Defining Sex and Gender

**Gender identity (Psychological sex)**
Inner sense of owns maleness / femaleness.
- Sex of rearing
- Gender role

**Sexual identity (Organic sex)**
The biologic sexual differentiation
- Chromosomal sex
- Gonadal sex
- Internal genital sex
- External genital sex
- Hormonal sex
Human sexual differentiation

Chromosomal sex

Gonadal sex

Internal genital sex

External genital sex

SEX ASSIGNMENT

Sex of rearing

Gender identity and role
Gonadal development
Gonadal development

SRY-gene (TDF) | Short arm of Y chromosome
---|---

**Present**

Bipotential Gonad

Receptors For H-Y antigen

**TESTES**

**Absent**

2 X chromosomes

**OVARY**
Internal genital organs development

- Female duct (Müllerian)
- Male duct (Wolffian)
- Urogenital sinus
- No MIS: No androgens
- MIS: androgens
- Gonad
- Bladder
- Female duct
- Uterus
- Vagina
- Male duct
- Seminal vesicle
- Prostate
External genital organs development

- Urogenital sinus
- Genital swelling
- Genital tubercle
- Genital fold
- Male
- Female
- Scrotal swelling
- Phallus
- Prepucce
- Glans
- Urethra
- Scrotum
- Labia majora
- Labia minora
- Vaginal opening
- Labial swelling
- Hooded clitoris
- Urethral groove

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Male development

TESTIS

Leydig cells  Sertoli cells

Testosterone  Mullerian inhibiting factor

Wolffian duct  5a-reductase

DHT

Male internal Genital organs  Urogenital sinus

Male external genitalia  Regression of Mullerian ducts
Female development

Neutral Development

OVARY

Urogenital sinus

- Female external genitalia
  - Lower part of vagina

Absence of androgen exposure

Mullerian ducts

- Female internal genital Organs
  - Most of upper vagina
  - Cervix and uterus
  - Fallopian tubes
Summary of Normal Sex Differentiation

- Genetic sex is determined at fertilization.
- Testes develop in XY fetus, ovaries develop in XX fetus.
- XY fetus produces MIS and androgens and XX fetus does not.
- XY fetus develops Wolffian ducts and XX fetus develops Mullerian ducts.
- XY fetus masculinizes the female genitalia to make it male and the XX fetus retains female genitalia.
INTERSEX

An individual in whom there is discordance between chromosomal, gonadal, internal genital, and phenotypic sex or the sex of rearing.

- **INTERSEXUALITY:**
  Discordance between any two of the organic sex criteria

- **TRANSSEXUALITY:**
  Discordance between organic sex and psychological sex components
CLASSIFICATION OF INTERSEXUALITY

1. Virilization of genitically female foetus
   Female pseudohermaphroditism

2. Incomplete musculinization of genitically male foetus
   Male pseudohermaphroditism (XY-FEMALE)

3. The presence of both ovarian and testicular tissue in the same individual
   True hermaphroditism

4. Chromosomal abnormality
   Mixed gonadal dysgenesis (45,X0 / 46,XY)
How many children are born with intersex conditions?

- A conservative estimate is that 1 in 2000 children born will be affected by an intersex condition.
- 98% of affected babies are due to congenital adrenal hyperplasia.
FEMALE PSEUDOHERMAPHRODITISM

**EXCESS FETAL ANDROGENS**

- Congenital adrenal hyperplasia
  - 21-hydroxylase deficiency
  - 11-hydroxylase deficiency
  - 3β-hydroxysteroid dehydrogenase deficiency

**EXCESS MATERNAL ANDROGENS**

- Maternal androgen secreting tumours (ovary, adrenal)
- Maternal ingestion of androgenic drugs
21-hydroxylase deficiency
congenital adrenal hyperplasia

Cholesterol
Pregnenolone
Progesterone
17-OH progesterone

21-hydroxylase
Cortisol
Androgens

Pituitary
ACTH
Adrenal cortex
Cortisol
Androgens
Congenital adrenal hyperplasia

- The commonest cause of genital ambiguity at birth
- 21-Ohas deficiency is most common form
- Autosomal recessive
- Salt wasting form may be lethal in neonates
- ↑SERUM 17OH-progesterone (21OHase)
- ↑ SERUM deoxycorticosterone, 11-deoxycotisol (11- OHase)
- Treatment: cortisol replacement and ? Surgery
Drugs with Androgenic side effects ingested during pregnancy

