Cases of syndrome with Genetic lesions: Dilemmas and Diagnoses

Presenters-

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Case scenario 1

A 16-year-old female patient, presented with

- Primary amenorrhea with hirsutism
- Absence of breast development
- At birth, her mother discovered the presence of a genital bud.

On general examination :

✓Male morphotype with lack of breast development (S1 of Tanner)

On genital examination :

✓Ambiguous genitalia – clitoromegaly

✓Absence of gonad palpation

Differential diagnosis :

- Congenital adrenal hyperplasia
- Androgen insensitivity syndrome
- Polycystic ovary syndrome
- Adrenal tumor

Case scenario 2

A 13-year-old person, reared as female, presented with

- Primary amenorrhea
- H/O bilateral inguinal hernias (repaired at age 2)

On general examination :

✓Normal intellectual function

✓Feminine habitus and voice

✓Height: 171 cm

✓Tanner stage 3 breast development and pubic hair growth (dark, coarse)

Gynecological examination:

✓Ambiguous genitalia – Short vagina

- Cervix not visualize by speculum

Differential diagnosis :

- Complete androgen insensitivity syndrome
- Leydig cell hypoplasia

Case scenario 3

A 14-year-old girl, presented with

- Primary amenorrhea
- Recurrent ear infections.

On general examination:

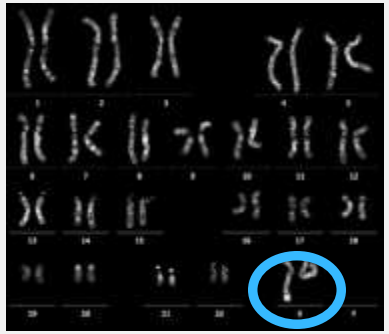
- ✓ Short stature and had webbed neck with a low hair line
- ✓ Low set ears, shield chest, cubitus valgus, high arched palate, short fourth metacarpals
- ✓ Tanner stage 1 of breast development and pubic hair growth

Differential diagnosis:

- Turner syndrome
- primary ovarian failure
- Gonadotropin deficiency

Investigations

- **Hormonal assays:**
  - ✓ Testosterone: ↑ (3.69 ng/ml)
  - ✓ SDHEA: ↑ (752.5 µg/dl)
  - ✓ 17 OH Progesterone after synacthen stimulation T60 min(confirmatory): ↑ (354 ng/ml)
  - ✓ S. Cortisol: ↓ (62 g/ml)
- **USG:**
  - ✓ Hypoplastic uterus
  - ✓ Macro-polycystic ovaries
  - ✓ Abdominal scan: No abnormalities.
- **Karyotype:** 46XX



Diagnosis

Confirmatory diagnosis:

Congenital adrenal hyperplasia (CAH)

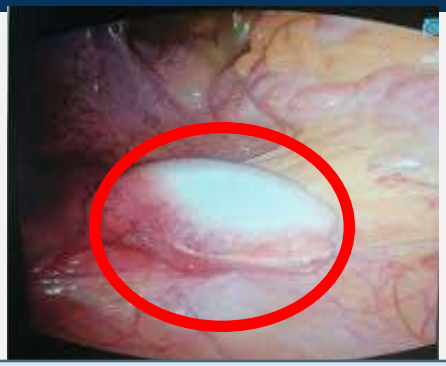
Investigations

- **Hormonal assays:**
  - ✓FSH: ⟷ (1 mUI/mL)
  - ✓LH: ⟷ (20 mUI/mL)
  - ✓Estradiol: ⟷ (29 pmol/L)
  - ✓Total testosterone: ↑ (32 ng/ mL)
  - ✓Anti - Müllerian hormone (AMH): ↑ (212.9 µg/L)

- **MRI:**
  - ✓Hypoplastic vagina
  - ✓Absent uterus and ovaries, intra-abdominal gonads (likely testes)

- **Surgical Findings:**

✓ Intra-abdominal testes identified and removed laparoscopically.

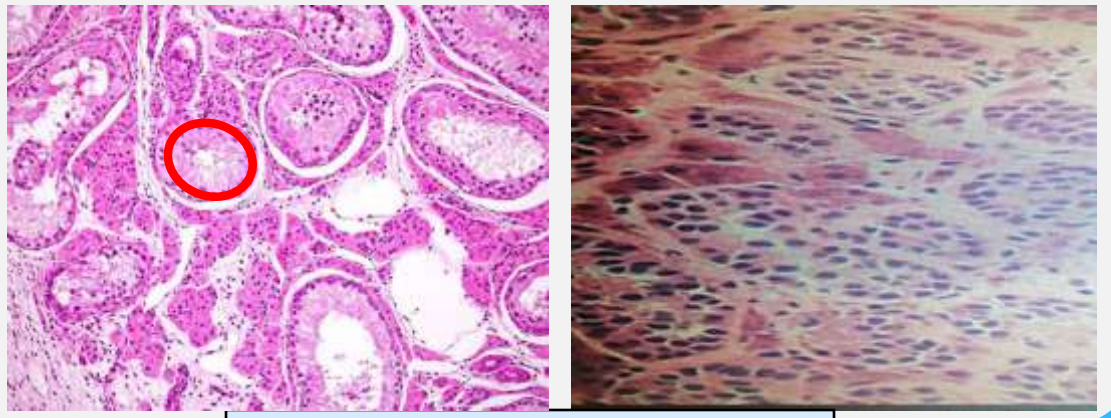


Intra-abdominal testes

- **Histopathology:**

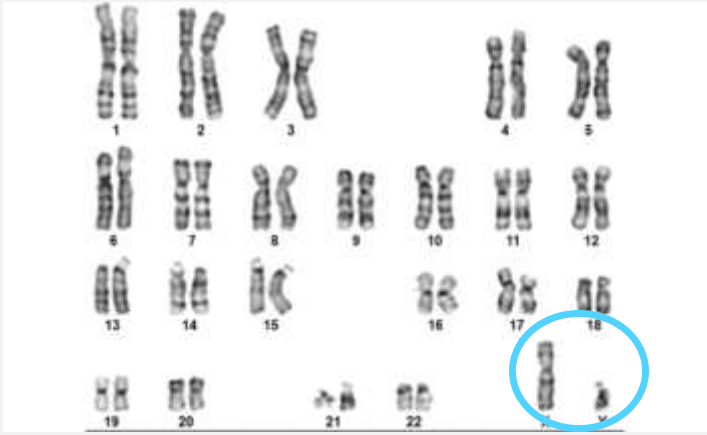
✓ Atrophic seminiferous tubules with only Sertoli cells; Leydig cell hyperplasia.

Normal testicular tissue



Atrophic Testicular tissue

- Genetics:
  - ✓ Karyotype: 46XY



  - ✓ AR Gene sequencing: Homozygous p.R856C mutation in exon 7

Diagnosis

Confirmatory diagnosis:

Complete androgen insensitivity syndrome

Investigations

- **Hormonal assays:**
  - ✓ FSH: ↑ (131.05mIU/ml)
  - ✓ Estradiol: ↓
  - ✓ LH: ↓ (27.90mIU/ml)
  - ✓ Testosterone: ⟷ (0.16ng/ml)
- **Thyroid function test:** Normal
- **USG:**
  - ✓ Bilateral streak ovaries
  - ✓ Hypoplastic uterus
- **Echocardiography:** Normal
- **Chromosomal analysis:**
  - ✓ Karyotype: 46 XY
  - ✓ Whole gene sequencing:

    45,X[17]/46,X,psuidic(Y)(q11.23)

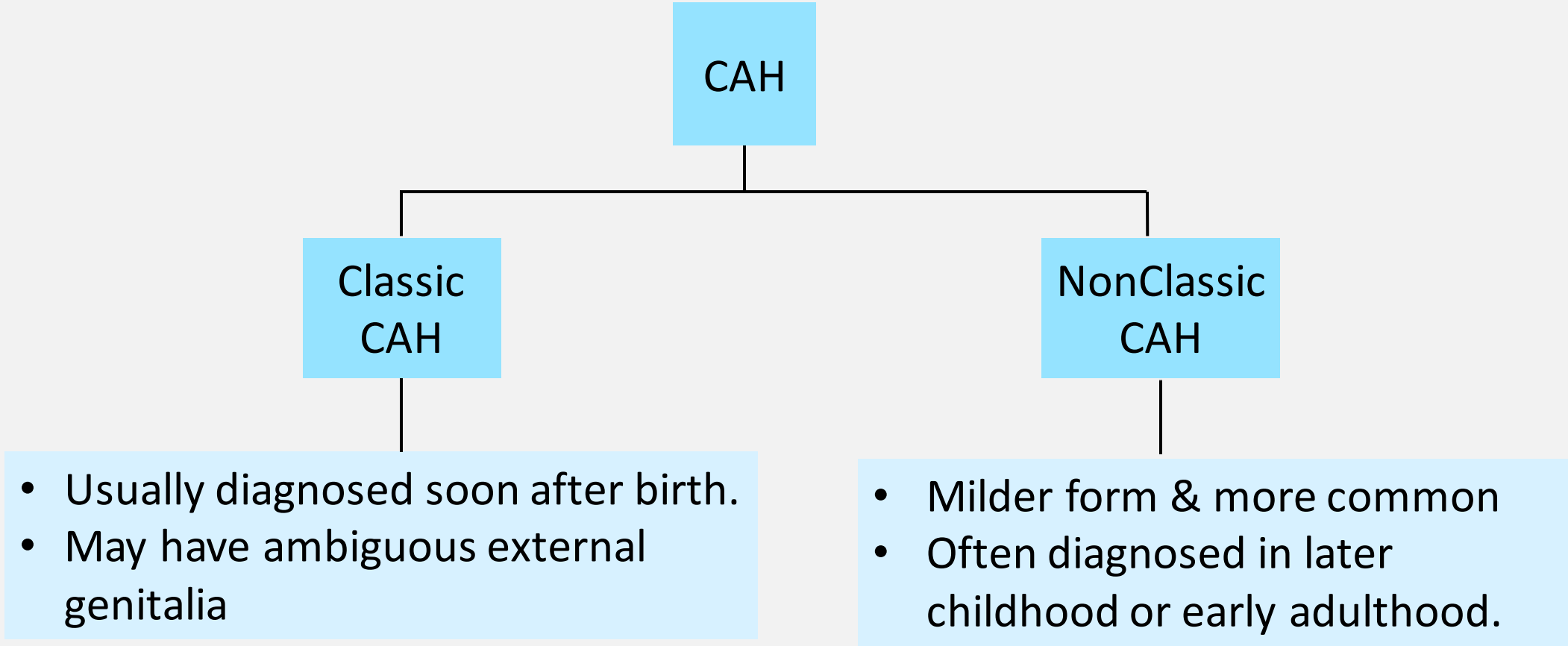
Diagnosis

Confirmatory diagnosis:

