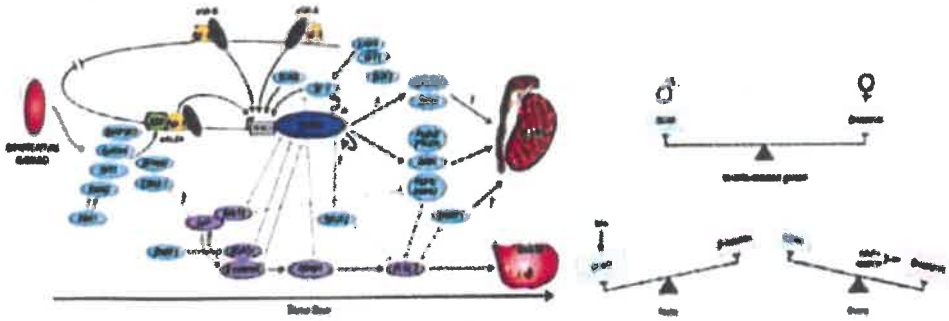
Sex determination :

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.

Sex differentiation :

Leydig cells in testis :

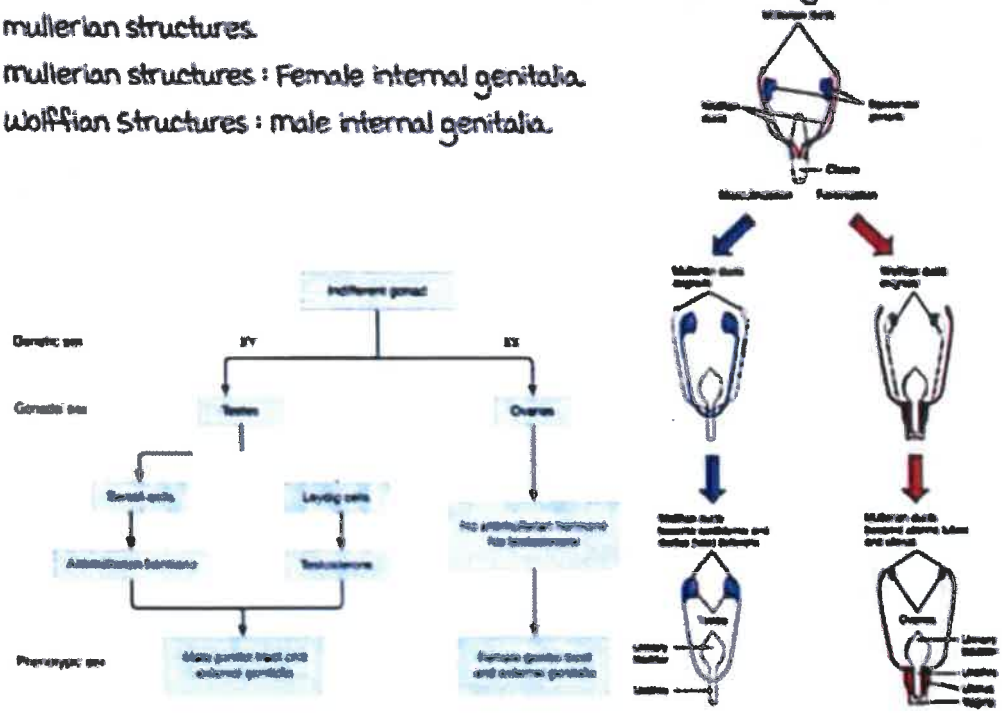
- Secrete testosterone : Development of internal genitalia/wolffian structures.
- Dihydrotestosterone (DHT) → Testosterone (by 5α reductase) : Development of external genitalia.

Feedback

Sertoli cells in testis : Secrete AMH (Antimullerian hormone) → Regression of mullerian structures.

