1) **Intersexuality - Dr. Huda**

**DSD (Disorders of sex development)** occur when there is disruption of either:

- Gonadal differentiation
- Fetal sex steroid production or action

**Mullerian abnormalities and Wolffian remnants**

- Occur when there is disruption of embryological development of these systems.
- Presentation may be at infancy or at puberty (amenorrhea or infertility), urological abnormalities.

**Human sex development:**

- Can be divided into three main parts:
  1. Chromosomal sex (presence of X and/or Y chromosome).
  2. Gonadal sex (development of the gonads into either testes or ovaries).
  3. Phenotypic or anatomic sex (the appearance of internal and external genitalia).
- **Gender (brain sex)** related to psychosexual development – one’s self representation, gender role behavior and sexual orientation.
- SRY gene (sex determining region of the Y chromosome) presence directs the gonads to become testis.
- SRY gene absence with presence of anti-testis genes differentiate the gonads to the ovary.
- The presence or absence of androgen acting via receptors determine external genital development.
- The presence of gonadal testosterone production leads to Wolffian duct differentiation into vas deferens, epididymis, seminal vesicle.
- The presence of gonadal AMH (anti-mullerian hormone) production leads to Mullerian duct regression.
- The absence of AMH hormone allows Mullerian duct differentiation into the upper vagina, cervix, uterine glands and fallopian tubes.
- The absence of testosterone production allows Wolffian duct regression.
- The genital and urinary system are closely associated, therefore abnormalities occur in the Mullerian system commonly affect urinary system.

![Diagram of SRY gene (TDF) and Gonad Development](image)

- Traditional terms are confusing, inaccurate and often considered negative by the patient involved.
- Updated classification system (2005) was proposed, which divides conditions into:
  - Sex chromosome DSD: wider range of disorders, including Turner syndrome (45X) and Kleinfelter syndrome 47XXY were not previously considered as intersex.
  - 46 XX DSD (including congenital adrenal hyperplasia –CAH–).
  - 46 XY DSD.
### Updated Nomenclature

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<th>Terminology used previously</th>
<th>Proposed new terminology</th>
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<td>Male pseudohermaphrodite:</td>
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<td>- undervirilization XY male</td>
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<td>XX male or XX sex reversal</td>
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### Presentation:

1. Ambiguous genitalia.
2. Mismatch of fetal chromosomal results, such as amnioncentesis or CVS with phenotype at birth.
4. Sibling history of intersex.
5. Ambiguity of genitalia developing in childhood or at puberty.
6. Inguinal hernia with unexpected gonads.
7. Pelvic mass with gonadal tumor.
8. Primary amenorrhea or delayed puberty.
10. Sexual dysfunction.
11. Part of a syndrome with other renal anomalies as in (Denys- Drash syndrome).

### Investigations depends on the presentation, include:

1. Karyotype
2. Pelvic and renal US
4. 24 hr urine collection for steroid metabolites.
5. Synaethen test.
6. MRI
7. DNA for genetic testing

### Management

The area consider in intersex management are:

1. Accurate diagnosis
2. Need for HRT
3. Screening for associated medical conditions.
6. Genetic counselling for the family members.
7. Sex assignment for the child.
11. Vaginal enlargement options.
46 XX DSD (abnormal embryological development of The Mullerian ducts and persistence of Wolffian structures):

- Can lead to a wide range of conditions.
- Often remain asymptomatic or require no treatment.
- May be associated with other renal or spinal anomalies, rarely with developmental defects of the cloaca (bladder extrophy, cloacal anomalies, anorectal anomalies).
- Ovarian development is independent of mullerian duct development.

Mullerian anomalies:

Falls into one of three groups

1- Normally fused single Mullerian system with agenesis of one or more parts.
2- Unicornuate system (unilateral hypoplasia or agenesis of one Mullerian duct).
3- Lateral fusion failure (didylephus or bicornuate anomalies).

