PUSAT STUDI BIOETIK DAN
HUKUM KEDOKTERAN ISLAM

BIO HUKI

Fakultas Kedokteran
Universitas Islam Indonesia

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Materi Seminar & Workshop

PERSISTENT CONTROVERSY OF INTERSEX: SCIENCE, HUMAN RIGHT AND ISLAMIC BIOETHICS PERSPECTIVE

Intersex: ditinjau dari Sisi Medis

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Defining Sex and Gender

Gender identity (Psychological sex)

Inner sense of owns maleness / femaleness.

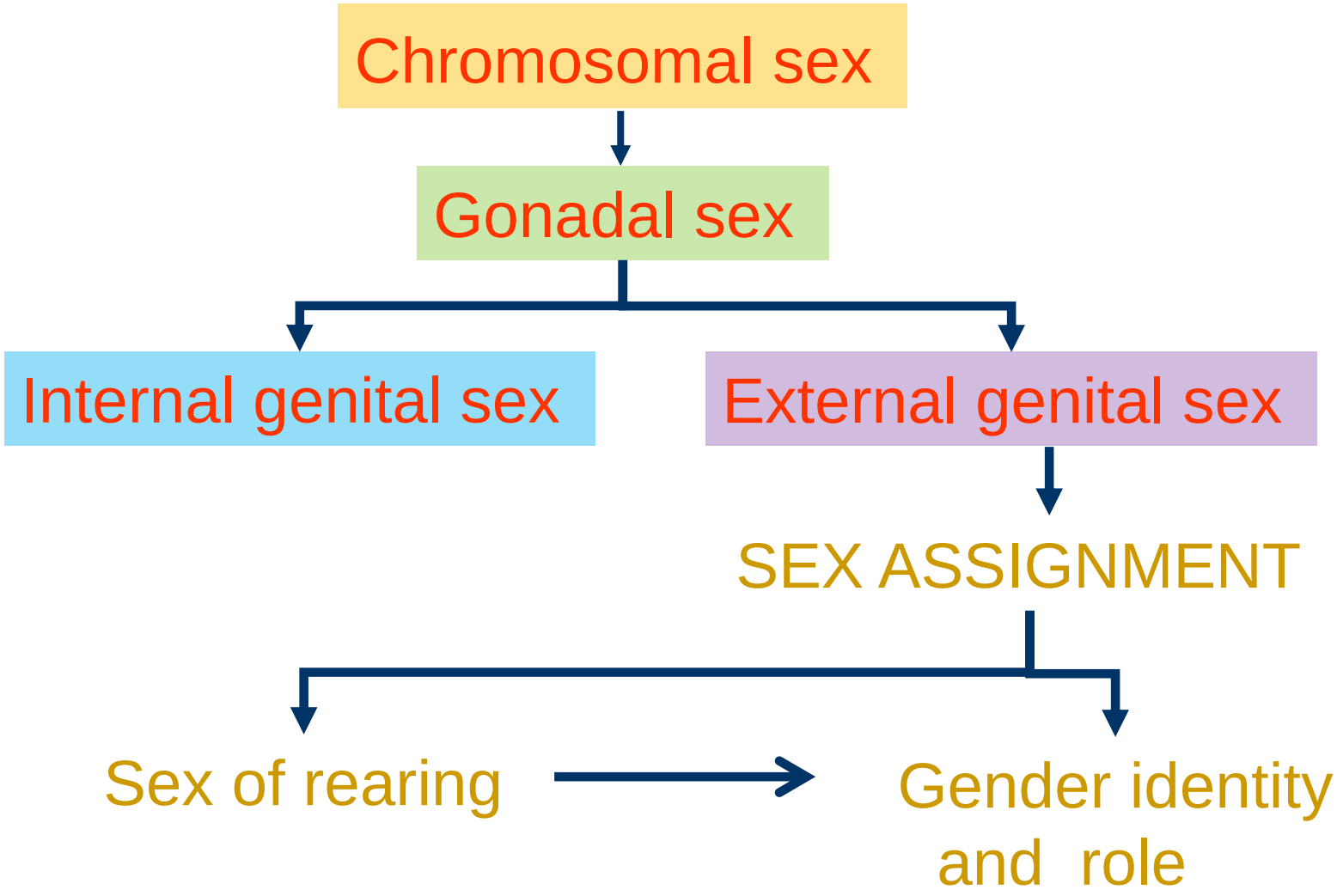
- Sex of rearing
- Gender role

Sexual identity (Organic sex)

The biologic sexual differentiation

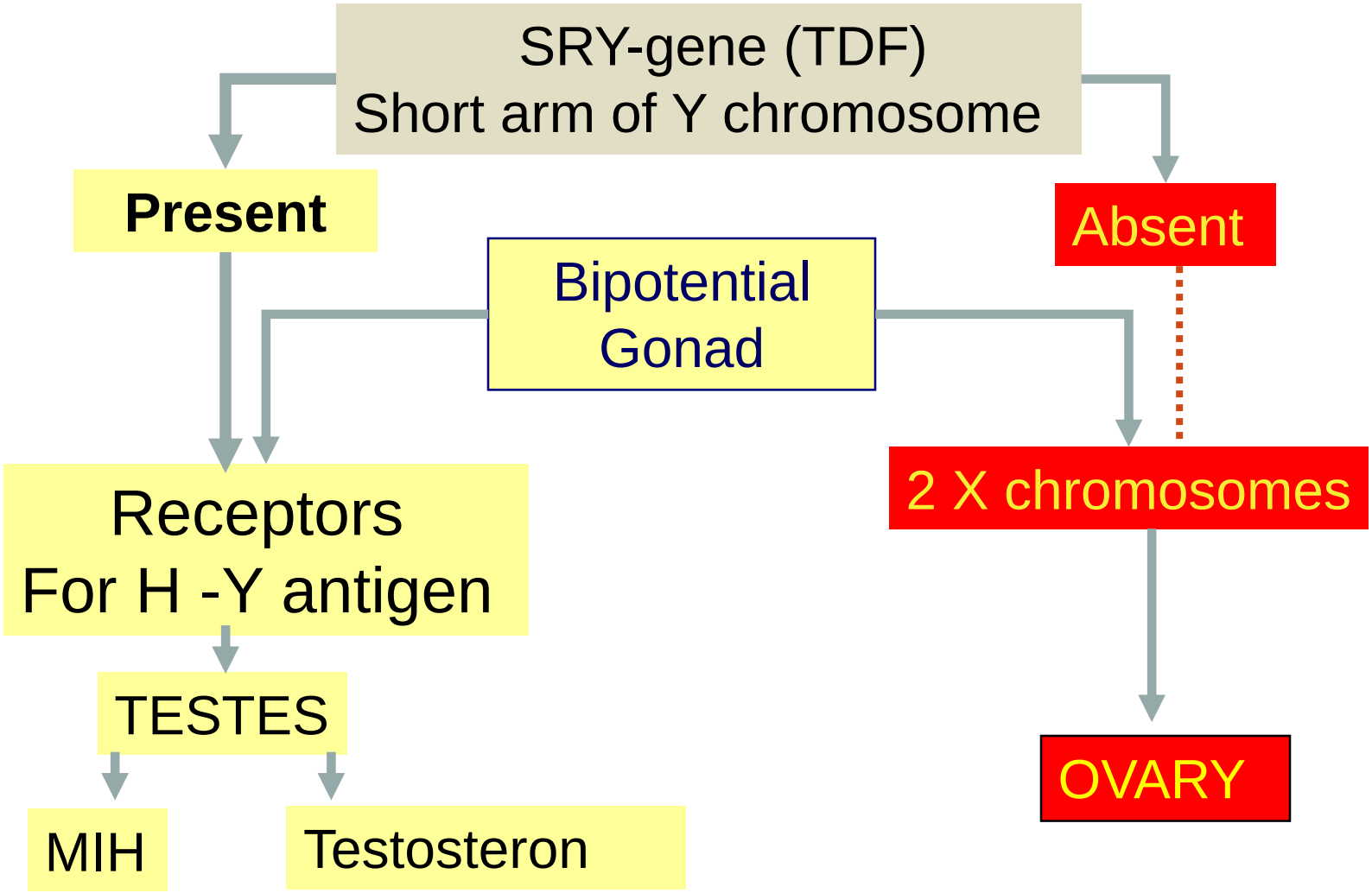
- Chromosomal sex
- Gonadal sex
- Internal genital sex
- External genital sex
- Hormonal sex

