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 condition in which development of chromosomal, gonadal, and anatomic sex is atypical.

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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Proposed</th>
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<tbody>
<tr>
<td>• Intersex</td>
<td>• DSD</td>
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<tr>
<td>• Male Pseudohermaphroditism, undervirilization of an XY male, and undermasculinization of an XY male</td>
<td>• 46, XY DSD</td>
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<tr>
<td>• Female Pseudohermaphroditism, overvirilization of an XX female, and masculinization of an XX female</td>
<td>• 46, XX DSD</td>
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<tr>
<td>• True Hermaphroditism</td>
<td>• Ovotesticular DSD</td>
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<tr>
<td>• XX male or XX sex reversal</td>
<td>• 46, XX testicular DSD</td>
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<tr>
<td>• XY sex reversal</td>
<td>• 46, XY complete gonadal dysgenesis</td>
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</table>
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)

<table>
<thead>
<tr>
<th>Sub classification</th>
<th>Clinical condition</th>
</tr>
</thead>
</table>
| **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  
- Glucocorticoid 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 abnormalities (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, metabolic 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

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

Accelerated 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 $\rightarrow$ 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 $\rightarrow$ presence or absence of uterus
INVESTIGATION

• Laboratory examination
  – Chromosomal analysis or genetic evaluation
  – FISH and karyotyping
  – Serum electrolyte $\rightarrow$ 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 management of DSD:
  – Avoid gender assignment in newborn
  – Evaluation and long term management with multidisciplinary team
  – Gender assignment
  – Communication with patient and families
  – Respect with patient and family concerns

• Multidisciplinary approach → pediatric endocrinology, surgery, urology, psychology/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 \( \rightarrow \) hypogonadism
  – Cortisol \( \rightarrow \) avoid adrenal crisis

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

• Surgery: vaginoplasty, testis removal, clitoroplasty
  \( \rightarrow \) 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