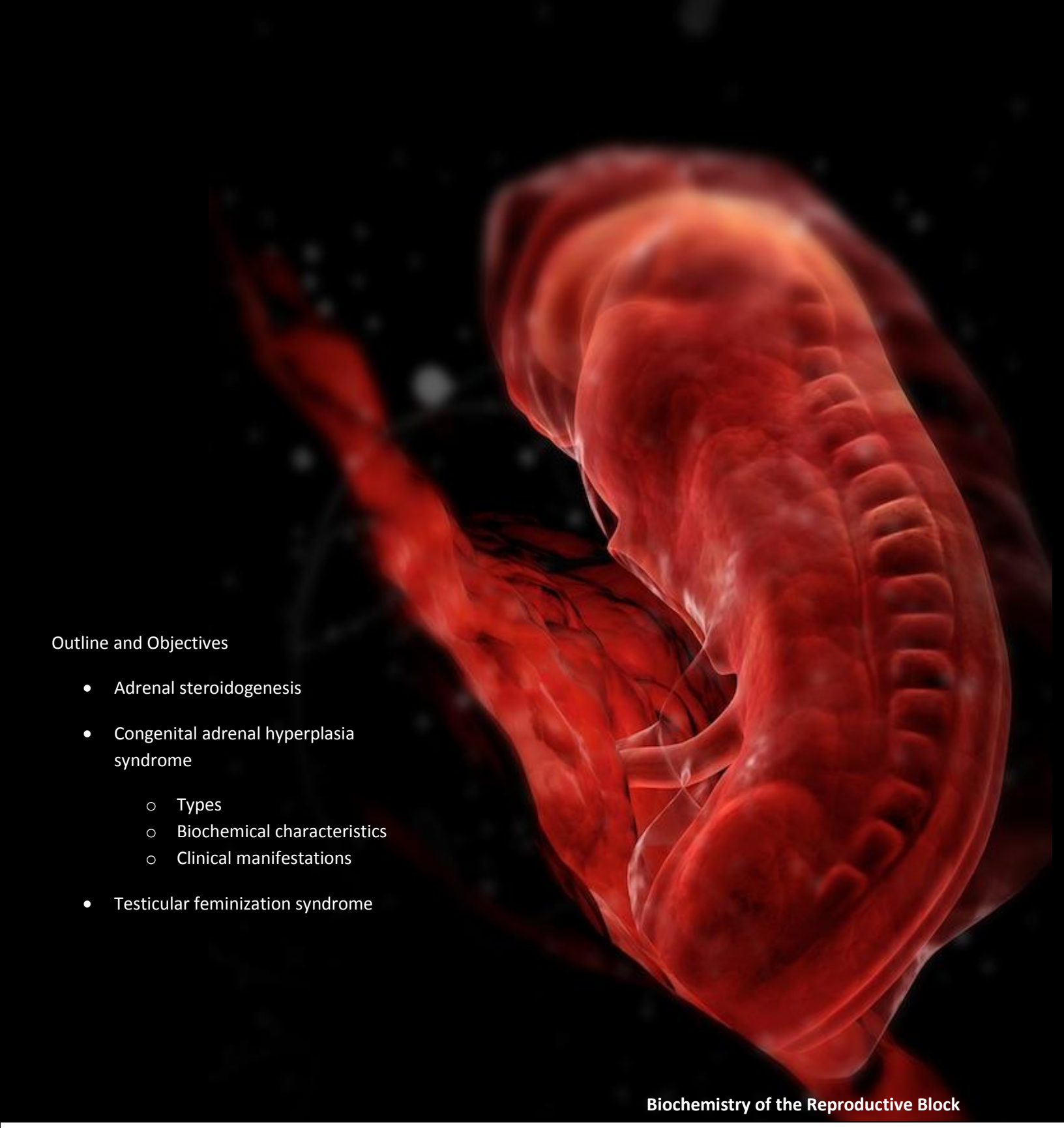

Outline and Objectives

- Adrenal steroidogenesis
- Congenital adrenal hyperplasia syndrome
    - Types
    - Biochemical characteristics
    - Clinical manifestations
- Testicular feminization syndrome