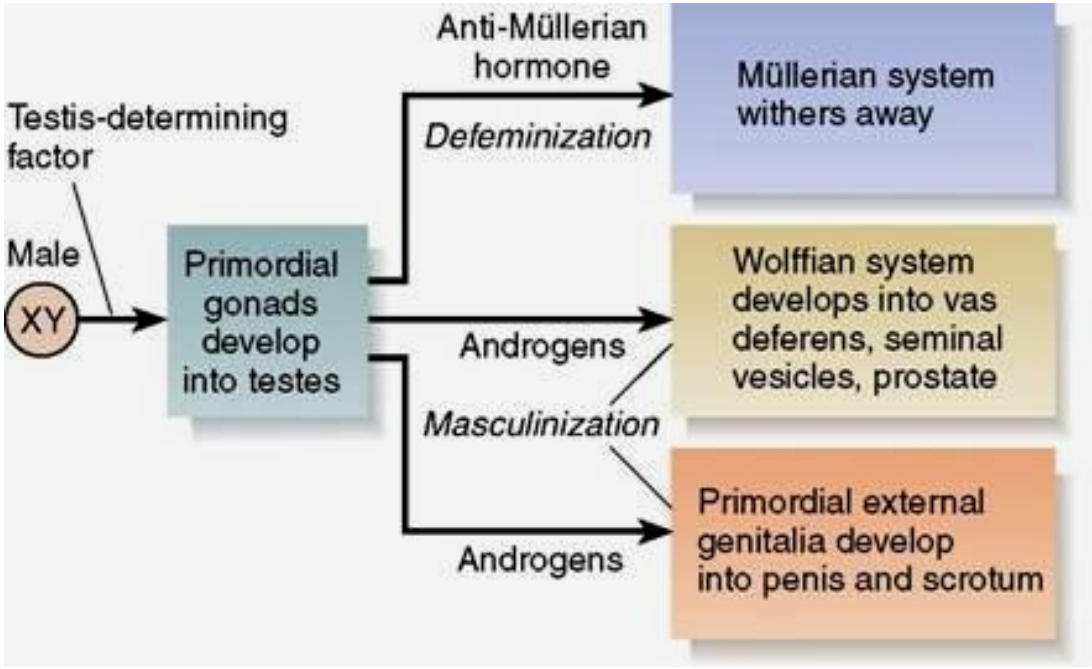
Human sexual differentiation

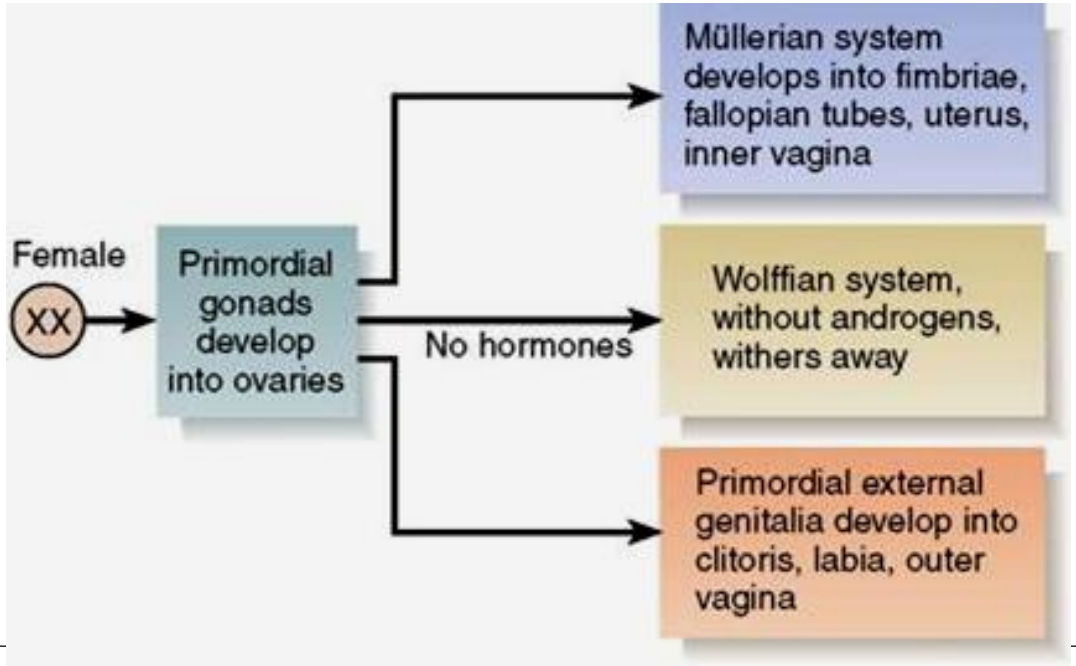


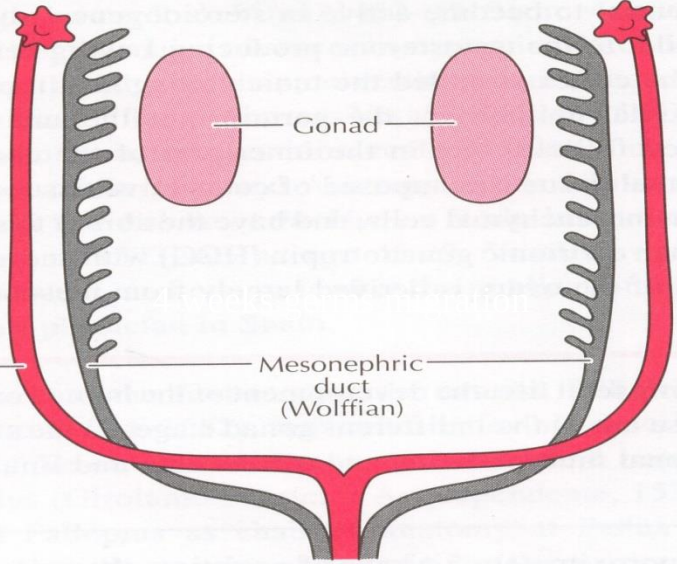
Gonadal development

The Y chromosome contains a gene called SRY (for sex-determining region of Y)



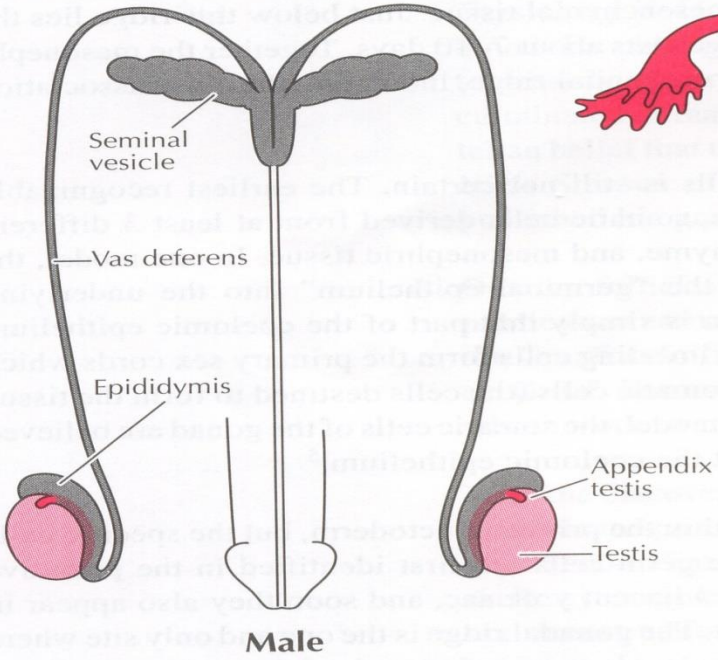

Anti-Müllerian hormone
Müllerian system withers away
Testis-determining factor
Defeminization
Male
XY
Primordial gonads develop into testes
Wolffian system develops into vas deferens, seminal vesicles, prostate
Androgens
Masculinization
Primordial external genitalia develop into penis and scrotum
Androgens