- Incidence: about 0.5 - 6%, substantially higher in infertile women.
- Unknown cause, may be genetic errors, teratogenic events or a combination of these.
- Presentation: 75% are asymptomatic, secondary sexual characteristic features are normal.
  - Can be presented as:
    1- Primary amenorrhea.
    2- Cyclical abdominal pain (obstruction to menstruation)
    3- Severe dysmenorrhoea
    4- Pelvic mass (haematometra, haematocolpos)
    5- Menorrhagia
    6- Dyspareunia
    7- Infertility & recurrent miscarriage
    8- Ectopic pregnancy, preterm birth, abnormal lie, uterine rupture.

Investigation of Mullerian anomalies:

- Assessment of internal and external uterine contours by; US, MRI, HSG.
- Laparoscopy and hysteroscopy.
- Imaging of renal tract.

Management depends on the type and presenting features;

- Hysteroscopically resection of uterine and longitudinal vaginal septum.
- Metroplasty for bicornuate uterus.
- Surgery to relieve obstruction and prevent endometriosis
- Vaginal surgery to remove the septum
- For thick transverse vaginal septum - a combined abdomino-perineal surgery is required.
- Imperforated hymen can be treated by surgery to create an adequate window for vaginal drainage.

Rokitansky syndrome (Mayer-Rokitansky–Kuster- Hauser MRKH –syndrome):

- Is agenesis or hypoplasia of the vagina & uterus, uterus is either absent or consist of a small central uterine bud or bilateral uterine buds on the pelvic side wall
- Unknown etiology
- Presentation as primary amenorrhea and normal secondary sexual characteristics.
Management involve:

- Psychological intervention to accept the diagnosis.
- Vaginal enlargement techniques (surgical vaginoplasty or self-applied vaginal dilators therapy) to improve sexual function.
- As ovarian function is normal, fertility is possible via surrogacy.

Incomplete regression of the Wolffian system:

- Presenting as cysts lateral to the Mullerian duct.
- Incidental finding & usually asymptomatic.
- Epoophoron and paraoophoron can be found beside the ovary in the mesosalpinx.
- Gartner’s duct (the lower part of the Wolffian duct) cysts can occur anywhere from the broad ligament down to the vagina, and may be present as vulval or vaginal mass.

46 XX DSD – Congenital adrenal hyperplasia (CAH):

- Occurs in XX fetus due to an enzyme deficiency (usually 21 hydroxylase) in adrenal gland.
- The XX fetus proceeds down the female development pathway with ovarian formation & development of Mullarian ducts into uterus, cervix and upper vagina.
- Cortisone production is deficient, so adrenal gland undergoes hyperplasia as a trial to produce sufficient cortisone.
- A byproduct of this survival mechanism is the production of large amount of androgens that lead to masculinization of the external genitalia (ambiguous genitalia or normal looking male genitalia at birth).
- Is one of the most common DSD.
- It is the only DSD that can be life threatening because of that unrecognized cortisone deficiency can lead to a salt wasting crisis in the neonate.
- Gender assignment at birth is usually female due to the presence of the ovaries and uterus.
- Genital surgery to cosmetically feminize the appearance has been standard practice in the past, but now there is controversy concerning the benefits and risks of the procedure.
- Actual risk of damage to the clitoral orgasm during surgery is estimated at 20-25%.
- At puberty a review of the vagina is necessary to identify obstruction, stenosis or hypoplasia.
Other causes of XX fetal virilization:

- Other exogenous causes of androgens like maternal androgen secreting tumours or using virilizing drugs such as danazol in pregnancy.

46 XY DSD – androgen receptor defects:

I. Complete androgen insensitivity syndrome (CAIS).
II. Partial androgen insensitivity syndrome (PAIS).

CAIS:

- Occurs due to complete inability of the body to respond androgens.
- There is a disruption of the androgen receptor gene on the long arm of the X chromosome.
- Previously it was called testicular feminization.
- An XY fetus proceeds initially down the pathway of male sexual determination.
- SRY leads to normal testicular development and both AMH & testosterone are normally produced.
- Because of disability of all body androgen receptors to respond to androgen; external female genital develop and female central nervous system organization occurs.