Biochemistry of the Reproductive Block

Congenital Adrenal Hyperplasia Syndrome & Testicular Feminization Syndrome

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Remember :

The adrenal glands comprise 3 separate hormone systems:

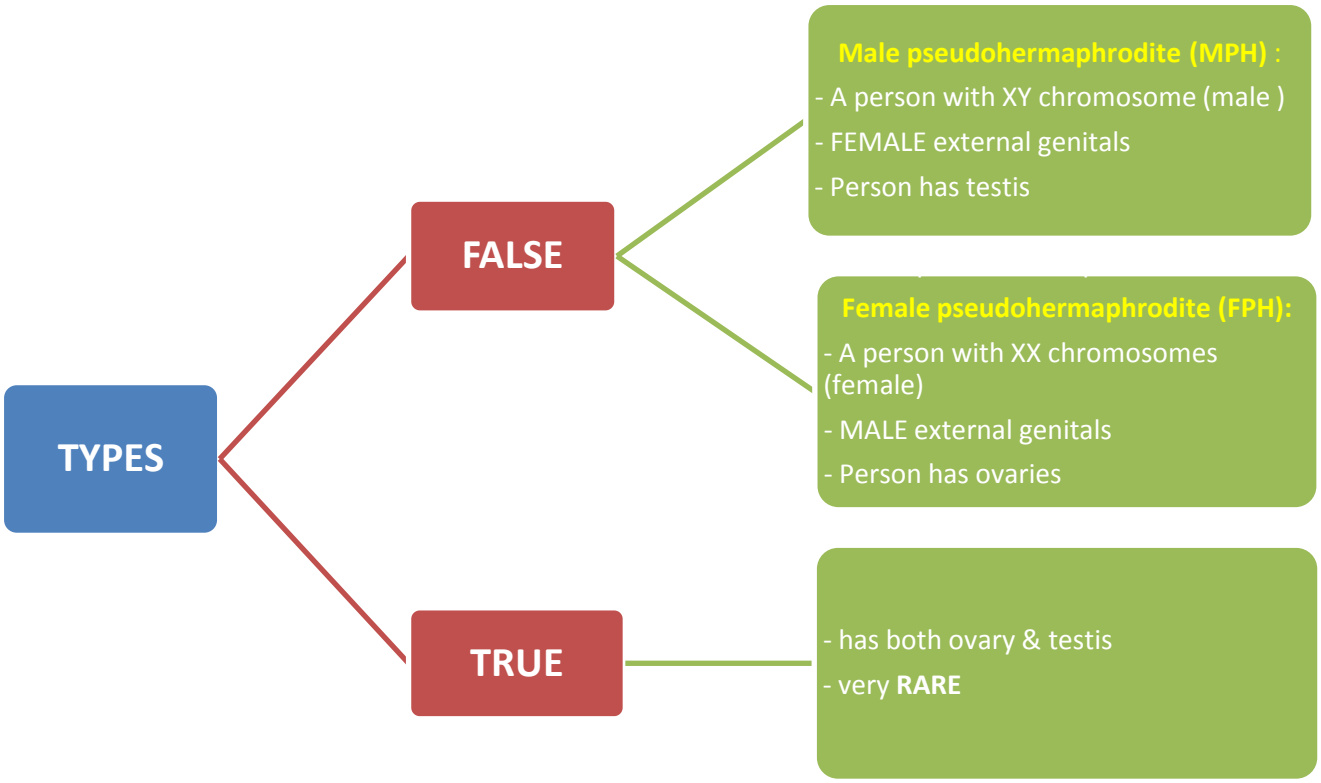
1. The zona glomerulosa: secretes aldosterone.
2. The zona fasciculata & reticularis: secrete cortisol & the adrenal androgens.
3. The adrenal medulla: secretes adrenaline.