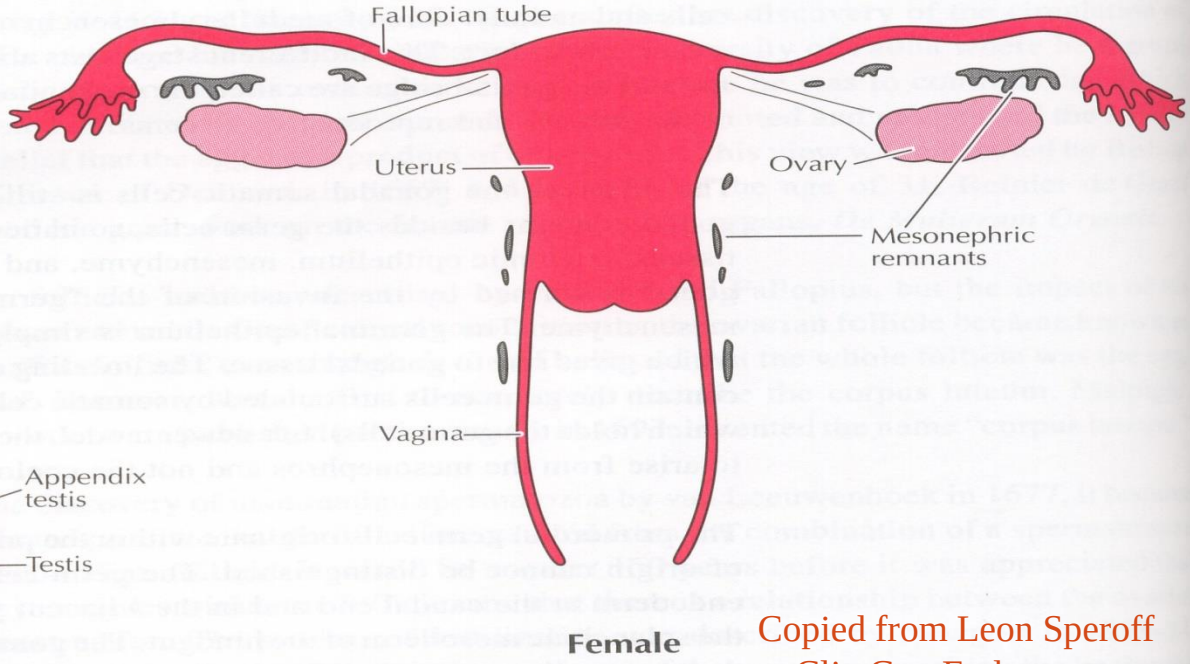

Müllerian system develops into fimbriae, fallopian tubes, uterus, inner vagina
Female
XX
Primordial gonads develop into ovaries
Wolffian system, without androgens, withers away
No hormones
Primordial external genitalia develop into clitoris, labia, outer vagina



TDF+, MIF+, TESTOSTERON +

TDF - , MIF -





Copied from Leon Speroff
Clin Gyn End

EXTERNAL GENITALIA

1-UNDEFERENTIATED STAGE (4-8 WK)

The neutral genitalia includes:

genital tubercle (phalus)

labioscrotal swellings

urogenital folds

urogenital sinus

2-♂ & ♀ EXTERNAL GENITAL DEVELOPMENT

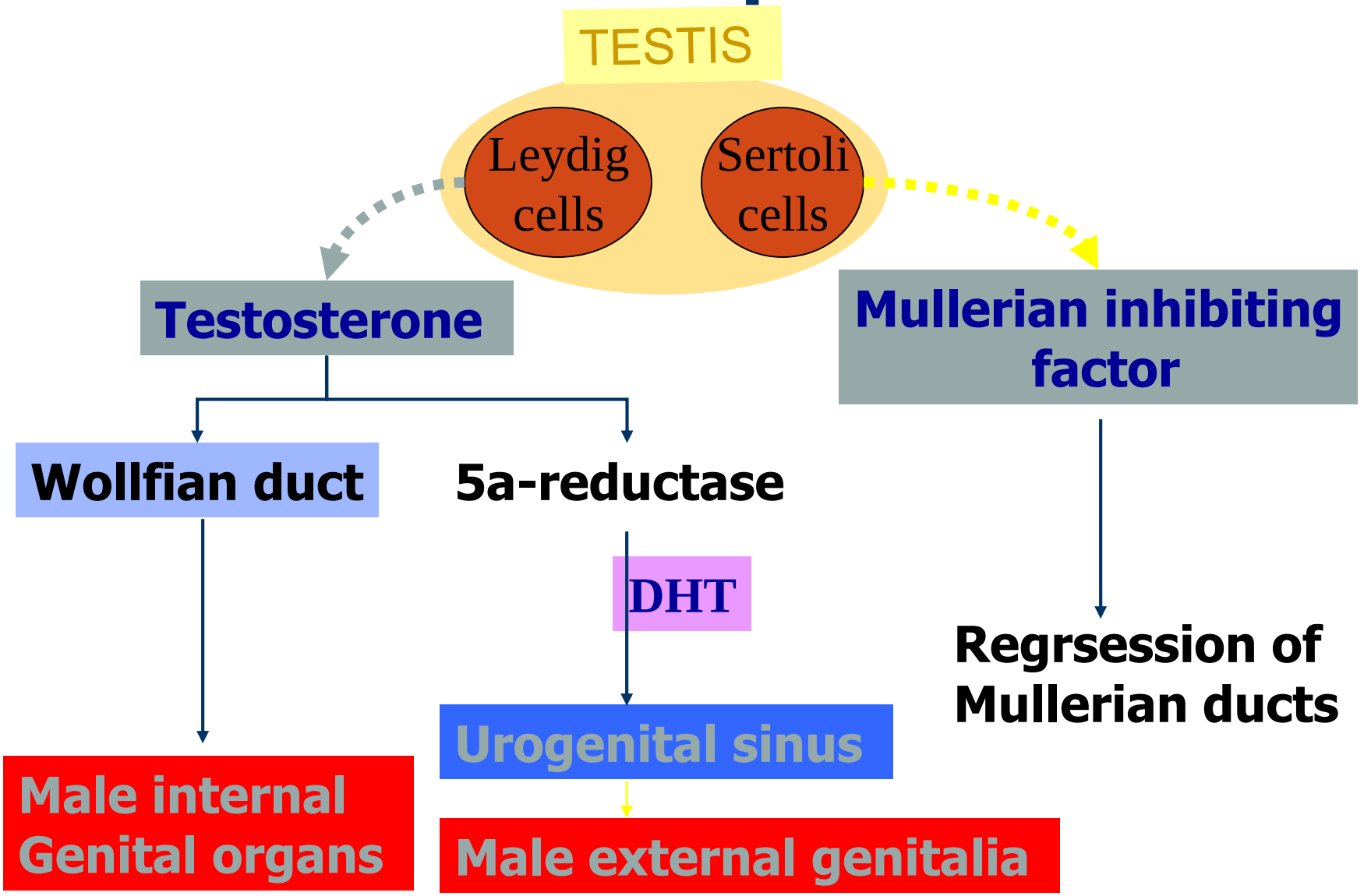
(9-12 WK)

- By 12 wk gestation ♂ & ♀ genitalia can be differentiated
- In the absence of androgens ⇨ ♀ external genitalia develop
- The development of ♂ genitalia requires the action of androgens, specifically DHT

5 alpha reductase

testosterone ⇨ ⇨ ⇨ ⇨ ⇨ DHT

Male development



Female development

Neutral Development

Urogenital sinus

Mullerian ducts

Female external genitalia
. Lower part of vagina

Absence of androgen exposure

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.
- The female external genitalia represents the neutral sex
  - 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 tow of the organic sex criteria

- **TRANSSEXUALITY:**

  Discordance between oganic sex and psychological sex components

CLASSIFICATION OF INTERSEXUALITY

1. **Virilization of genitically female foetus**
   - Female pseudohemaphroditism
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