Mosaic - Turner syndrome

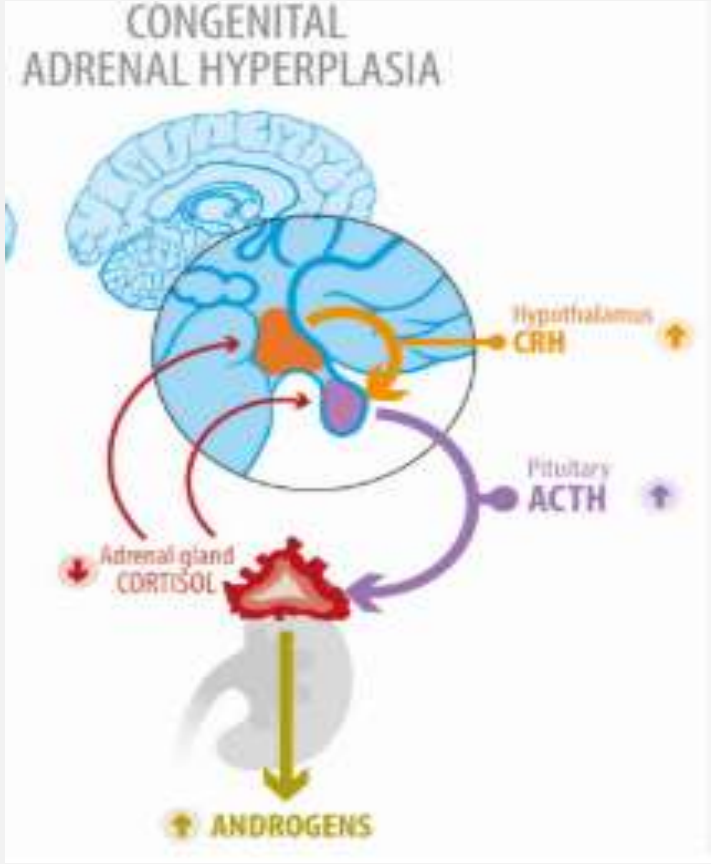
Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) describes a group of hereditary (inherited) genetic disorders affecting adrenal glands.



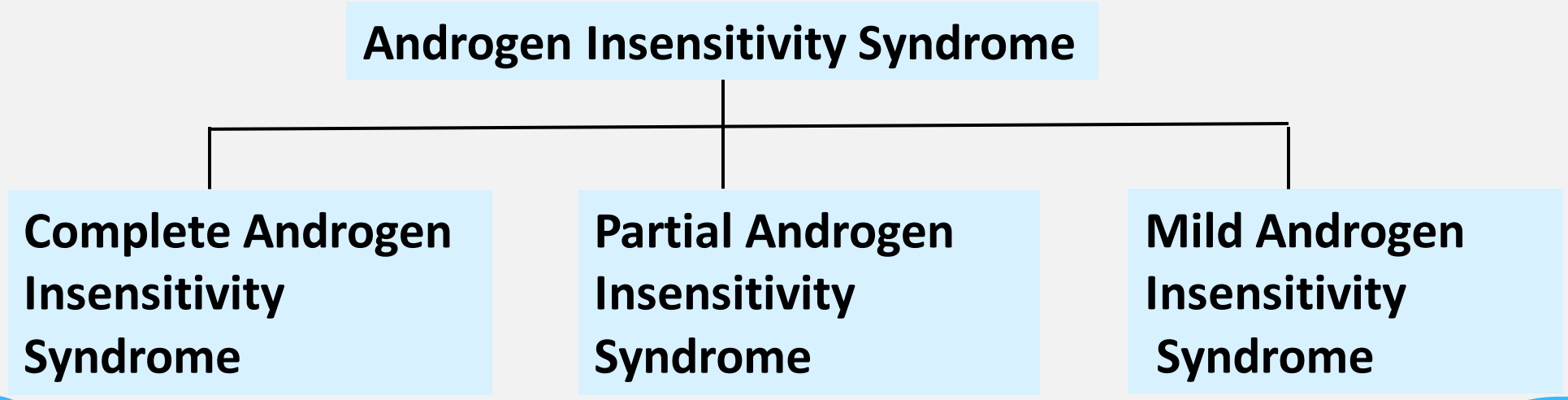
Congenital Adrenal Hyperplasia

- Incidence rate : 55%
- CAH → 21-hydroxylase deficiency → excess androgen production by adrenal gland → virilization of female genitalia , resulting in ambiguous genitalia .
- Diagnosis:17 OH Progesterone after synacthen stimulation T60 min(confirmatory)



Complete Androgen Insensitivity Syndrome

- Androgen insensitivity syndrome (AIS) is a rare condition that affects sexual development
- It occurs when someone is genetically male, but their body doesn't respond to male sex hormones androgens
- This results in a person having male sex chromosomes (one X and one Y chromosome) but not having male genitals.

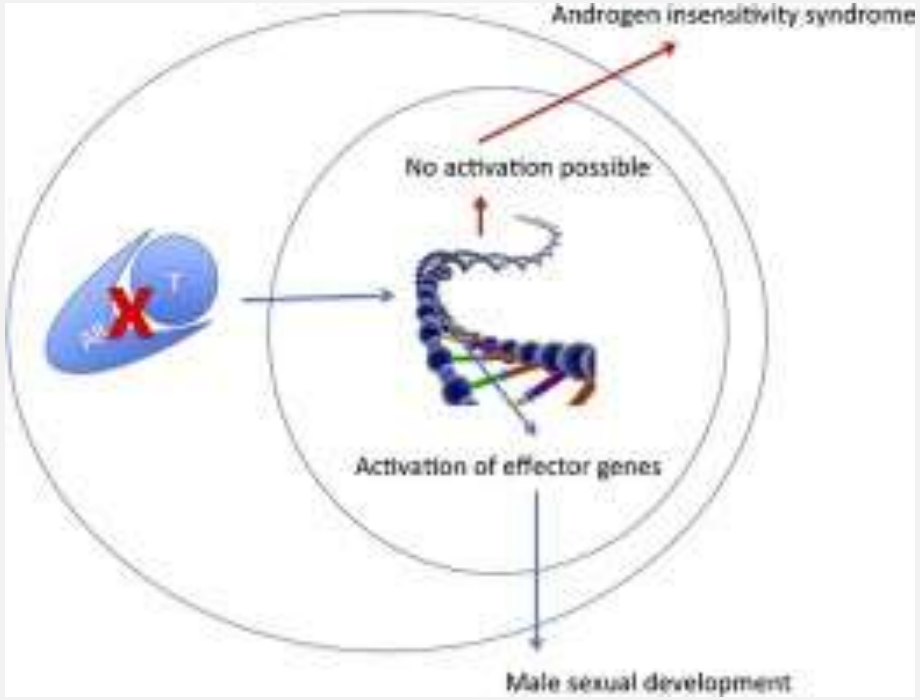


Androgen Insensitivity Syndrome

- Incidence rate : 30%

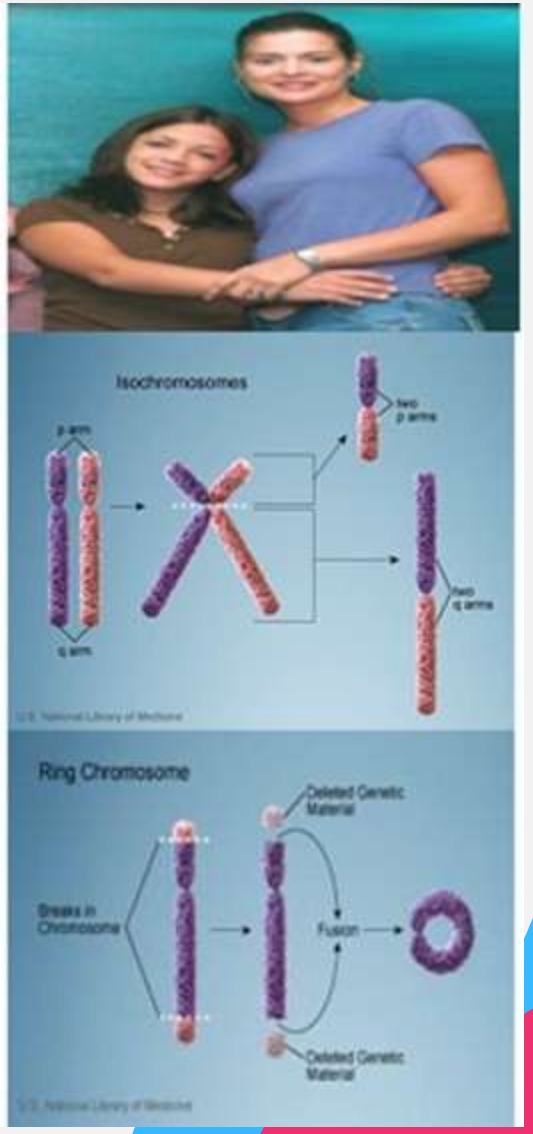
- Mutations in the androgen receptor gene → dysfunctional AR that can not bind to androgens or transmit their signal properly → feminization of the external genitalia & other male characteristics

- Diagnosis: AR Gene sequencing



Mosaic Turner Syndrome

Mosaic turner syndrome is when some, but not all of the cells of the individual having turners syndrome have an unusual combination of sex chromosomes.