Glucocorticoids: Steroids with cortisol-like activity and Potent metabolic regulators & immunosuppressants.

Mineralocorticoids: Steroids with aldosterone-like activity and Promote renal sodium retention.

Hermaphroditism or Intersex:

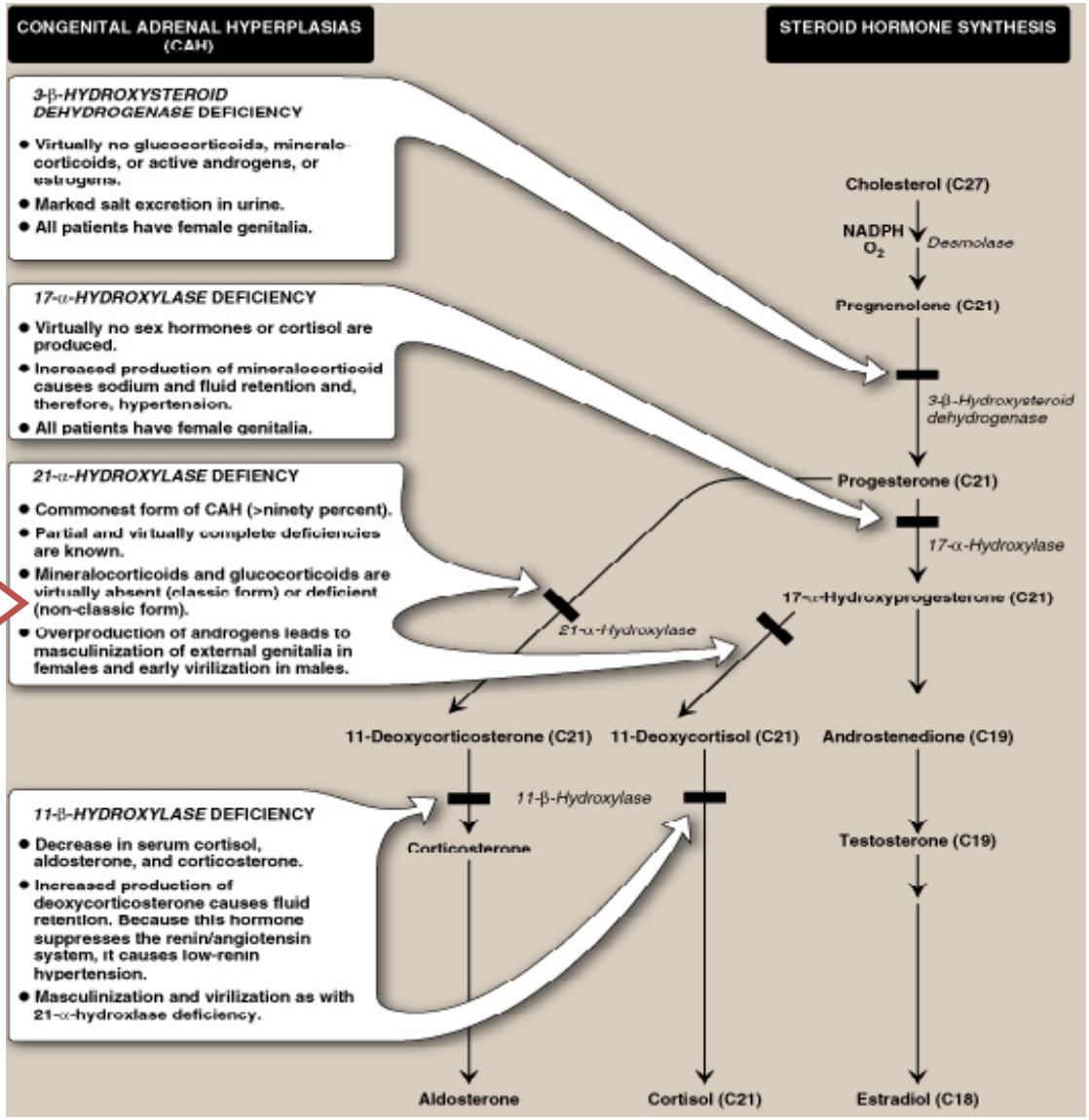
- Intersex: A person has neither standard male or standard female anatomy.
- Discrepancy between type of gonads and external genitalia.