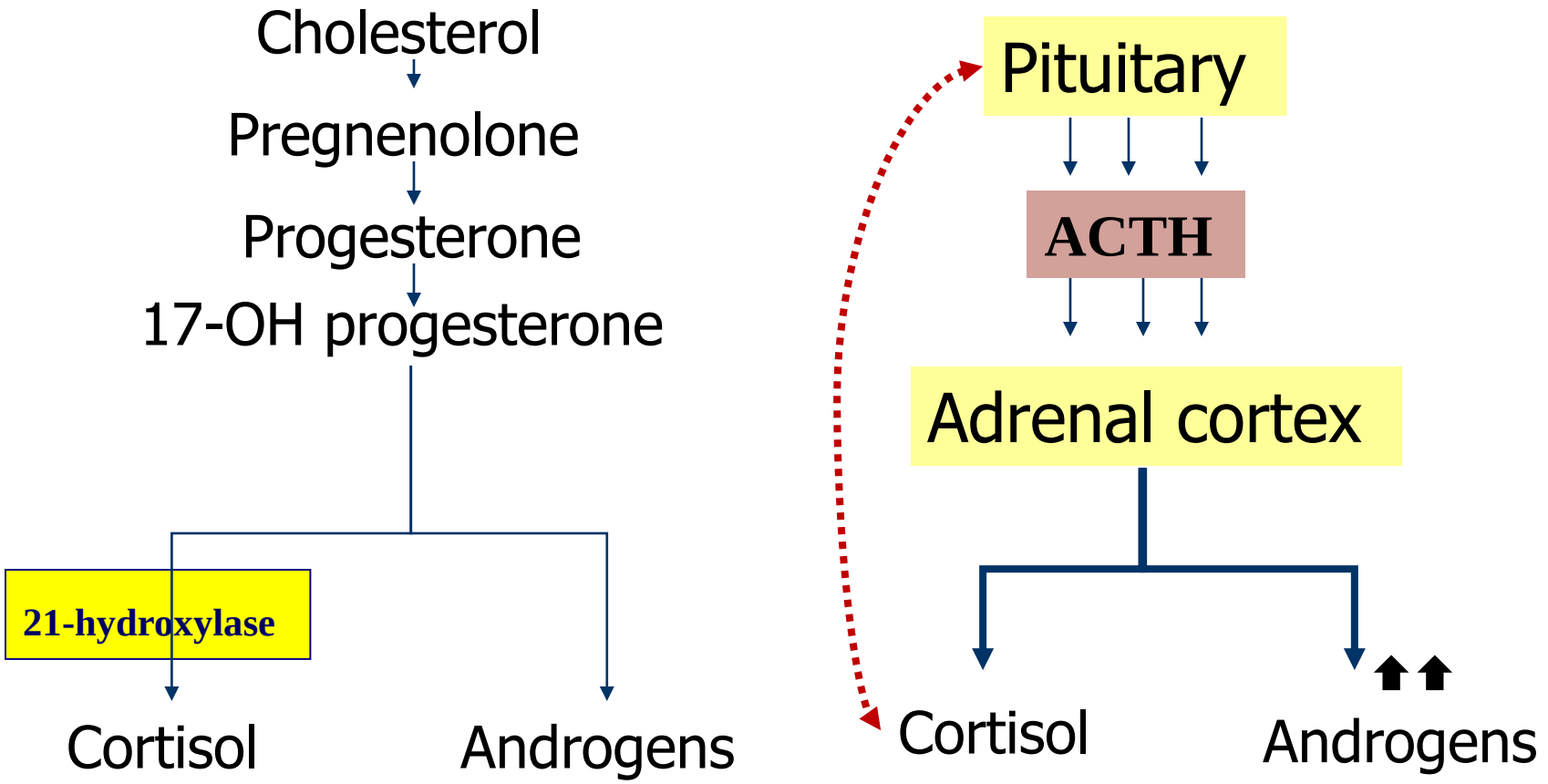
Congenital adrenal hyperplasia

- 21 -hydrxylase deficiency
- 11-hydroxylase deficiency
- 3ß-hydroxysteroid dehydrogenase deficiency

EXCESS MATERNAL ANDROGENS

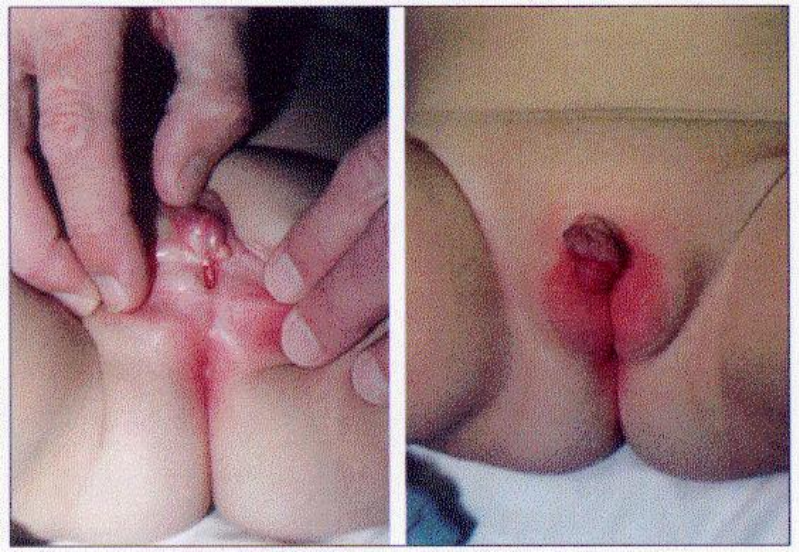
- Maternal androgen secreting tumours (ovary, adrenal)
- Maternal ingestion of androgenic drugs

21-hydrxylase deficiency congenital adrenal hyperplasia



Congenital Adrenal Hyperplasia

- The commonest cause of genital ambiguity at birth
- 21-Ohase deficiency is most common form
- Autosomal reccessive
- 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

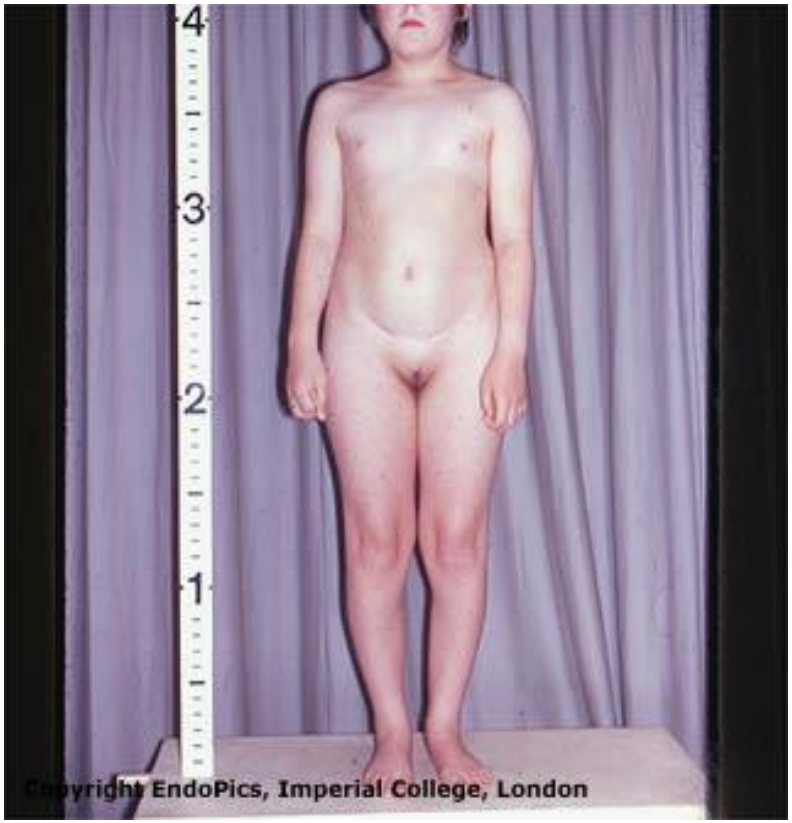
46, XY

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 ⇨ MIF (self destruction)