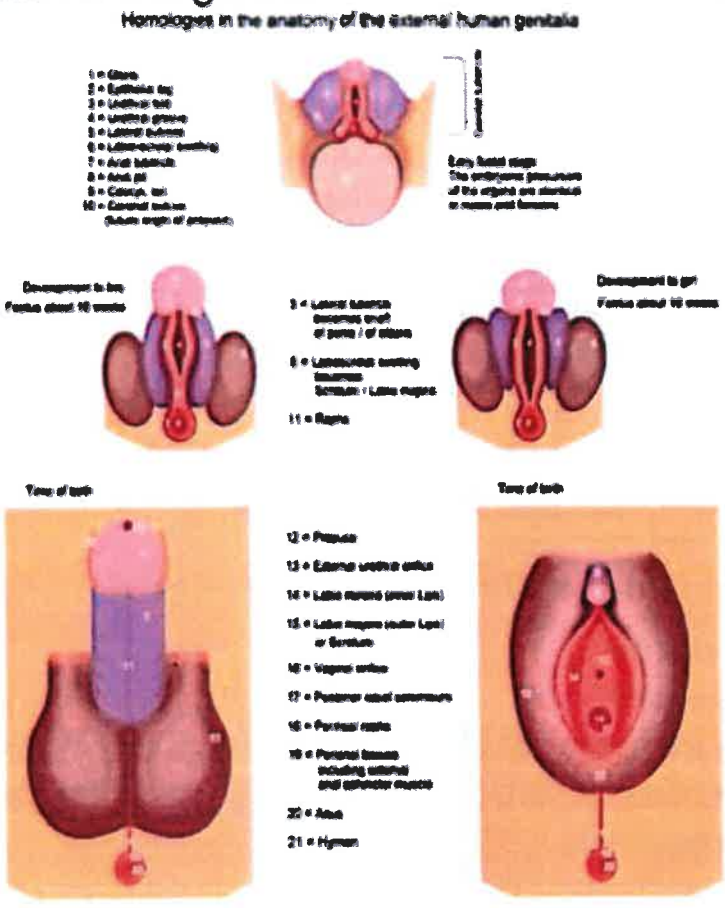
mullerian structures : Female internal genitalia.

Wolffian Structures : male internal genitalia.



Phenotypic sex differentiation.

Development of external genitalia : 00:12:11



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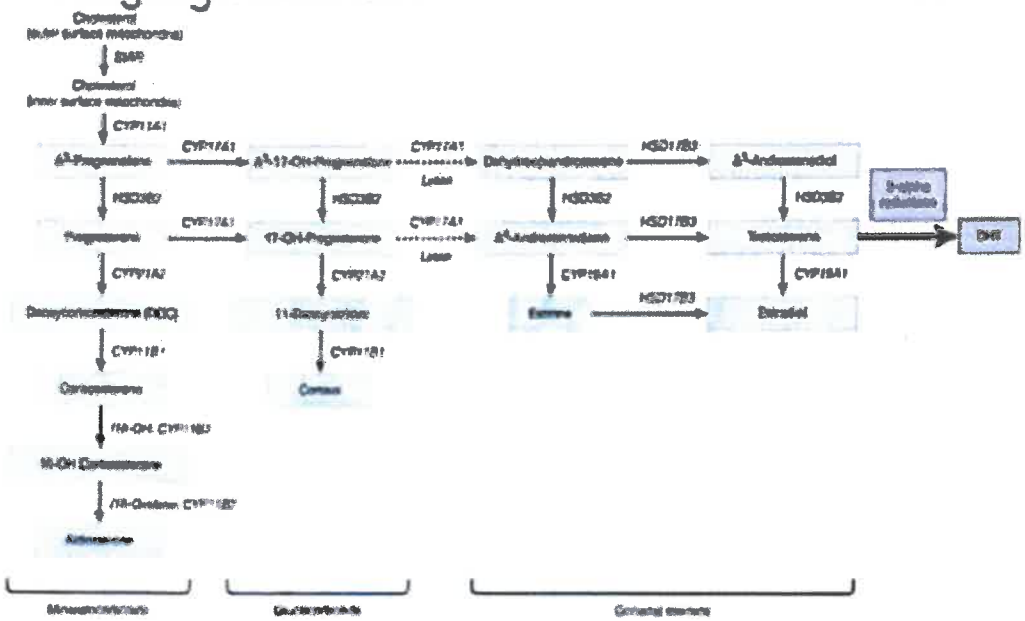
In presence of dihydrotestosterone, male external genitalia develops.
In absencee of DHT, female external genitalia develops.

Androgen synthesis in testes : 00:13:57



Androgen synthesis in testis :

- In fetal life (5th-12th week of IUL) : Stimulated by hCG (Placenta).
- In post pubertal period : Stimulated by luteinising hormone (LH).