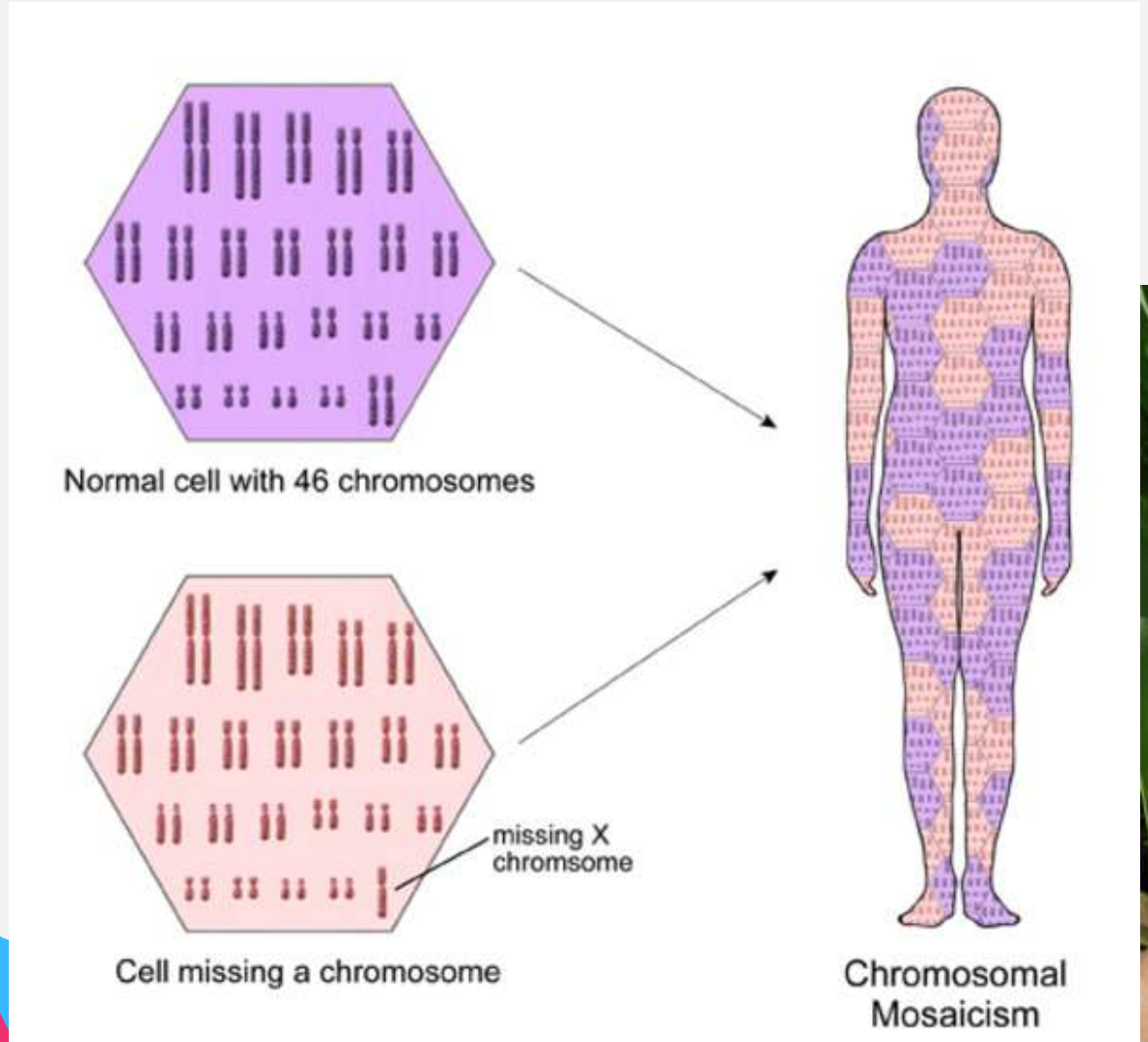


Genotype:

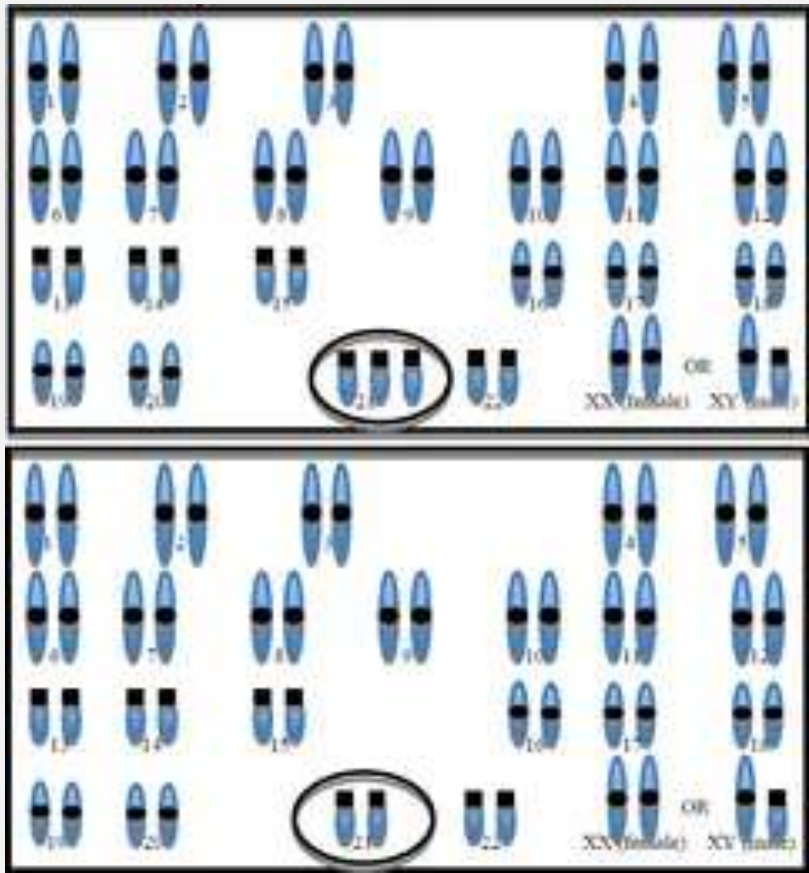
- 45,X / 46,XX
- 45,X / 47,XXX
- 45,X / 46,XY

Causes:

Some type of error that occurs during cell division, leading to abnormalities in the chromosomes of some but not all of the cells .



Tulip flower with mosaicism. In Mosaic Turner Syndrome, typically 20 to 25 cells are examined. If some of the cells have trisomy 21and some don't, then the diagnosis mosaicism is made



Disorders of Sex Development (DSD)

Disorders of Sex Development (DSD)

DSDs are congenital anomalies characterized by discrepancy between -

- Genetic sex (karyotype),
- Gonadal structure (ovary/testis), and
- Phenotypic sex (external genitalia),

often requiring multidisciplinary evaluation

Classification

Based on the underlying chromosomal and gonadal sex.