- Testosterone
- Synthetic progestins
- Danocrine
- Diazoxide
- Minoxidil
- Phenetoin sodium
- Streptomycin
- Penicillamine
Male pseudohermaphroditism (XY- FEMALE)

**Failure to produce testosterone**
- Pure XY gonadal dysgenesis (swyer’s syndrome)
- Anatomical testicular failure (testicular regression syndrome)
- Leydig-cell agenesis
- Enzymatic testicular failure

**Failure to utilize testosterone**
- 5-alpha-reductase deficiency
- Androgen receptor deficiency
  - * Complete androgen Insensitivity (TFS)
  - * Incomplete androgen Insensitivity
Swyer’s syndrome

46, XY

No SRY OR its receptors

STREAK GONADS
- NO MIF (Uterus +)
- NO SEX STEROIDS

Female external Genitalia

Female Internal Genitalia
Testicular regression syndrome (congenital anorchia)

46-XY/SRY

Testis $\Leftrightarrow$ MIF (self destruction)

$\pm$ testosterone $\pm$ DHT

Female or ambiguous External genitalia

$\pm$ Male Internal genitalia
Leydig-cell agenesis

46-XY/SRY

TESTIS ↔ MIF
( partial/ complete absence
Of leydig-cells)

No or ↓ testosterone
No or ↓ DHT

Female or ambiguous external Genitalia

± Male Internal Genitalia
Testicular enzymatic failure

46-XY/SRY

Testis $\Rightarrow$ MIF
(defects in testosterone Synthesis)

↑ testosterone precursors
↓ DHT

Ambiguous
External
Genitalia

Male
Internal
Genitalia

Autosomal recessive enzyme deficiency:
-20-22 desmolase
-3-β-ol-dehydrogenase
-17-α-hydroxylase
-17,20-desmolase
-17-β-hydroxysteroid oxyreductase
5-alpha-reductase deficiency

46-XY/SRY

Testis ⇔ MIF

Testosterone

↓ 5-α-reductase

↓ DHT

Female or Ambiguous external Genitalia

Male Internal Genitalia
Testicular feminization syndrome

46-XY/SRY

TESTIS $\Rightarrow$ MIF

Testosterone

5-$\alpha$-reductase

DHT

Absent androgen receptors

Female External Genitalia

Male Internal Genitalia

Incomplete form $\Rightarrow$ Ambigious genitalia
Diagnosis of XY Female

Testosterone concentration

- Low
  - Concentration of Testosterone precursors
    - High
      - Testicular enzyme Failure
    - Low
      - Absent testes or Absent leydig-cell
        - Surgical exploration

- Normal Male level
  - DHT
    - Low
      - 5α-reductase Deficiency
    - Normal
      - Testicular Feminization Syndrome
MIXED GONADAL DYSGENESIS

- Combined features of Turner’s syndrome and male pseudohermaphroditism
- Short stature
- Streak gonad on one side with a testis on the other
- Unicornuate uterus & fallopian tube- side of streak gonad
- Karyotype 46XY / 45X0
- Considerable variation in the sexual phenotype
TRUE HERMAPHRODITISM

- Gonads:
  - ovary one side and testis on the other or
  - bilateral ovotestis
- Karyotype:
  46,XX most common (57%); XY (13%) and XX/XY (30%)
- Internal genitalia:
  Both mullerian and wolffian derivates
- Phenotype is variable
- Gonadal biopsy is required for confirming diagnosis
DYSEMBROGENESIS

genital ambiguity with associated anomalies

- Can occur in both genetic males and genetic females
- Most common genital malformation:
  - Penoscrotal transposition
  - Agenesis of phallus in a genetic male
- Coexistence of other caudal or urologic abnormalities should strongly suggest dysembryogenisis
CLINICAL PRESENTATION OF INTERSEXUALITY

- AT BIRTH
  Ambiguous genitalia
- DURING CHILDHOOD
  Heterosexual features
- AT ADOLESCENCE
  Delayed or Heterosexual Puberty
The external genital organs look unusual, making it impossible to identify the sex of the newborn from its outward appearance.

Any one of the following:

- A small, hypospadiac phallus and unilaterally undescended gonad.
- An enlarged phallus with bilaterally impalpable gonads.
- An enlarged phallus and a vagina in the same infant.
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

GENERAL GUIDELINES

- Medical and social emergency
- Avoid immediate declaration of sex
- Proper counselling of the parents
- Team management; obstetrician, neonatologist, pediatric endocrinologist, genetist and paediatric surgeon.
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

DIAGNOSIS

- History: pregnancy; family
- Detailed examination: abdomen; pelvis; external genitalia; urethral and anal openings.