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

- 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.
- 17β hydroxy steroid dehydrogenase Type 3/17BHSD3 : Converts androstenedione to testosterone.
- Aromatase : Converts androgen precursors to estrogen precursors.

Psychological sex (Brain sex) : 00:21:10

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 and group interactions Labeling (e.g., "tomboy") Grooming behavior
Sexual orientation	Pattern of sexual and romantic attraction

Components of psychosexual development.

Feedback

Ambiguous genitalia

00:24:04 ..... Active space .....

Causes :

1. Undervirilized male.
2. Virilized female.

Virilisation : Exposure to androgens/male hormones.

Classification of disorders of sex differentiation (DSD) :

Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 47,XXY (Klinefelter syndrome) and variants B: 45,X (Turner syndrome) and variants C: 45,X/46,XY (mosaicism) and variants D: 46,XX/46,XY (chimerism)	A: 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** B: 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*) 3β-hydroxysteroid dehydrogenase 2 (*HSD3B2*) 17α-hydroxylase/17,20-lyase (*CYP17*) P450 oxidoreductase (POR) Cytochrome b_5 (*CYB5A*) Aldo-keto reductase 1C2 (*AKR1C2*) 17β-hydroxysteroid dehydrogenase (*HSD17B3*) 5α-reductase 2 (*SRD5A2*) Disorders of androgen action Androgen insensitivity syndrome Drugs and environmental modulators C: Other 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	A: 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*) B: Androgen excess Fetal 3β-hydroxysteroid dehydrogenase 2 (*HSD3B2*) 21-hydroxylase (*CYP21A2*) P450 oxidoreductase (POR) 11β-hydroxylase (*CYP11B1*) Glucocorticoid receptor mutations Fetoplacental Aromatase (*CYP19*) deficiency Oxidoreductase (POR) deficiency Maternal **Maternal virilizing tumors** (e.g., luteomas) Androgenic drugs C: Other Syndromic associations (e.g., cloacal anomalies) Müllerian agenesis/hypoplasia (e.g., *MKRN3*) **Uterine** abnormalities (e.g., MODY5) Vaginal atresias (e.g., McKusick-Kaufman) Labial adhesions

45 X/46 XY mosaicism and variants :

- 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 hairline, cardiac and renal abnormalities.

Feedback

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

Ovotesticular DSD :

- Chimerism.
- 2 sets of cells from a 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 :

00:47:00

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

Feedback

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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.

Phenotype of disorders of testicular development :

Sweyer syndrome, 46 XY :

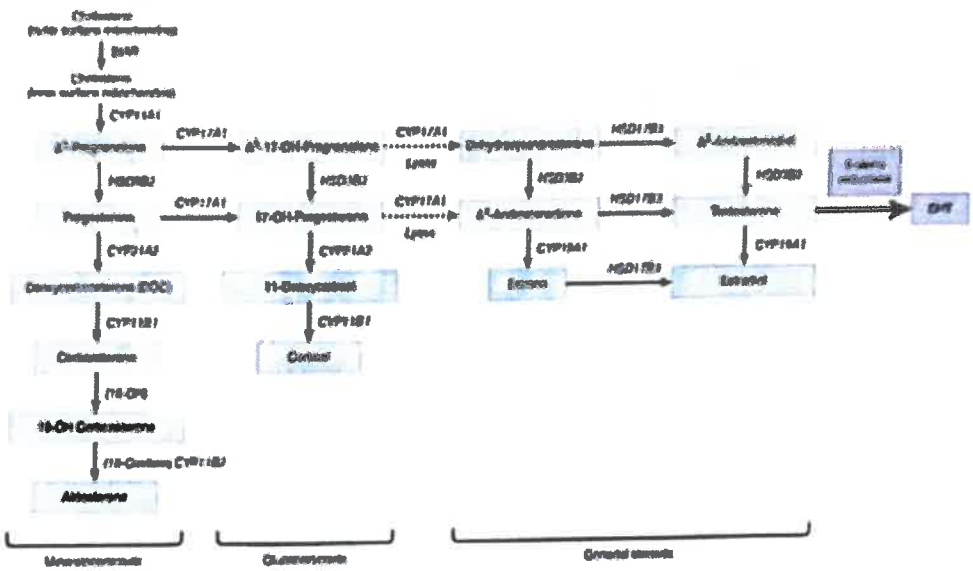
- Complete gonadal dysgenesis → Female genitalia.
- Remnants of mullerian structures present.
- Female with delayed puberty.