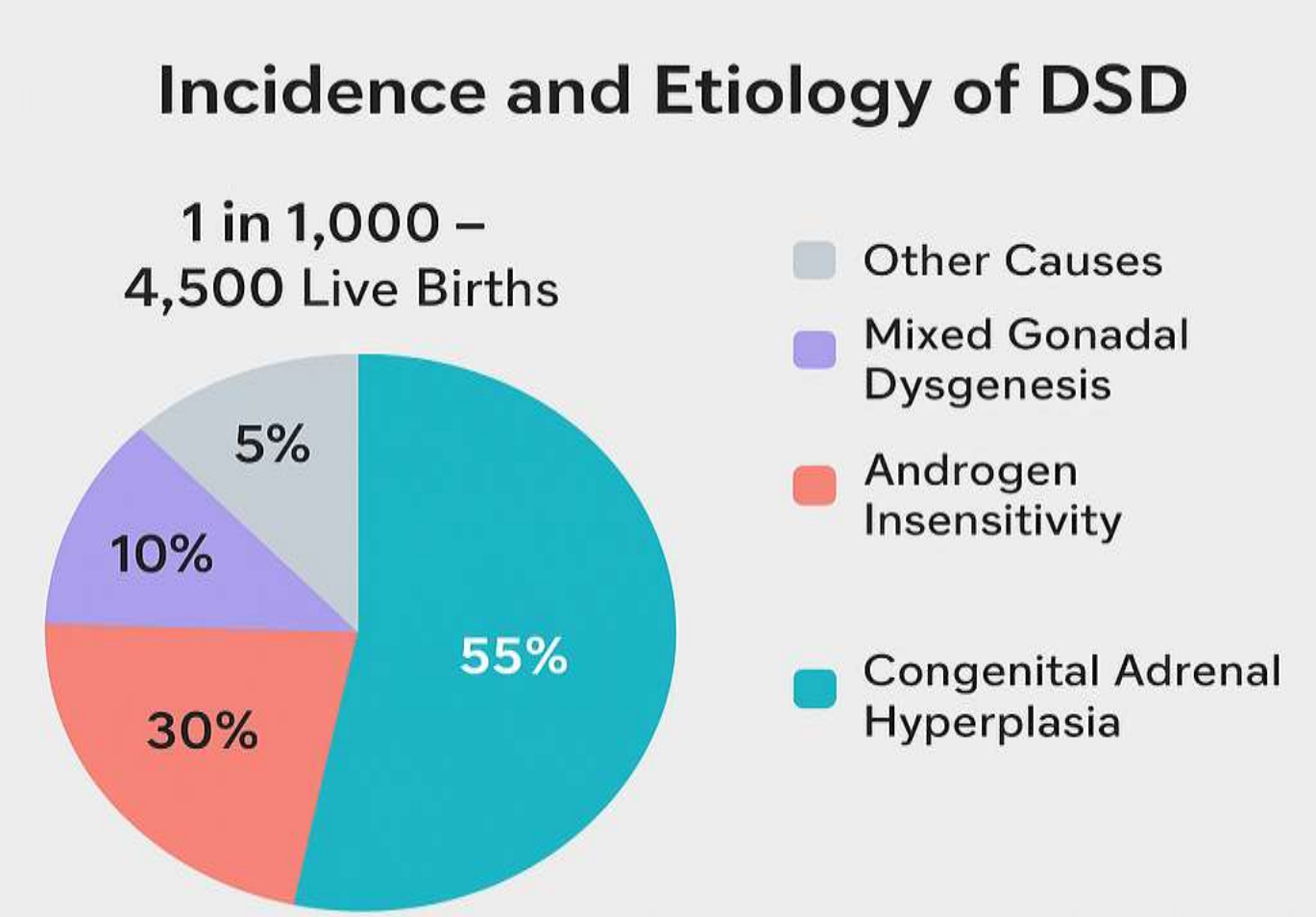
- 46,XX DSDs
- 46,XY DSDs
- Sex Chromosome DSDs

TABLE 1. **Disorders of Sex Development (DSDs): Chicago Classification**

Sex chromosome DSD	46,XY DSD	46,XX DSD
• 45,X (Turner syndrome and variants) • 47,XXY (Klinefelter syndrome and variants) • 45,X/46,XY (mixed gonadaldysgenesis, ovotesticular DSD) • 46,XX/46,XY (chimeric, ovotesticular DSD)	Disorders of gonadal (testicular) development • Complete gonadal dysgenesis (Swyer syndrome) • Partial gonadal dysgenesis Gonadal regression Ovotesticular DSD Disorders in androgen synthesis or action • Androgen biosynthesis defect (17-hydroxysteroid dehydrogenase deficiency, 5α-reductase deficiency) • Defect in androgen action (CAIS, PAIS)	Disorders of gonadal (ovarian) development • Ovotesticular DSD • Testicular DSD (SRY+, dup SOX9) • Gonadal dysgenesis Androgen excess • Fetal (21- or 11-hydroxylase deficiency) • Fetoplacental (aromatase deficiency, POR) • Maternal (luteoma, exogenous)

Incidence of DSD

The incidence of a child with a disorder of sexual development (DSD) is approximately 1 in 1000 to 4500 live births.

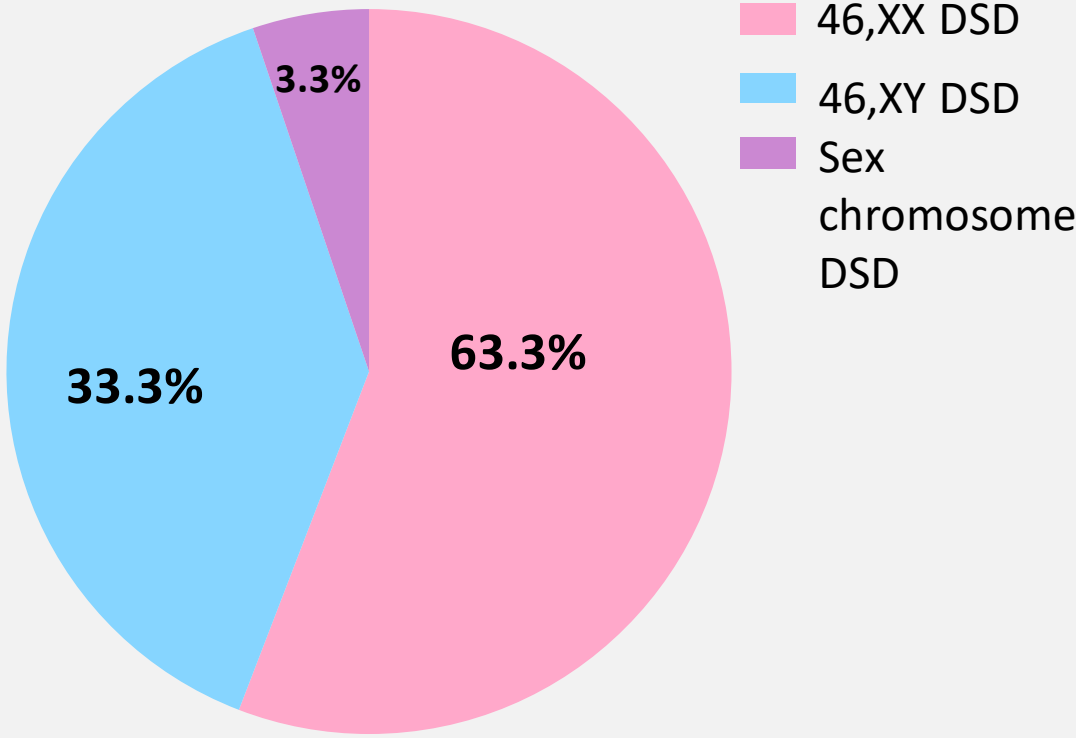


Source: National Institute of Health (NIH)

In Bangladesh,

Total population with DSD: 30,000 - 150000

- 46,XX DSD in 63. 3% of cases
- 46,XY DSD in 33.3% of cases
- Sex chromosome DSD in 3.3% of cases

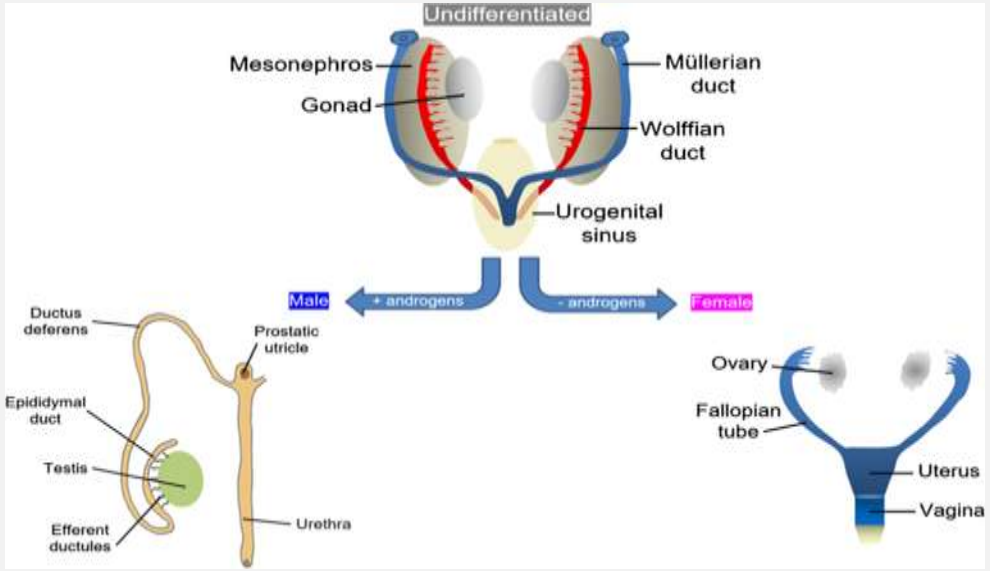


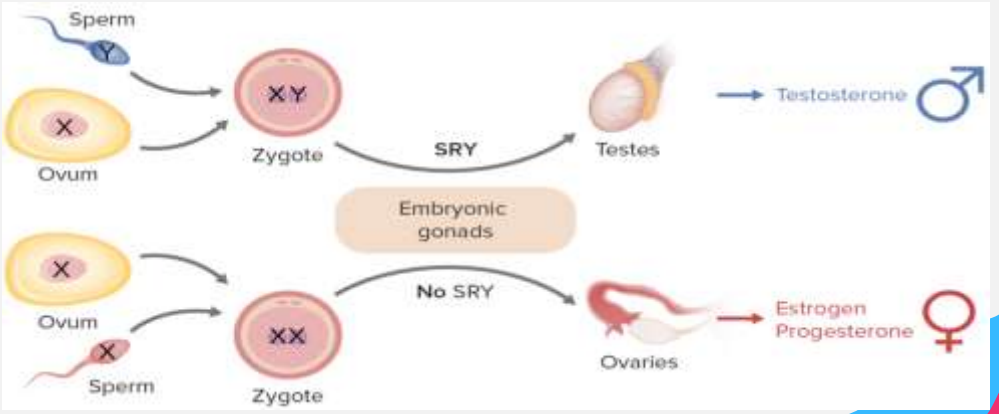
Source: Mymensingh Medical Journal 33(1):140-145