_Federman’s rule: a palpable gonad below the inguinal ligament is testes until proven otherwise_
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

Investigations

• Rule out cong. Adrenal hyperplasia: Serum electrolytes; 17-OHP level and urinary levels of 17-ketosteroids
• Karyotype (buccal smear; blood)
• Pelvic US and sometimes MRI or Genitogram
• Skin biopsy; fibroblast culture to measure 5alpha-reductase activity or dihydrotestosterone binding
• Laparoscopy
• Gonadal biopsy (laparotomy)
A PROTOCOL FOR INVESTIGATION OF A NEWBORN WITH AMBIGUOUS GENITALIA

Karyotype all

Palpable gonad

NO

CAH Screen

Positive

- US / MRI
- ? Genitogram

Negative

YES

- Biochemical profile
- US / MRI / ? genitogram
- ? Gonadal biopsy
Sex assignment

General guidelines

• Sex assignment should be decided after detailed assessment, investigations and accurate diagnosis

• Complete gender assignment by age 18 months
Sex assignment

• Male gender assignment:
  - stretched phallus > 2 cm
  - erectile tissue
  - lack of severe hypospadias

• Female gender assignment:
  - inadequate phallus
  - cervix and uterus present

In difficult cases; sex assignment should be to the sex which can be surgically made to be adequate for coitus
SURGICAL CONSIDERATIONS

- Phallic / clitoral reduction if the assigned sex is female, before 3 years of age
- Removal of intra-abdominal gonads / streaks in newborns carrying Y chromosome
- Vaginal construction / repair is better performed around puberty
Concluding remarks on Management of newborn with genital ambiguity

- The causes of ambiguous genitalia are many and complex, so it is important to approach the treatment of children with this disorder in a systematic fashion.
- Evaluation should be done expeditiously, and parents should be kept informed during the evaluation to help them understand the embryologic anomaly that led to their child's genital ambiguity.
- Endocrine supplementation should be instituted when necessary, and a pediatric surgeon should be actively involved in assigning the child's sex of rearing as well as performing any necessary reconstructive surgery.
## INTERSEXUALITY PRESENTING AT ADOLESCENCE

<table>
<thead>
<tr>
<th>Primary amenorrhea</th>
<th>Ambiguous genitalia</th>
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</thead>
<tbody>
<tr>
<td>- Complete androgen insensitivity (TFS)</td>
<td>- Neglected congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>- Congenital anorchia (early testicular regression syndrome)</td>
<td>- Mixed gonadal dysgenesis</td>
</tr>
<tr>
<td>- Complete leydig-cell agenesis</td>
<td>- Partial androgen resistance</td>
</tr>
<tr>
<td>- Some forms of enzymatic testicular failure</td>
<td>- Congenital anorchia (Late)</td>
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<td></td>
<td>- Testicular enzymatic failure</td>
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<td></td>
<td>- True hermaphroditism</td>
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</tbody>
</table>
MANAGEMENT OF INTERSEXUALITY PRESENTING AT ADOLESCENCE

- Cortisol replacement therapy and corrective surgery in CAH
- Corrective surgery in drug induced cliteromegally
- In almost all other instances (XY-FEMALE), whatever the diagnosis is to **Maintain the gender role as female**
- In some cases of enzymatic testicular defects or 5α-reductase deficiency: Some May seek to change the gender role
INTERSEXUALITY PRESENTING AT ADOLESCENCE

Surgical aspects of management

- Clitoral reduction
- Removal of gonads in the presence of Y chromosome
- Vaginal repair and construction
VAGINAL CREATION
Vaginal dilatation
McIndoe Vaginoplasty
Colovaginoplasty
Transsexualism

- Transsexualism occurs when a person strongly believes that he or she belong to the opposite sex.
- This is typically a lifelong feeling and results in varied degrees of physical/external changes.
- These patients should be referred to the psychiatrist.
Concluding remarks

Management of adolescent with intersex

- By following an approach that is based on a few embryological; physiological and anatomical principles-and with a minimum of tests- the clinician can arrive at a prompt and accurate diagnosis in patients with intersexuality.

- If such a patient is managed correctly, she or he may live a happy, well adjusted life and may even be fertile.

- If the patient is managed incorrectly, she or he may be doomed to live as a sexual freak in loneliness and frustration.

- Gynecologists, endocrinologists, plastic surgeons, urologists and psychiatrists should be actively involved in the management of these patients.
Thank You For Your Attention