Partial gonadal dysgenesis :

- Ambiguous genitalia.
- Cryptorchidism.

DISORDERS OF SEX DIFFERENTIATION PART II

Androgen synthesis in testes :



Disorders of androgen biosynthesis 00:00:15

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.

Hormone profile :

- Low testosterone, dihydrotestosterone.

Active space

- Elevated LH, exaggerated LH response to LHRH stimulation.
- 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 ambiguous, 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.
- Biochemical and physiological features : Severe adrenal insufficiency in infancy, poor virilisation at puberty with gynaecomastia.
- Hormone : Increased concentrations of $\Delta 5C21$ and C19 steroids (17 hydroxypregnenolone/cortisol ratio).

Feedback

17α hydroxylase/17,20 – lyase deficiency :

- Karytype : 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 :
- Absent or poor virilisation at puberty, gynaecomastia, hypertension.
- At puberty : Primary amenorrhoea, absence of 2° sexual characters.
- Hormone profile :
  - Decreased testosterone, increased LH and FSH.
  - Increased plasma deoxycorticosterone, corticosterone, progesterone.
  - Decreased plasma renin activity.
  - Low renin hypertension with hypokalemic alkalosis.

P450 oxidoreductase deficiency :

- Karytype : 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.

Hormone profile :

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

Feedback

Active space

17 β hydroxysteroid dehydrogenase Type 3 deficiency :

- Karytype : 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.

5α reductase type 2 deficiency :

- Karytype : 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.

Feedback

Hormone profile :

- Decreased ratio of 5α/5β C21 and C19 steroids in urine.
- Increased testosterone/dihydrotestosterone ratio before and after hCG stimulation.
- Modest increase in plasm LH.
- Decreased conversion of testosterone to dihydrotestosterone in vitro.

Disorders of androgen action 00:19:35

Complete androgen insensitivity syndrome :
Karytype : 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.
- Partially/completely descended testis.
- Pubertal virilisation.

Hormone and metabolic profile :

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

Feedback

Active space

46 XX DSD

00:22:56

1. 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 andrenal and lung dysgenesis) syndrome.

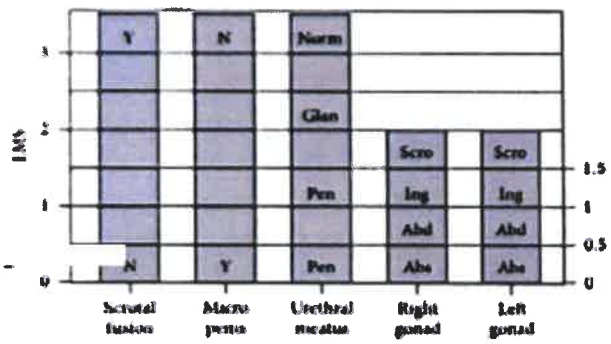
2. Androgen excess :

- 3β Hydroxysteroid dehydrogenase type 2 deficiency.
- 21 Hydroxylase deficiency.
- P450 oxidoreductase deficiency.
- 11β 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 :

Scoring systems to assess virilisation/undervirilisation.

Prader score.



External masculinisation score (EMS).