Pathogenesis of Disorders of Sex Development (DSD)

Physiology of Sex Determination

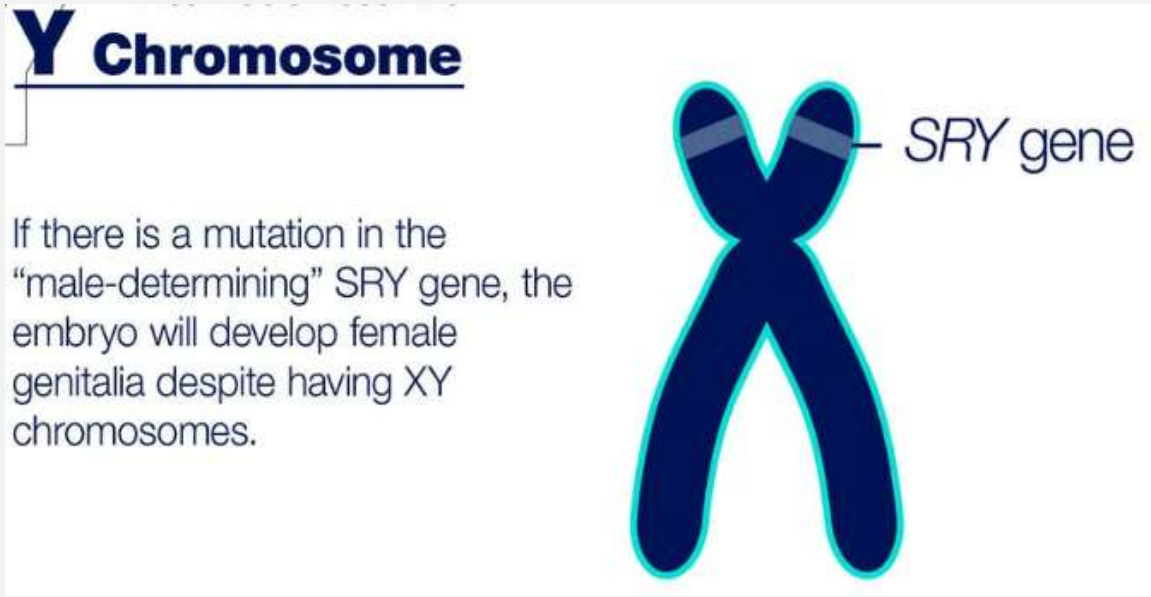
- Sexual differentiation is a stepwise process involving genes, hormones, and tissue response.
- Up to 7 weeks of fetal life, male and female embryos share a common anlage, after which sex-specific development begins.
- SRY gene on the Y chromosome initiates testis development
- Absence of SRY gene→ promote Ovary development.





Pathogenesis of Disorders of Sex Development

- DSD arises from disruption at any step: chromosomal → gonadal → hormonal.
- Disruption in genes (e.g., SRY, SOX9) or hormonal pathways → DSD.
- Mutations in SRY → 46,XY gonadal dysgenesis.
- Abnormal expression in 46,XX individuals → male or ambiguous genitalia.



Pathogenesis

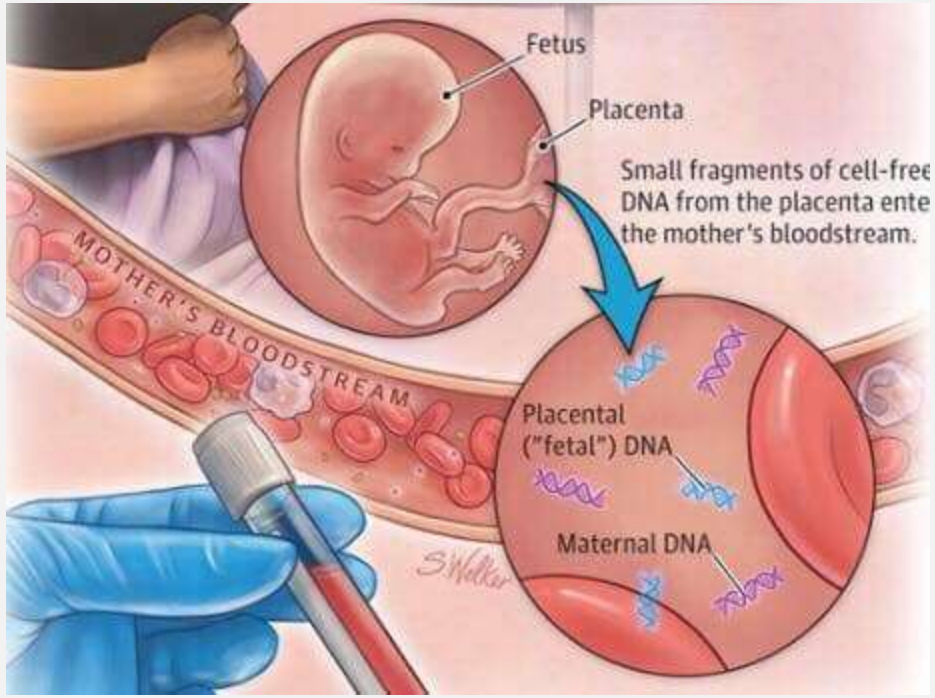
Disruptions Leading to DSD:

- SRY mutation/translocation → 46,XY females / 46,XX males.
- SOX9 mutations → campomelic dysplasia with DSD.
- FOXL2, CYP19A1 (aromatase) → 46,XX gonadal dysgenesis, female virilization.
- CAH (21-OH, 11β-OH, 3β-HSD) → excess androgens, virilized females.
- 5α-reductase deficiency → undervirilized males.
- Androgen insensitivity → 46,XY with female phenotype.
- AMH/AMH-R deficiency → Persistent Müllerian Duct Syndrome

Prenatal Investigations

Non-Invasive Prenatal Testing (NIPT)

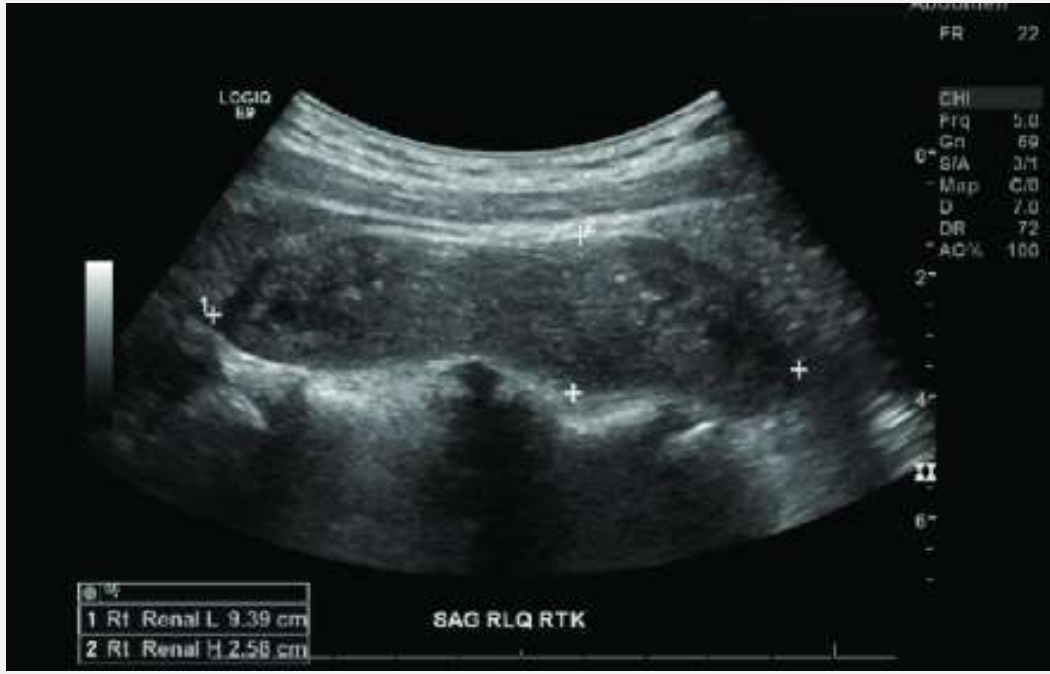
- Sample: maternal blood.
- Detects sex chromosome anomalies (e.g., Turner syndrome 45,X Klinefelter syndrome 47,XXY).
- Determines fetal sex (XY or XX) within 9–10 weeks.



Prenatal Investigations

❖ **Ultrasound (Anomaly Scan)**

- May detect ambiguous genitalia or absence of uterus in suspected cases.
- **Limitations**: Cannot confirm karyotype or hormonal function.