Steroidogenesis and Congenital adrenal hyperplasia syndrome

Here, you should know the name of the deficient enzyme

Very important



Note:

- What you need to know is that the cholesterol is the precursor of aldosteron, cortisol and sex hormones.

-in general, if we have a block of any enzyme we will have accumulation of the precursor and deficiency of the final product

-for (**3-β-Hydroxysteroid dehydrogenase** and **17-α-Hydroxylase**) only memories their names and no need to memories their diseases

Congenital Adrenal Hyperplasia (CAH)

- It is the result of an inherited enzyme defect in steroid biosynthesis
- The adrenals :

A. **Cannot** secrete **cortisol** → absent **negative feedback** to the pituitary) → **ACTH** continues to drive steroid biosynthesis → **adrenal hyperplasia** and **accumulation of cortisol precursors** (depending on which enzyme is lacking)

B. **Cannot** secrete **aldosterone → electrolyte disturbances** :

Hyponatremia (because aldesterone causes sodium water retention)
Hyperkalemia (because aldersterone causes K^+ secretion outside the body)

Approximately 50% of patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency have salt wasting due to inadequate aldosterone synthesis.

- The condition might be fatal unless diagnosed early

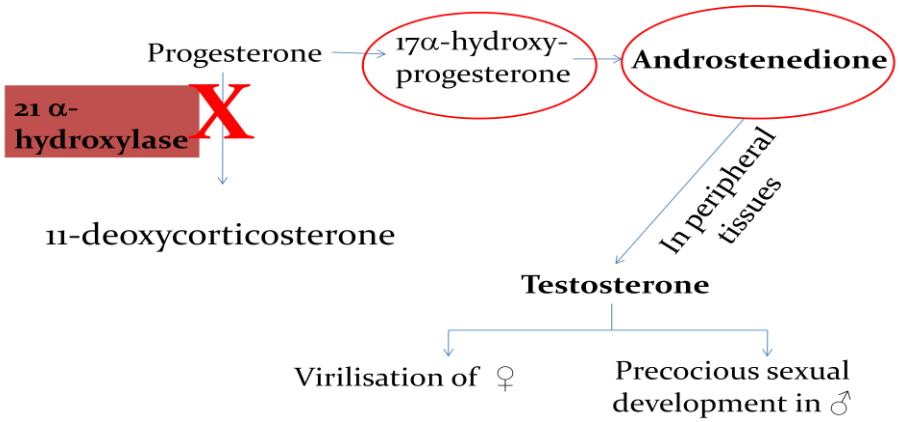
❖ **The most common type of CAH is due to 21-hydroxylase deficiency (95% of CAH cases)**
❖ Diagnosis of the most common type (21-hydroxylase deficiency) is by finding ↑ **plasma [17-hydroxyprogesterone] as early as 4 days after birth.**
❖ ↑ Stimulation of adrenal **androgen** production → **virilization in baby girls, & precocious puberty in boys.**
❖ Partial enzyme defect → late onset form → menstrual irregularity & hirsutism in young females.

Note: If we have deficiency of **21-α-Hydroxylase** we will have:

1- An accumulation of **17-α -Hydroxyprogesterone (C21)**
2- low aldosteron = hypotension = adrenal crisis (hyponitremia and hyperkalimia)
3- low cortisol
4- high testosterone