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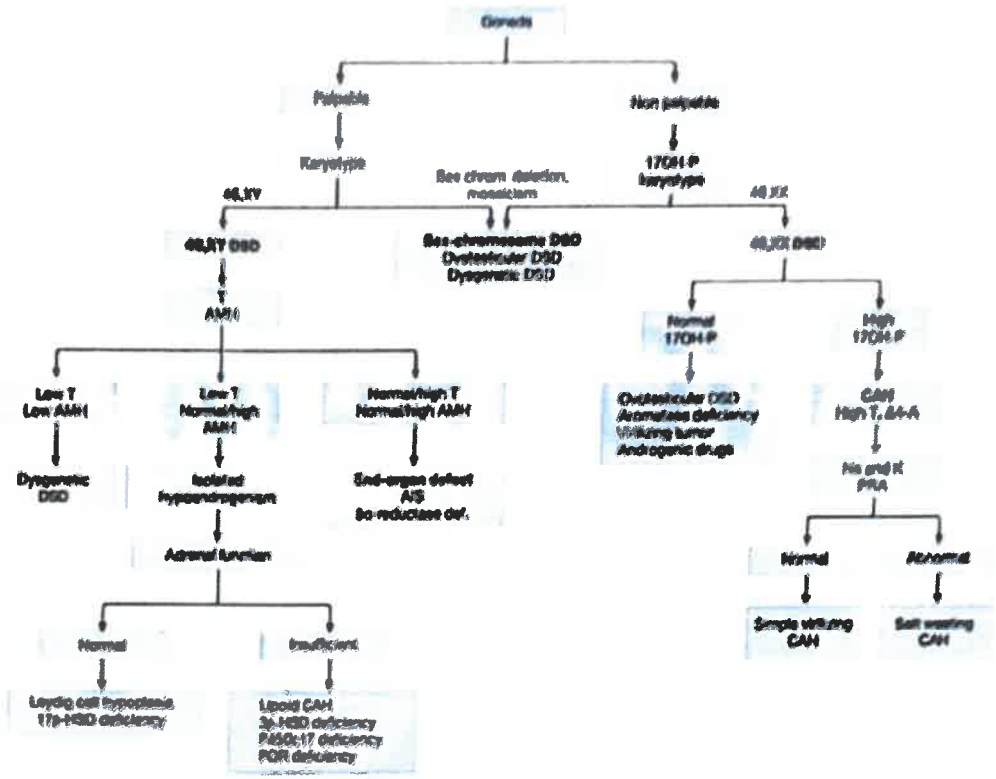

Approach to a case with DSD.

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 suggestive of 17β HSD3 deficiency.

  Testosterone : DHT >10-20 is suggestive of 5α reductase deficiency.

Imaging :

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

Feedback

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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

Physiology of puberty 00:00:39

Puberty is the sexual maturation of an organism for reproduction.

Gonadal hormones :

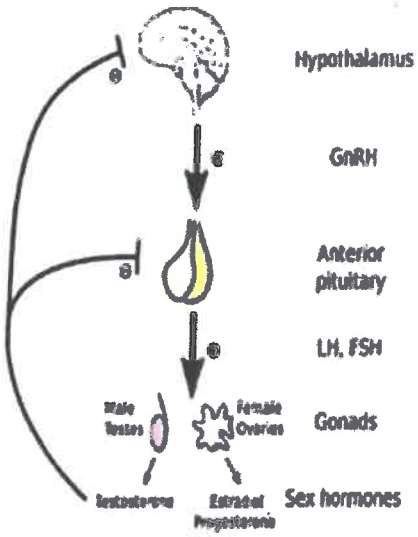
- Testosterone : Males.
- Estrogen, progesterone : Females.

These hormones are required at 2 stages in life :

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

HPG axis :

- Hypothalamo pituitary 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 upto 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.

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

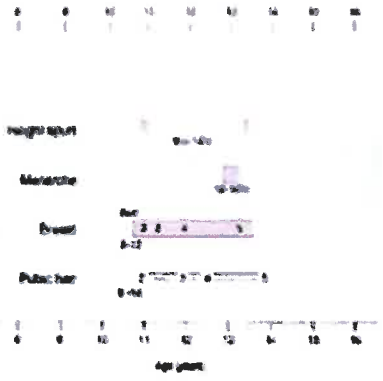
- If GnRH pulsation frequency is more → Favours secretion of LH (Luteinising hormone).
- Role of FSH and LH in ovaries : Ovarian steroidogenesis.
  Follicular development and ovulation.
- Role of FSH and LH in testes :
  LH → Stimulates leydig cells → Production of testosterone.
  FSH → Spermatogenesis → Sperm.
- Sex hormones have inhibitory effect on both pituitary and hypothalamus. Decreased gonadal hormones → Inhibitory control is lost → FSH and LH level is increased.

Pubertal changes 00:11:12

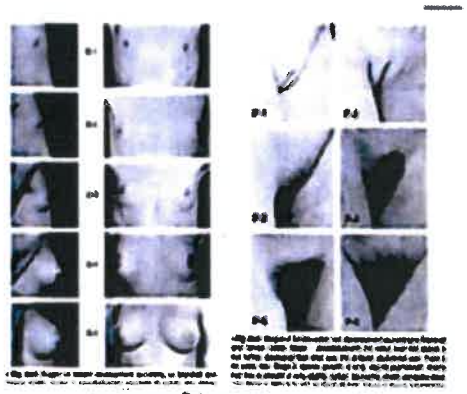
Pubertal changes in girls :
Secondary sexual characters develop during puberty.
Effect of estrogen and progesterone hormones :

i. Breast development.
ii. Pubic and axillary hair development is mainly due to adrenal androgens.
iii. Ovary enlarges and uterus matures and enlarges.
iv. Skeletal development → Estradiol causes epiphyseal development and closure.