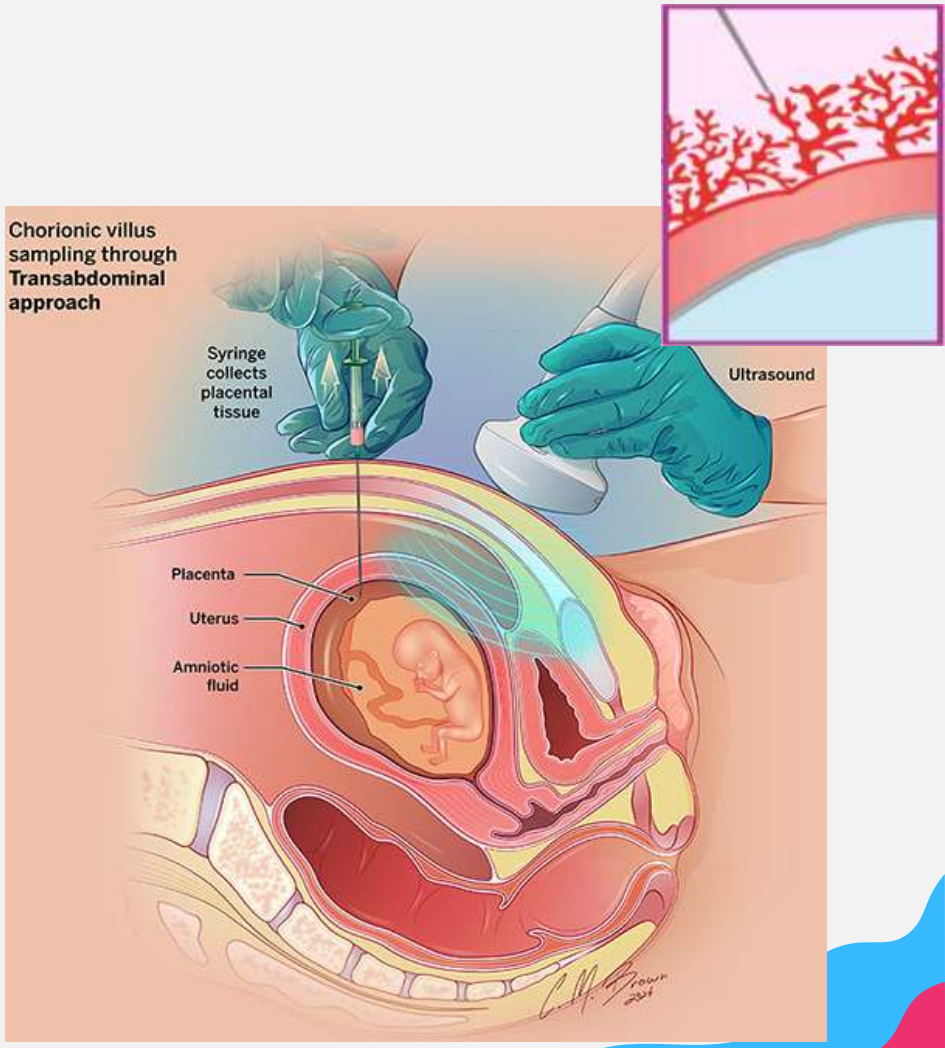
Absence of uterus in anomaly scan

Prenatal Investigations

❖Invasive Prenatal Testing

Amniocentesis or Chorionic Villus Sampling (CVS):

- Used for karyotyping and molecular genetic analysis.
- Confirms: Sex chromosomes (e.g., 46,XX; 46,XY; mosaic patterns).
- Mutations in genes involved in sex differentiation (e.g., SRY, SOX9).



Postnatal Investigations (after birth & puberty)

1. Hormonal Assays

Performed within first 48–72 hours, ideally before (~3 months)

Help to assess gonadal function and the cause of ambiguous genitalia.

a. Baseline Hormone Levels:

- 17-hydroxyprogesterone : Congenital adrenal hyperplasia (CAH)
- Testosterone/DHT: Androgen status
- LH/FSH: Pituitary response
- Anti-Müllerian Hormone & Estradiol : Gonadal origin & differentiation

Postnatal Investigations (after birth & puberty)

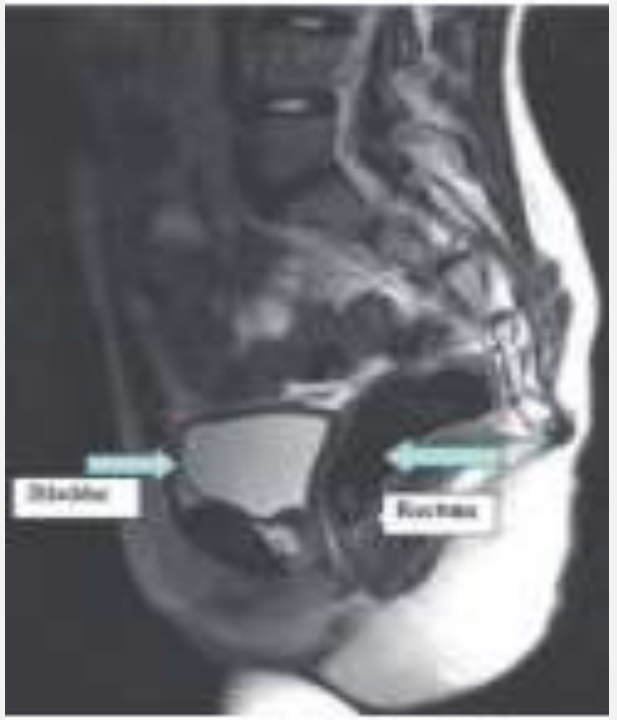
b. Stimulation Tests:

- ACTH stimulation test: CAH (21-hydroxylase deficiency)
- hCG stimulation test: Leydig cell function and testosterone production

Postnatal Investigations (after birth & puberty)

2. Imaging Studies

- Pelvic/abdominal ultrasound: Check for uterus, ovaries, testes
- MRI: Better visualization of internal structures
- Genitography / cystoscopy: To evaluate urogenital sinus or Müllerian structures

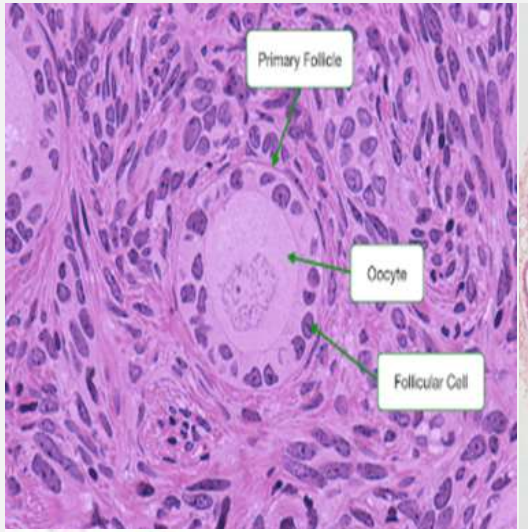


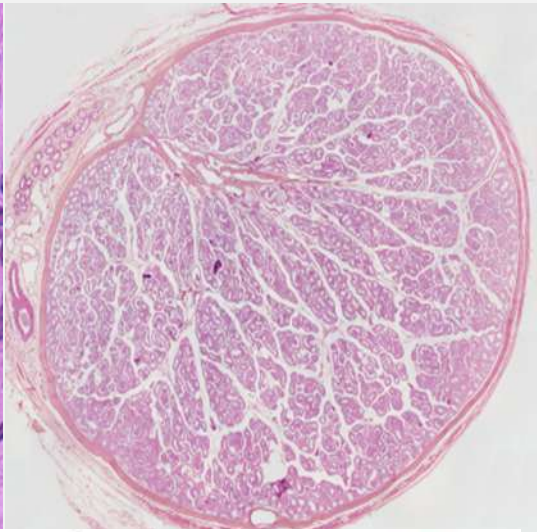
Absence of uterus in the MRI scan

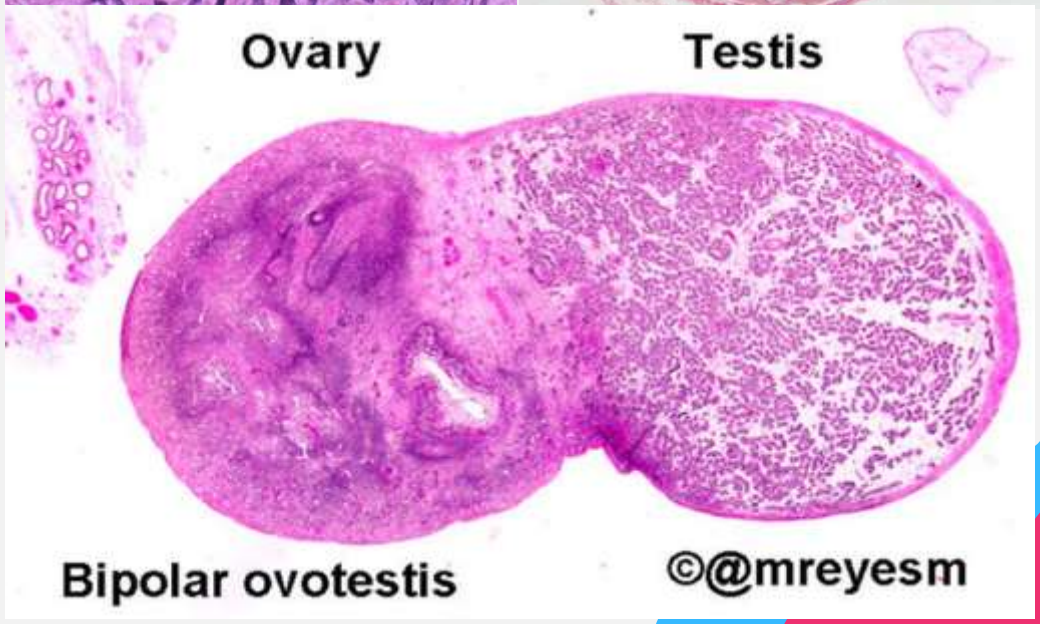
Postnatal Investigations (after birth & puberty)

3. Histopathology in DSD

- Identifies gonadal type (testis, ovary, ovotestis, or streak)
- Confirms gonadal development and differentiation
- Detects tumors or pre-cancerous changes (e.g., gonadoblastoma)
- Correlates with genetic and clinical findings
- Guides gender assignment, treatment, and counseling







Postnatal Investigations (after birth & puberty)