Congenital adrenal hyperplasia syndrome

A. 21 α-Hydroxylase Deficiency



- ✓ **Autosomal recessive** condition
- ✓ **Impairs** synthesis of **cortisol & aldosterone ↓ [cortisol]→↑ ACTH** secretion → Adrenal gland **hyperplasia**
- ✓ Some of the accumulated precursors are **diverted to the biosynthesis of sex hormones** →signs of androgen excess:
- ✓ **ambiguous genitalia in newborn girls (FPH)**
- ✓ Rapid postnatal growth in both sexes.
- ✓ **In severe cases,** mineralocorticoid deficiency is evident → salt & H_2O loss → **hypovolaemia & shock → neonatal adrenal crisis**
- ✓ Late presentation (adult life) is possible in less severe cases

Genetics of 21 α-Hydroxylase Deficiency

Mutations in the CYP21 gene:

- Deletions
- Nonsense
- Missense

- DNA testing and detection of mutations can be helpful for prenatal diagnosis and confirmation of diagnosis

Diagnosis

- ✓ Serum sample taken at least 2 days after birth (earlier samples may contain maternally derived 17-hydroxyprogesterone
- ✓ Classic 21-hydroxylase deficiency is characterized by **markedly elevated serum levels of 17-hydroxyprogesterone**
- ✓ **Late-onset** 21-hydroxylase deficiency may require **corticotropin stimulation test:**
  - inject a 0.125-mg or 0.25-mg bolus of corticotropin
  - Measure base-line and stimulated levels of 17-hydroxyprogesterone. High level after stimulation is diagnostic

B. 11 β -Hydroxylase Deficiency

- ✓ leads to **high** concentrations of **11-deoxycortisol**
- ✓ Leads to **high** levels of **11-deoxy-corticosterone** with **mineralocorticoid** effect **(salt and water retention)** → Suppresses renin/angiotensin system → low renin hypertension.
- ✓ **Musculanization in females (FPH) and early virilization in males**

Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

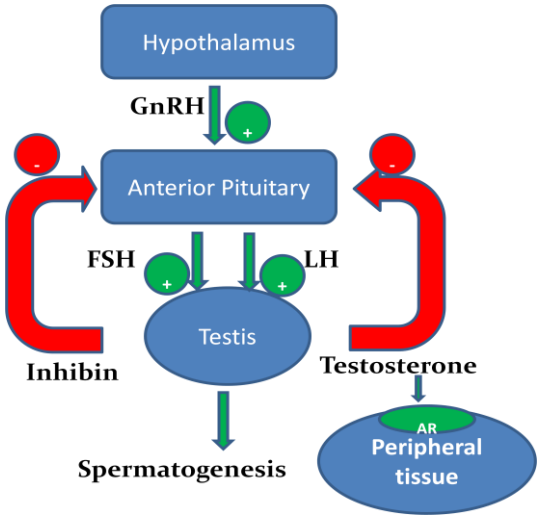
Disorders of Male Sexual Differentiation:

- ✓ They are rare group of disorders
- ✓ The defect may be in:
  -**Testosterone** production (impaired testosterone production)

-**Androgen** receptors sensitivity (**inactive** androgen receptors → target tissues cannot respond to stimulation by circulating testosterone; e.g., Testicular feminization syndrome)

Note:
Androgen Insensitivity Syndrome is a disease of receptor resistance the same concept of diabetes mellitus when insulin cannot bind to the receptors.

Control of testicular function by the gonadotrophins



Testicular Feminization Syndrome

- ✓ **46,XY** karyotype , **X-linked recessive** disorder
- ✓ Androgen receptor **resistance → high testosterone** blood level
- ✓ In peripheral tissue**, testosterone will be converted by aromatase into estradiol → feminization.**
- ✓ Patients have **normal testes** & produce **normal amounts of müllerian-inhibiting factor (MIF),** therefore, affected individuals **DO NOT have fallopian tubes, a uterus, or a proximal (upper) vagina.**

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Clinical diagnosis

- **Complete androgen insensitivity syndrome (CAIS) Female**: female external genitalia with normal labia, clitoris, and vaginal introitus (MPH)
- **Partial androgen insensitivity syndrome (PAIS) :** mildly virilized female external genitalia (**clitorimegaly** without other external anomalies) to mildly undervirilized male external genitalia **(hypospadias and/or diminished penile size**)

Diagnosis

Clinical picture

Laboratory Diagnosis

Karyotype:

to differentiate an undermasculinized male from a masculinized female.