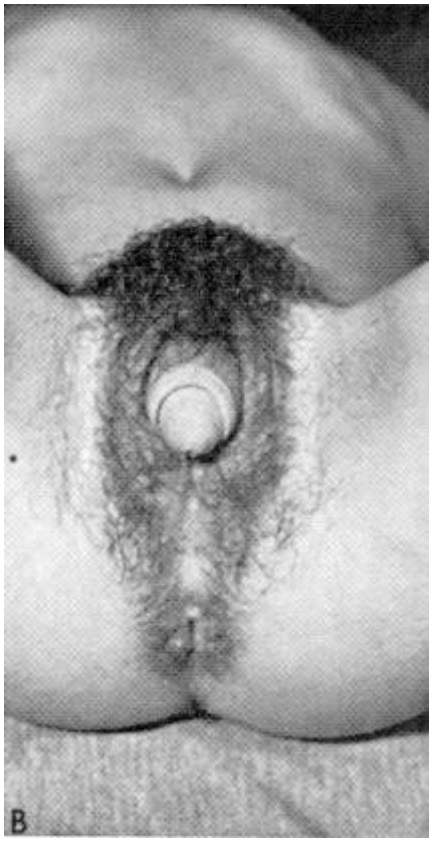
↓

± testosterone ± DHT

↓

Female or ambiguous External genitalia

± Male Internal genitalia



Leydig-cell agenesis

46-XY/SRY

↓

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

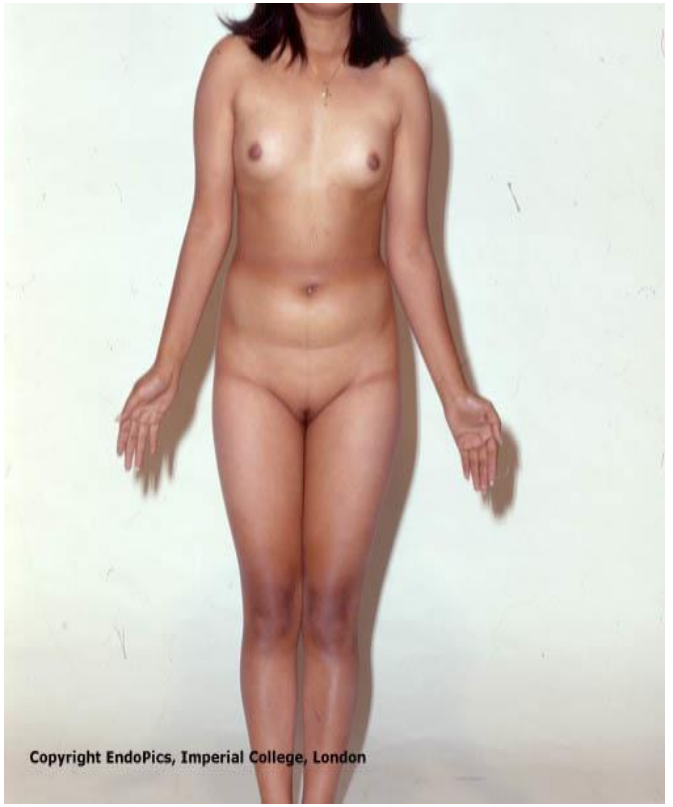
↓

No or ⬇ testosterone
No or ⬇ DHT

↓

Female or ambiguous external Genitalia

± Male Internal Genitalia



Testicular enzymatic failure

46-XY/SRY

↓

Testis ⇨ MIF
(defects in testosterone Synthesis)

↓

↑ testosterone precursors
↓DHT

↓

Ambiguous External Genitalia

Male Internal Genitalia

Autosomal recessive enzyme deficiency :

-20-22 desmolase
-3-ß-ol-dehydrogenase
-17- ∝ -hydroxylase
-17,20-desmolase
-17-ß –hydroxysteroid oxyreductase