4. Karyotyping / Chromosomal Analysis

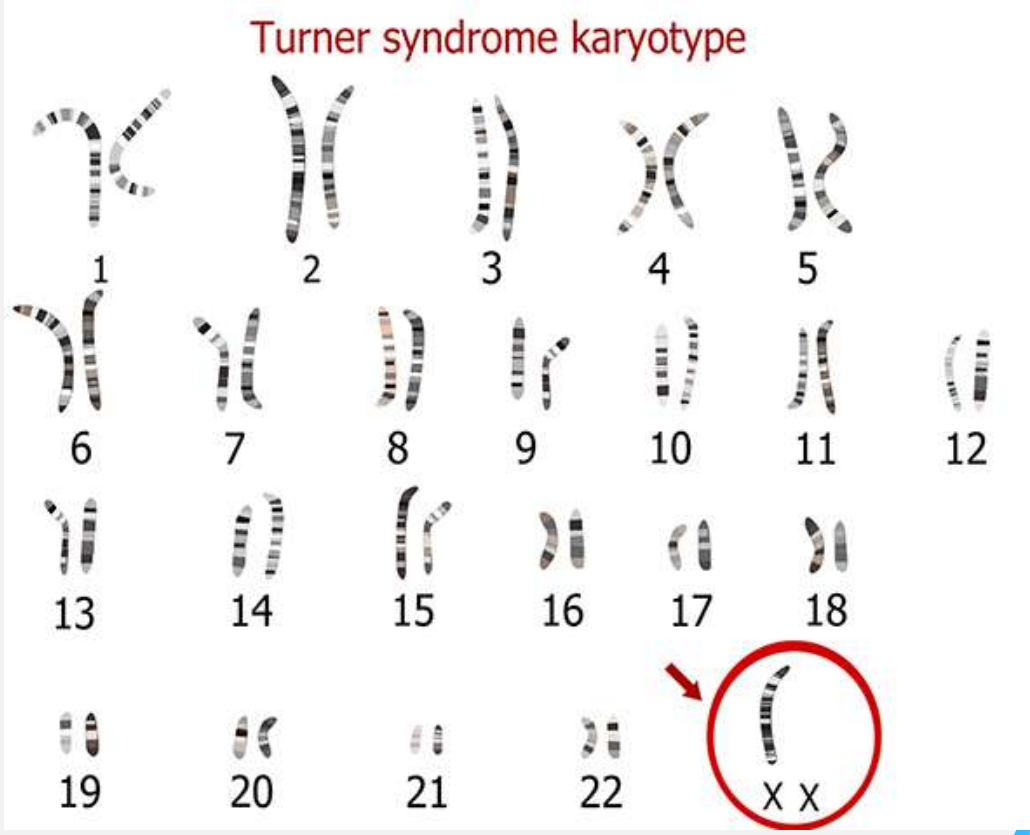
First-line test in newborns with ambiguous genitalia.

Sample : Blood

Purpose: Determines the chromosomal sex.

Examples: 46,XX → Suggests female genotype (possibly with virilization)
46,XY → Suggests male genotype (possibly with undervirilization)

Limitations : Can't determine specific point mutation



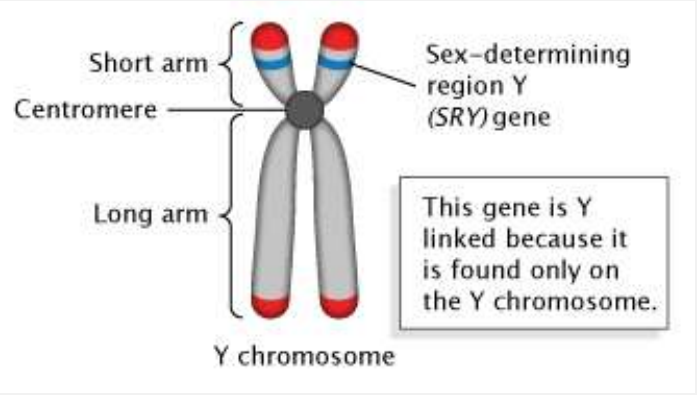
Postnatal Investigations (after birth & puberty)

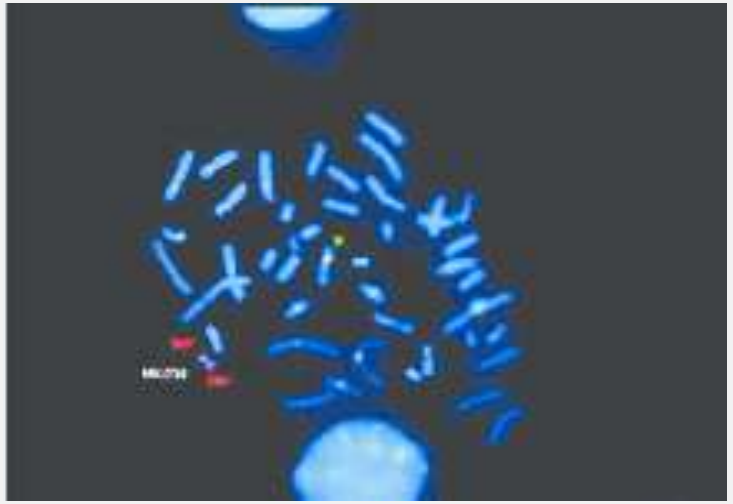
5. Molecular Genetic Testing

Fluorescence In Situ Hybridization (FISH) or PCR for SRY gene

Identify mutations SRY gene:

- CYP21A2 gene: 21-hydroxylase deficiency (CAH)
- Androgen receptor gene mutations: Androgen insensitivity syndrome



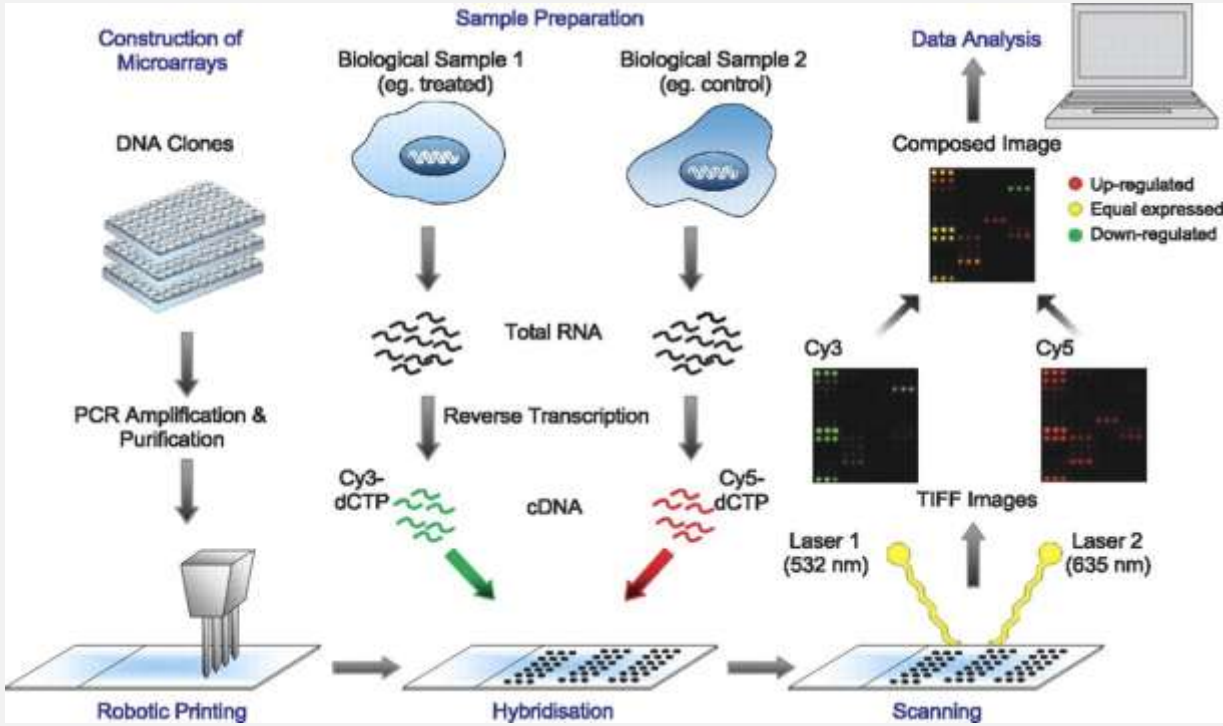


FISH: SRY gene

Postnatal Investigations (after birth & puberty)

Targeted gene sequencing for mutations in:

CYP21A2 (CAH),SRY, SOX9, DAX1, AR (androgen insensitivity, gonadal dysgenesis, etc.)



Take home message

- The incidence of Disorders of Sex Development (DSD) is not so uncommon than some other rare conditions.
- Early & accurate pathological evaluation is needed if patient come with hirsutism , amenorrhea, sterility, cryptorchidism, epispadias.
- For diagnostic evaluation hormonal analysis , radiological, histopathological & karyotyping analysis are needed.
- Advanced techniques (FISH or genome sequencing) sometimes need even in normal karyotype.

Take home message

- DSD are complex conditions requiring a multidisciplinary approach by Gynecology , surgery , pathology, endocrinology & psychiatry departments.

- Individuals with DSD should be treated with the same respect and dignity as any other human being.