So the result is an XY female with:

1. Absent Mullerian structures.
3. Variable vaginal hypoplasia.
4. Absent or spare pubic and axillary hair.
5. Normal breast development.
6. Normal fetal behaviour and gender identity
7. Intra-abdominal testes that produce high levels of circulating testosterone.

PAIS:

- There is some response to androgens occurs;
- The etiology is not well understood.
- Presentation is a spectrum from ambiguous genitalia to a normal male phenotype with infertility.

46 XY DSD - Gonadal dysgenesis (Swyer syndrome):

- Disruption at the very start of the male sex determination pathway causes an XY fetus to divert to the female development pathway.
- 15-30% the fault lies with SRY gene so gonadal differentiation does not occur.
- In the other remaining cases, disruption of other testis determining gene.
- Ovarian differentiation will occur but not sustained due to lake of the second X chromosome.
- Abnormal formed gonads (steak) with no normal hormonal production so the external female genital develop and Mullerian ducts develop into uterus, cervix and vagina.
- Clinical presentation is primary amenorrhea, poor breast development, normal axillary and pubic hair.
- Uterus is present and menstruation can be started with HRT.
- High gonadotrophines and low testosterone and estradiol.
- Gonadectomy is recommended due to high risk of malignancy.
- Other forms of partial gonadal dysgenesis there is unilateral testis and contra lateral steak gonad (presentation varies from genital masculinization to ambiguous genitalia).
46 DSD Androgen biosynthesis defects: (5 – Alpha reductase type 2 deficiency and 17 beta hydroxysteriod dehydrogenase type 3 deficiency):

- Both are autosomal recessive.
- An XY fetus initially undergo normal male development pathway.
- Due to deficiency of enzymes involved in androgen synthesis; female external genitalia will develop.
- 5 alpha reductase type 2 is responsible for the conversion of the testosterone to dihydrotestosterone (DHT) potent androgen required for fetal genital masculinization.
- 17 beta hydroxysteriod dehydrogenase type 3 is responsible for final step production of testosterone in fetal testis (androstenedione to testosterone).
- Activation of coenzymes is responsible for the virilization occur at puberty.
- Mullerian structures are absent, Wolffian structures are present.
- May be presented with mild ambiguity of the genitalia.
- Tests are intra-abdominal organs and will descend after puberty into inguinal region.
- If left without treatment the secondary sexual development is usually masculinize with poor breast development and normal axillary and pubic hair development.
- There is possibility of a change of gender identity from female to male at puberty in some individuals.
- Diagnosis is by DNA analysis and urinary steroid profile.

46 XY/XX ovotesticular DSD:

- 71% XX, 20% XX/XY, 7% XY, 2% other
- Presence of both ovarian and testicular tissue.
- Presented with ambiguous genitalia.
- Uterus or male ducts are present.
- Fertility is described as both male fathering a child or female carrying a pregnancy.

Turner syndrome (45 X and mosaics):

- Results from a complete or partial absence of one X chromosome (45XO).
- Is the most common chromosomal anomalies occur in female 1/2500.
- Most of the patients had typical clinical features (short stature, webbing of the neck and wide carrying angle).
- Associated medical conditions includes (coarctation of aorta, inflammatory bowel disease, sensorineural and conduction deafness, renal anomalies and endocrine dysfunction.
- Gonads are streaks don’t produce oocytes or estrogens.
- Diagnosis is made at childhood (clinical features) treatment is focused on growth.
- 10% at adolescence due to delayed puberty so induction of puberty is essential.
- Pregnancy is possible by ovum donation.
- Psychological input and support is essential.
- 47XXX female looks normal but they are subnormal academic performance +/- renal anomalies.
- 48XXXX, 49XXXXX all those girls have subnormal intelligence & ovarian dysfunction is quite common.