5-alpha-reductase deficiency

46-XY/SRY

Testis ⇨ MIF

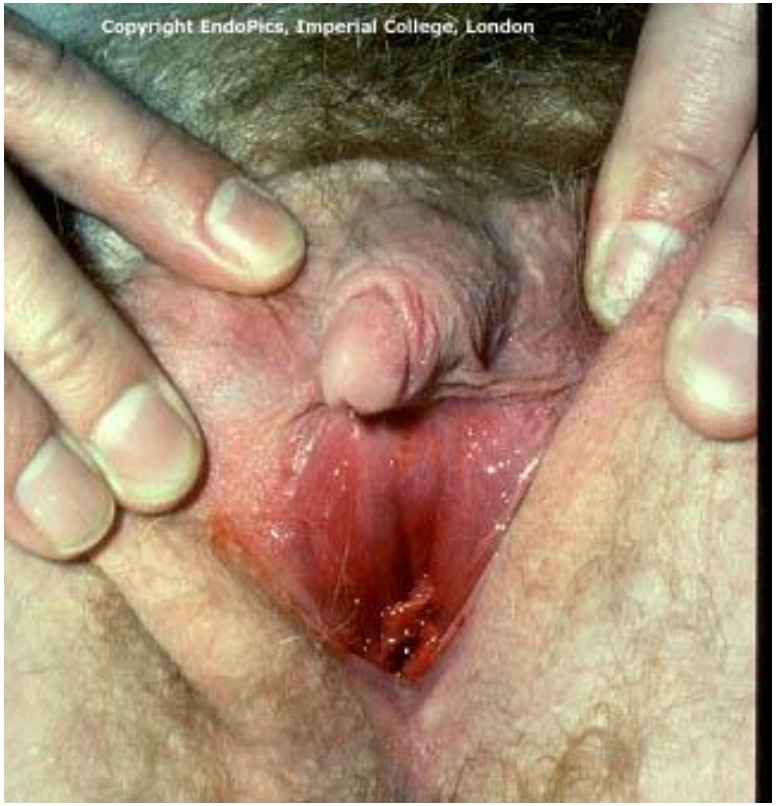
Testosterone

⬇5-∝-rductase

⬇DHT

Female or Ambiguous external Genitalia

Male Internal Genitalia



Testicular feminization syndrome

46-XY/SRY

↓

TESTIS ⇨ MIF

↓

Testosterone

↓

5-∝-reductase

↓

DHT

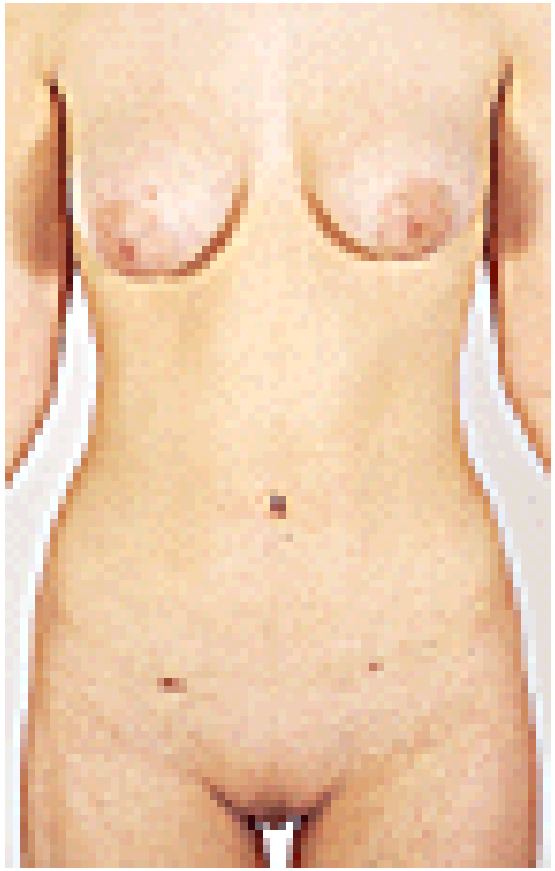
↓

Absent androgen receptors

↓

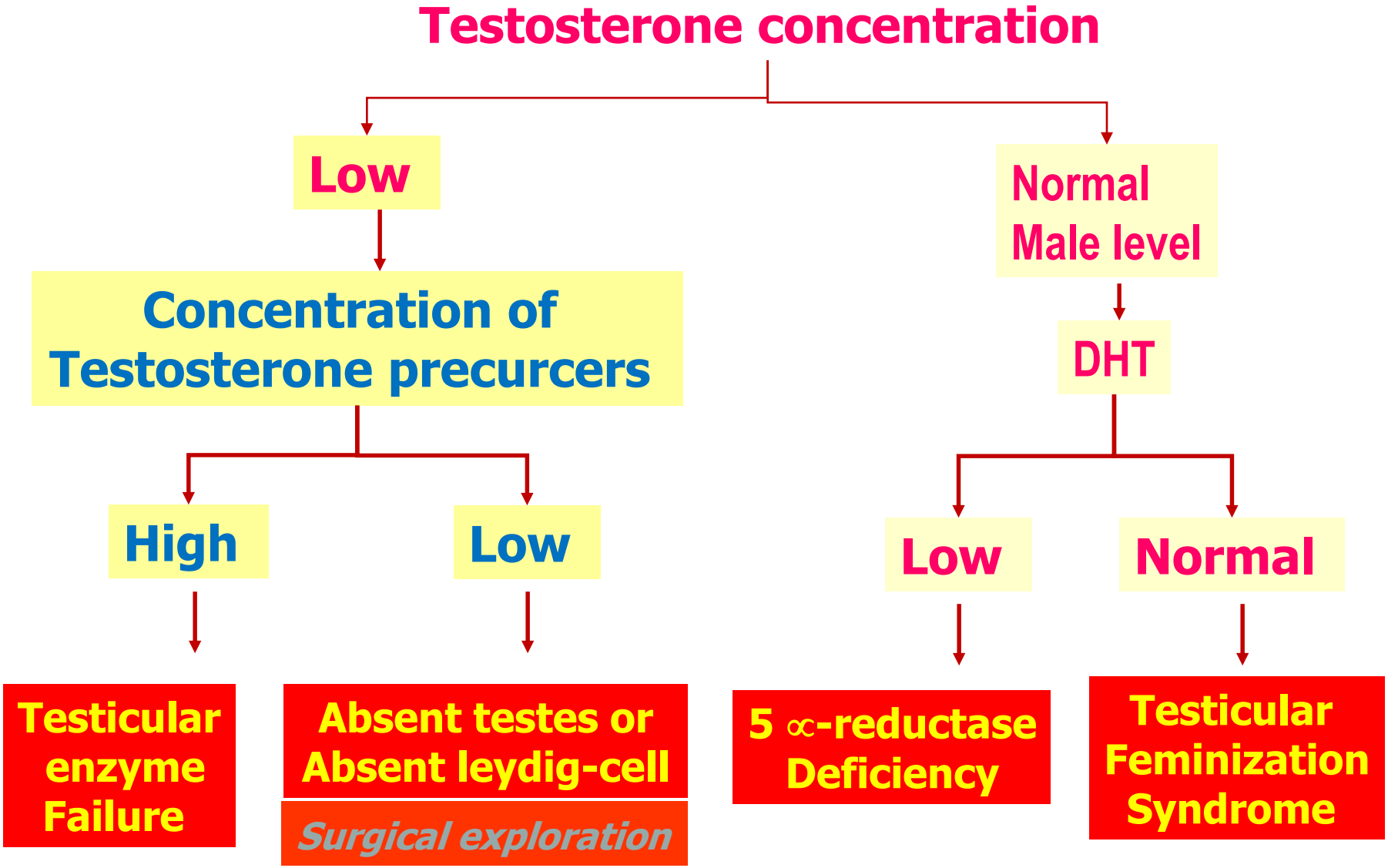
Female External Genitalia

Male Internal Genitalia



Incomplete form ⇨ Ambigious genitalia

Diagnosis of XY Female



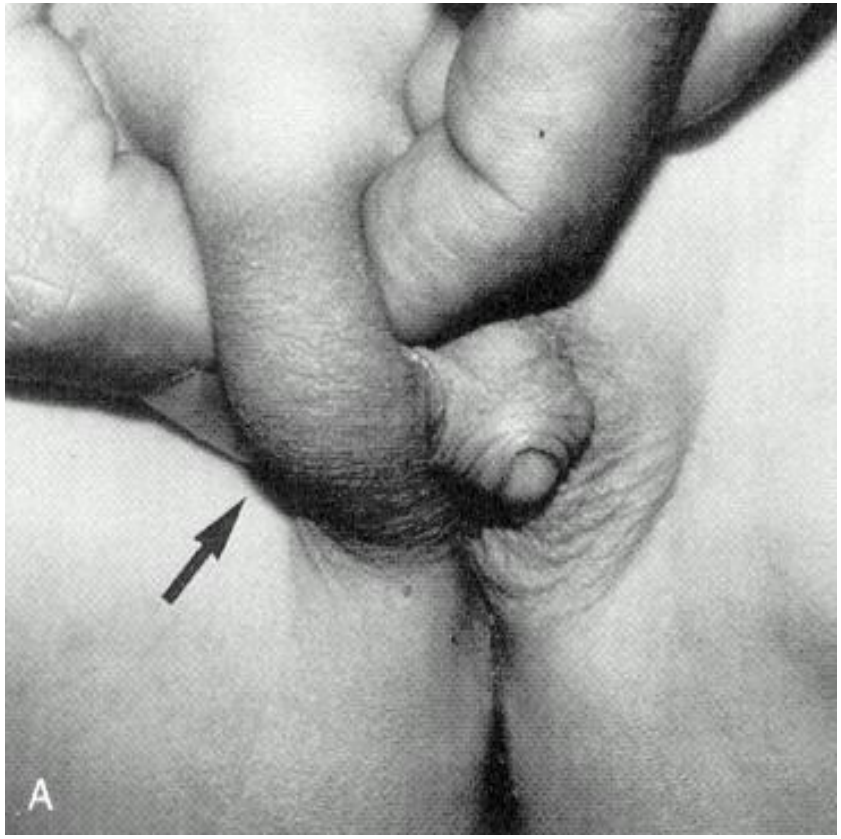
TRUE HERMAPHRODITISM

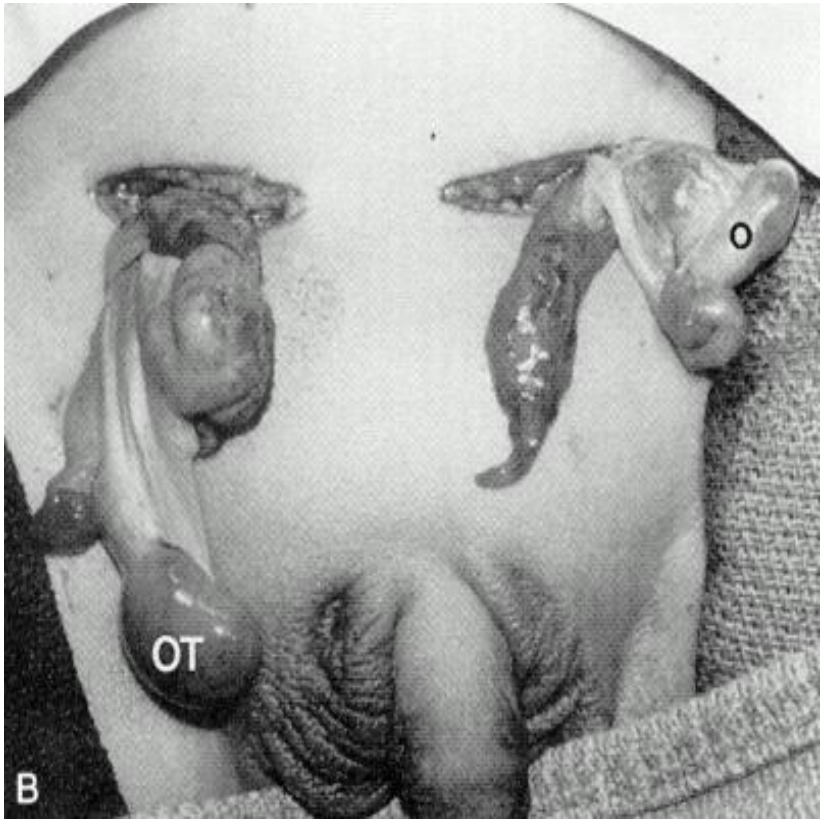
- Gonads :
  - ovary one side and testis on the other or
  - bilateral ovotestis
- Karyotype :

  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

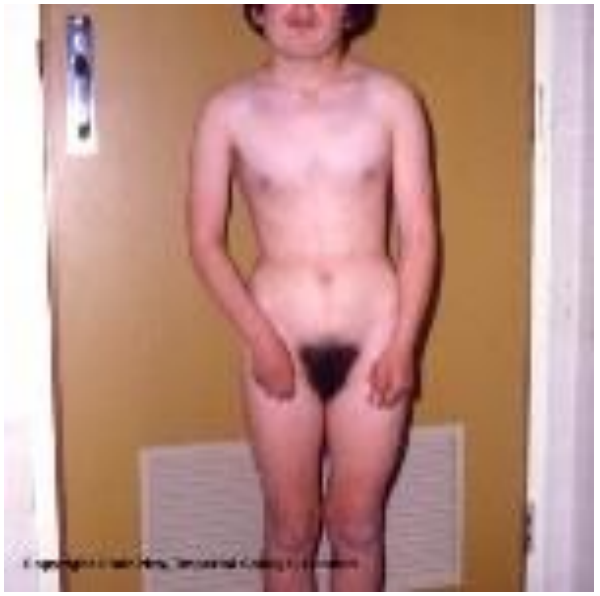
TRUE HERMAPHRODITISM





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
- Mosaic Karyotype 46XY / 45X0
- Considerable variation in the sexual phenotype



CLINICAL PRESENTATION OF INTERSEXUALITY

- At birth

  Ambiguous genitalia
- During childhood

  Heterosexual features
- At Adolescence

  Delayed or heterosexual puberty

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

AMBIGUOUS GENITALIA AT BIRTH

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 endocrinolgist, genetist and pediatric surgeon.

MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

DIAGNOSIS

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

Federman's rule:

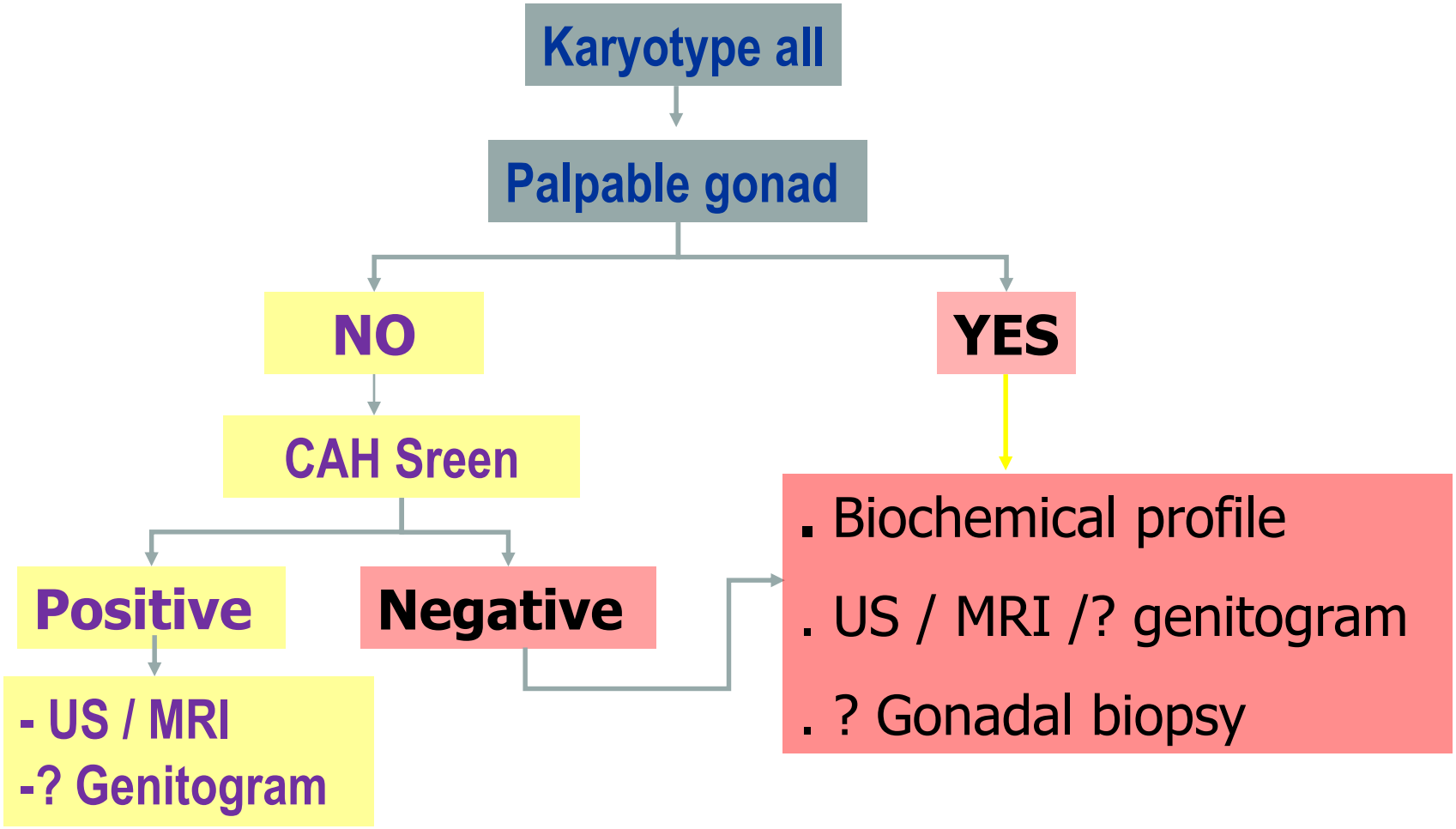
A palpable gonad below the inguinal ligament is a testes until proven otherwise

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



Sex assignment

General guidelines

- Sex assignment should be decided after detailed assessment, investigations and accurate diagnosis
- Complete gender assignment by age 18 months

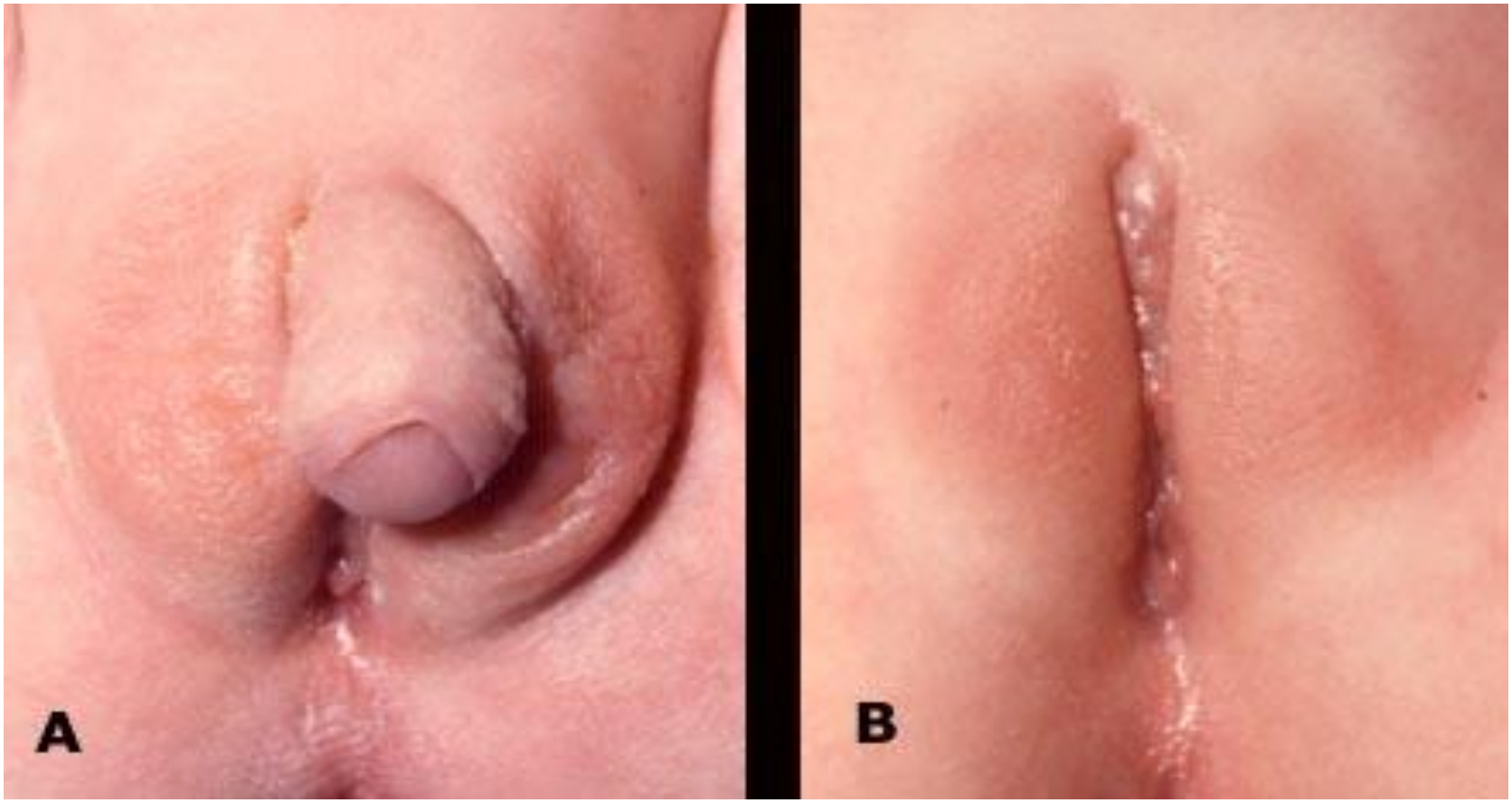
Sex assignment

- **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



Before surgery

After surgery

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

Primary amenorrhea

- Complete androgen insesitivity (TFS)
- Congenital anorchia (early testicular regression syndrome)
- Complete leydig-cell agenesis
- Some forms of enzymatic testicular failure

Ambiguous genitalia

- Neglected congenital adrenal hyperplasia
- Mixed gonadal dysgenesis
- Partial androgen resistance
- Congenital anorchia (Late)
- Testicular enzymatic failure
- Leydig cell agenesis (incomplete)
- True hermaphrotidism