References

- Source: National Institute of Health (NIH)

Ambiguous Genitalia and Disorders of Sexual Differentiation
https://www.ncbi.nlm.nih.gov/books/NBK557435/

- Source: Mymensingh Medical Journal 33(1):140-145

Disorders of Sex Development: Experience at a Tertiary Care Hospital in Bangladesh
https://www.researchgate.net/publication/377147004

THANK YOU

Case scenario 1

Genital examination :

- ✓ non-fused smooth pigmented and symmetrical genital folds,
- ✓ a clitoromegaly with peniform aspect measuring approximately 4.5 cm in length and 2 cm in width,
- ✓ two separate orifices below the clitoris (Prader II),
- ✓ absence of gonad palpation at the level of the folds and at the inguinal level

Case scenario2

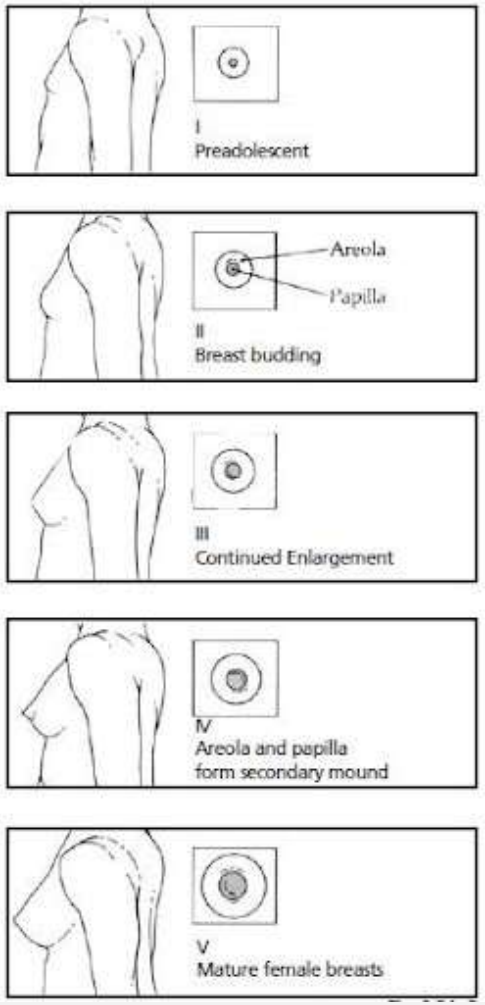
Gynecological examination:

✓Well-developed labia, small clitoris

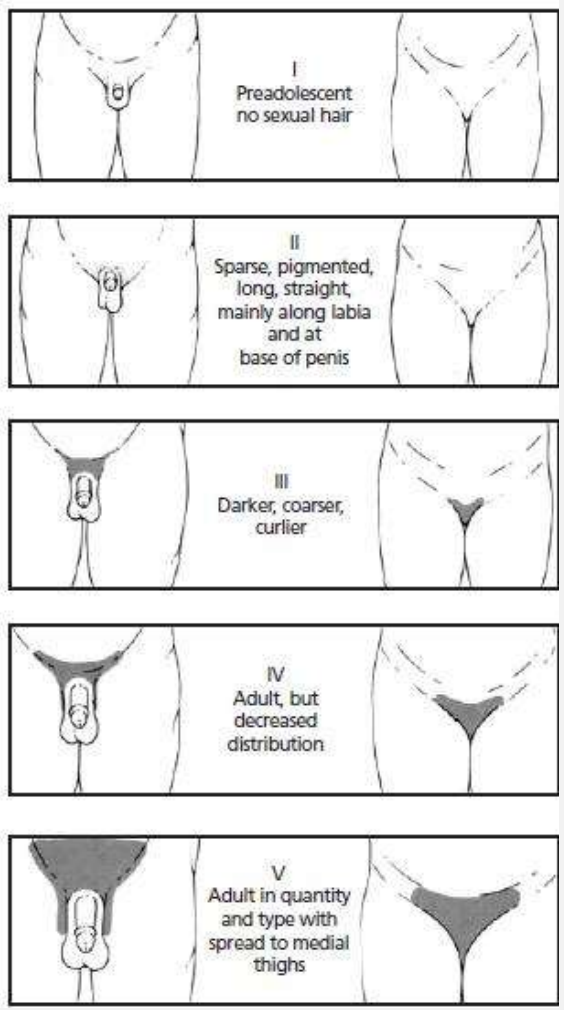
✓Short vagina (4 cm) with blind-ending pouch

✓Speculum examination: Cervix not visualized

Tanner scale :



Tanner stages for breast development



Tanner stagers for pubic hair growth

Terminology:

- Genetic sex : Genetic sex refers to an individual's sex as determined by their sex chromosomes, specifically the presence or absence of the Y chromosome.
- Gonadal sex: Gonadal sex refers to the type of gonads (testes or ovaries) that an individual develops, which is determined by the expression of specific genes.
- Phenotypic sex: It refers to an individual's sex based on their observable physical characteristics, including internal and external genitalia, and the expression of secondary sex characteristics.
- Hermaphroditism, which is an extremely rare condition, possess both testicular and ovarian tissues

- Sex reversal, in a biological context, refers to the phenomenon where an individual develops a sexual phenotype that is different from their genetic sex

- Intersex is a term used to describe individuals born with physical sex characteristics, such as reproductive organs, chromosomes, or hormones, that don't fit typical definitions of male or female. It's not a gender identity, but rather a variation in biological sex. Being intersex is a natural variation, and not a medical condition or a defect.

Pathogenesis

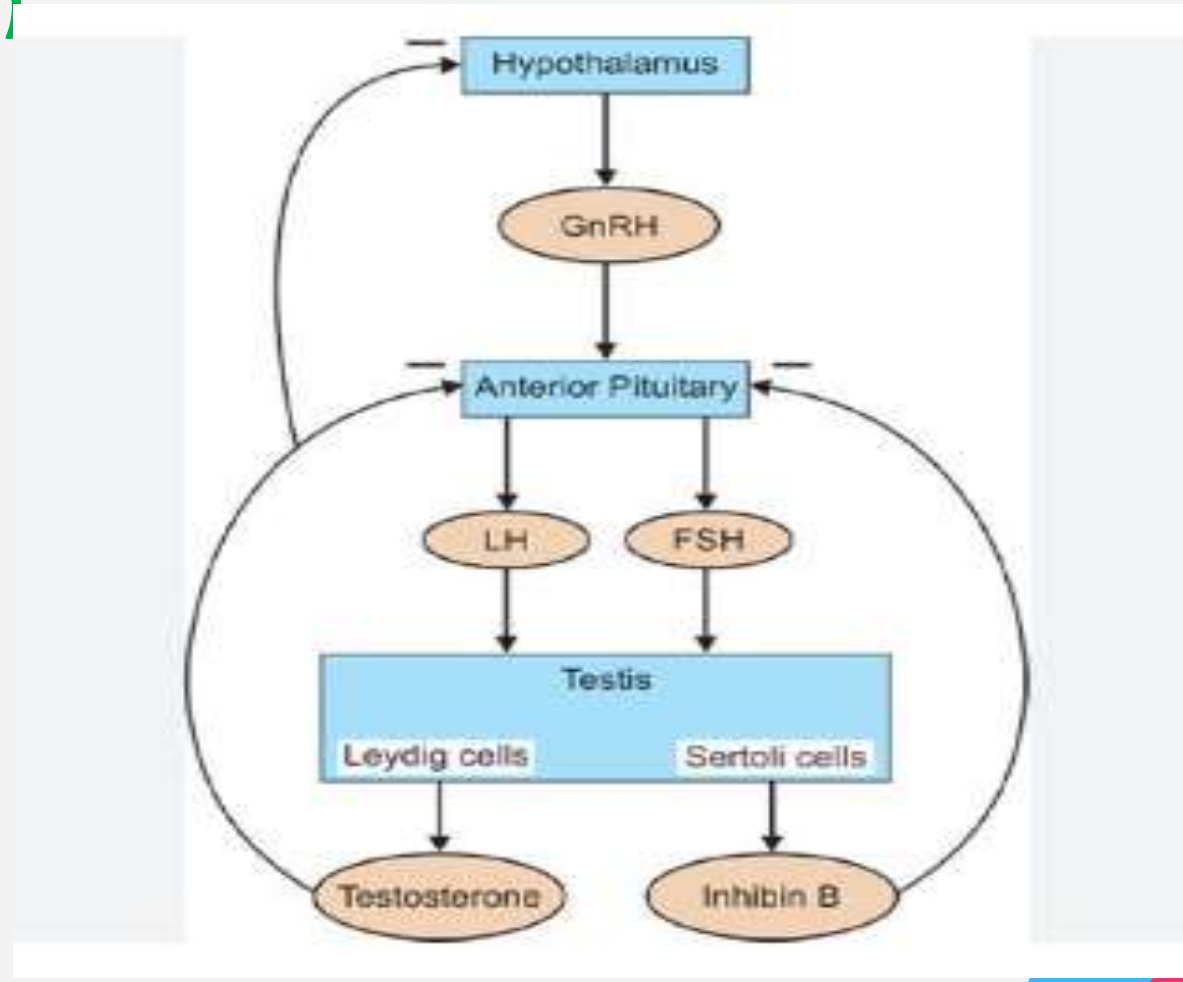
Male Differentiation Pathway (46,XY)

- The second most crucial gene in male sexual determination is SOX9 gene.
- Mutation → causes 46,XY genotype and female or ambiguous genitalia.
- Duplication → leads to male or ambiguous genitalia in 46,XX individuals.

Pathogenesis

Male Differentiation Pathway (46,XY)

- Once the testes have developed,
- Sertoli cells secrete → Anti-Mullerian Hormone (AMH) → regression of Müllerian ducts.
- Leydig cells produce→ testosterone, which stabilized mesonephric (Wolffian) ducts
- DHT (via 5α-reductase) → external male genitalia.



- **Klinefelter syndrome (47XXY)**
  - Individuals have extra X chromosome
  - Phenotypically male
  - Features: infertility , small testes ,tall stature, breast development after puberty