Thelarche >Take off height velocity >Peak height velocity >Menarche > Pubarche.



Pubertal events in females.



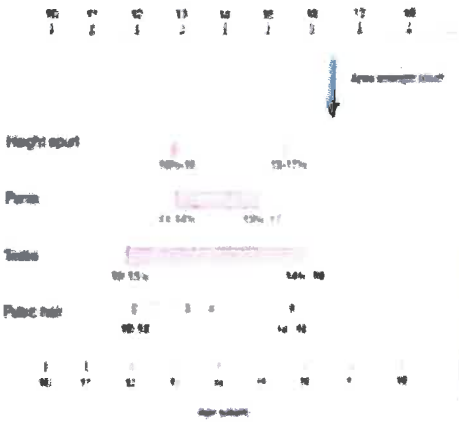
Stages of breast and pubic hair development.

Pubertal changes in boys :

- Testosterone leads to penis enlargement, pubic hair, axillary hair and advancement of bone age.
- At puberty testicular volume also increases.

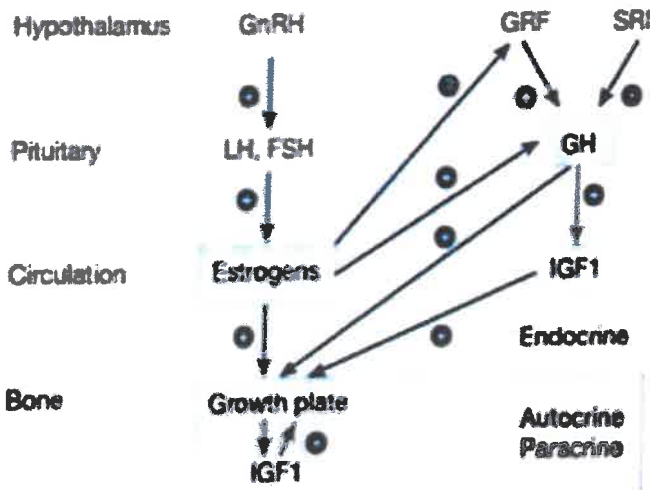
Feedback

Enlargement of testes > Take off height velocity > Peak height velocity > Pubic hair development.



Pubertal development stages.

Changes in gonads.



Effect of gonadal hormones on bone development.

In males, testosterone is converted to estradiol with the help of the enzyme aromatase → Estradiol brings about the bone development.

Precocious puberty

00:16:00

Definition :

Puberty : Not a de novo event but rather a phase in the continuum of development of gonadal function and the ontogeny of hypothalamic-pituitary-gonadal system from the fetus to full sexual maturation and fertility.

Puberty refer to the physical and endocrine changes of this period.

Adolescent : Refers to the profound psychologic changes encountered during this time.

Active space

Precocious puberty : Development of any secondary sexual characters before the age of 9 years in male and 8 years in female is called precocious puberty.

Types of precocious puberty :

GnRH-dependent sexual precocity/central precocity :

- Central precocity.
- True precocious puberty.
- Complete isosexual precocity.

GnRH-independent sexual precocity :

- Peripheral precocity.
- Pseudo precocious puberty.
- Incomplete ISP.
- Contrasexual precocity.
- Heterosexual precocity.

Variants of normal puberty :

- Premature thelarche.
- Premature pubarche.
- Premature isolated menarche.

GnRH dependant sexual precocity 00:21:18

Five times more common in girls.

Idiopathic central precocious puberty (CPP) 8 times more common in girls.

Causes :

Idiopathic :

- Common in girls.
- Chances of having CNS abnormalities : Boys (1 : 1), girls (4 : 1).

CNS tumors :

- Optic glioma (Neurofibromatosis type 1).
- Hypothalamic hamartoma.
- Hypothalamic astrocytoma.

Other CNS disorders :

- Developmental abnormalities including hypothalamic hamartoma.