MANAGEMENT OF INTERSEXUALITY PRESENTING AT ADOLESCENCE

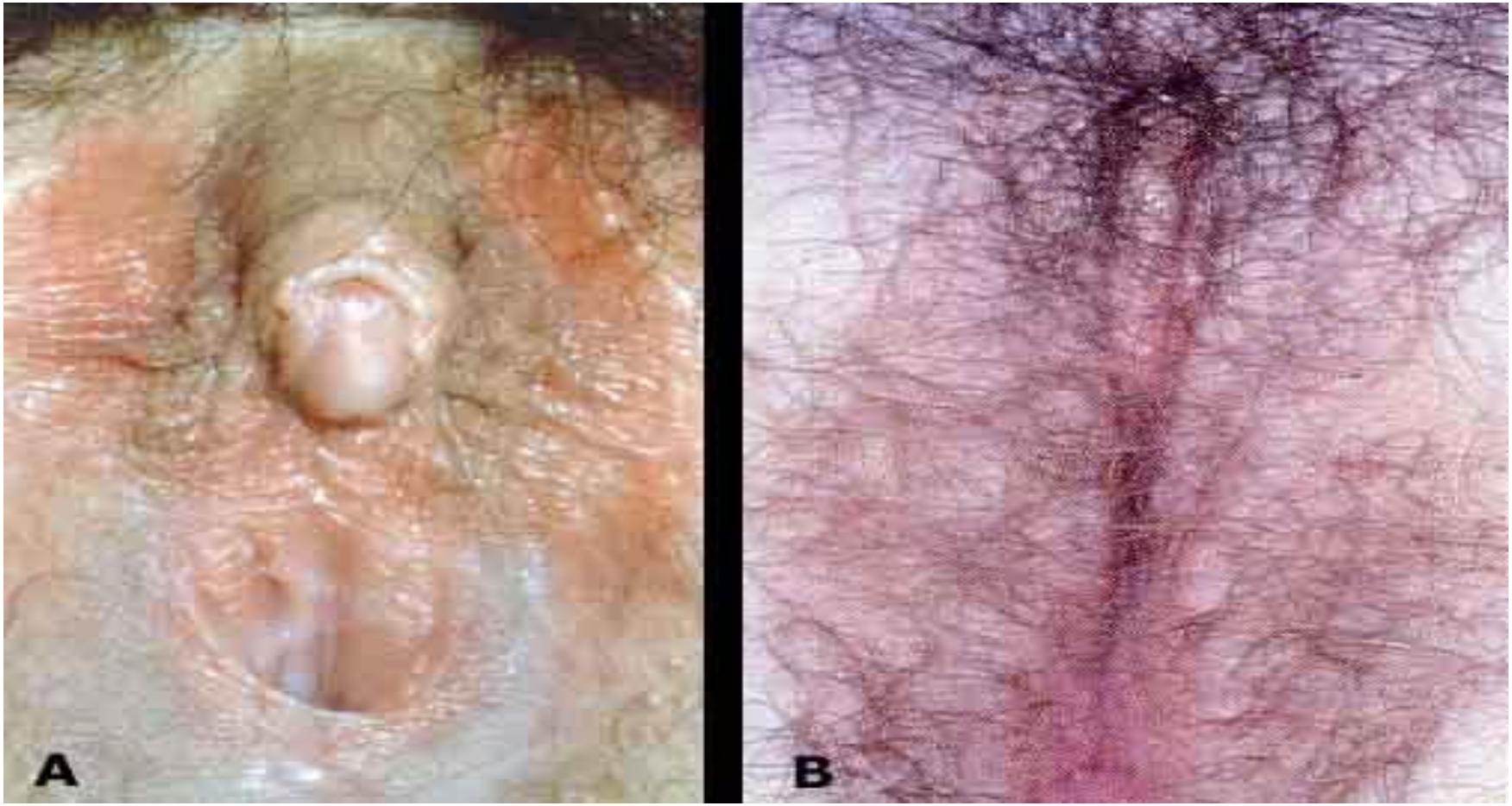
- Cortisol replacement therapy and ? Corrective surgery in CAH
- Corrective surgery in drug induced cliteromegally
- In almost all other instances (XY- FEMALE), whatever the diagnosis is to Maintain the gender role as female
- In some cases of enzymatic testicular defects or 5 $\propto$ -reductase deficiency :

  Some May seek to change the gender role

INTERSEXUALITY PRESENTING AT ADOLESCENCE

Surgical aspects of management

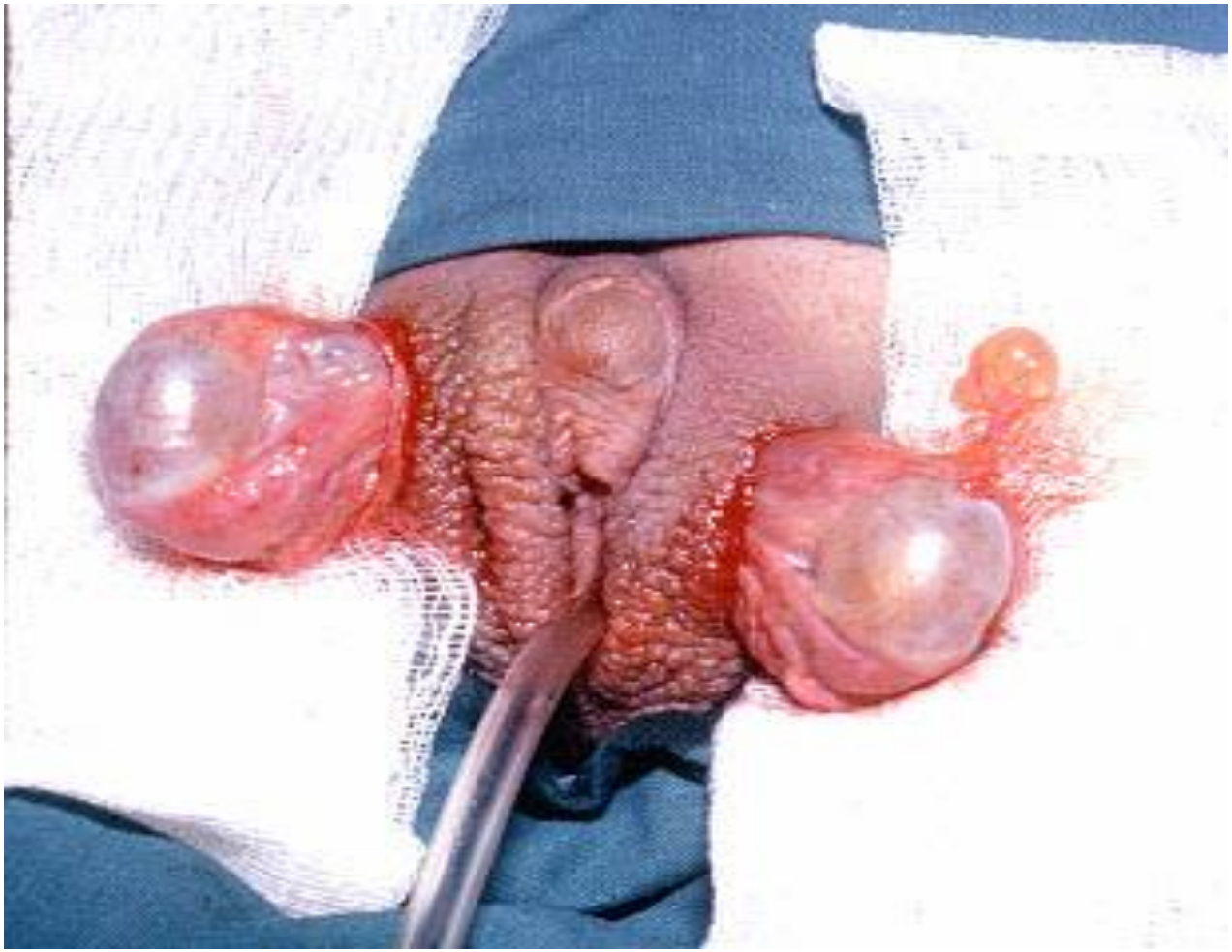
- Clitoral reduction
- Removal of gonads in the presence of Y chromosome
- Vaginal repair and construction



Before surgery

After surgery

GONADECTOMY



VAGINAL CREATION

Vaginal dilatation

Trans-sexualism

- 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**