DNA tests and mutation analysis:

f or androgen receptor gene where there will be complete and partial gene deletions,
point mutations, or small insertions/deletions

Imaging:

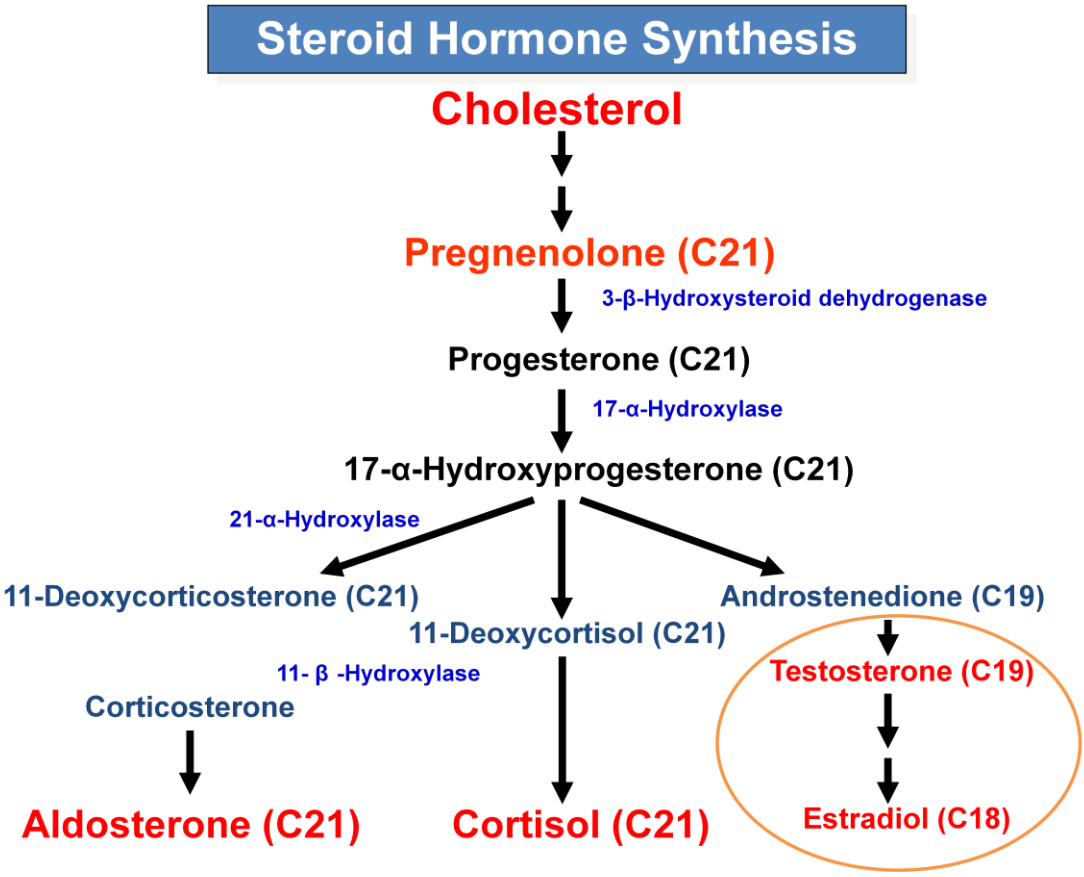
- Pelvic ultrasound
- Identification of any müllerian structures, such as uterus or fallopian tubes, is inconsistent with a diagnosis of complete or partial androgen insensitivity syndromes

Fluorescent in situ hybridization (FISH):

- presence of a ***Y*** chromosome can be confirmed by probes for the ***SRY*** region of the ***Y*** chromosome.
- These offer a much quicker turnaround time than conventional karyotypes.
- Increased (or normal) testosterone and dihydrotestosterone blood levels

Summary

- **Adrenal steroidogenesis**



- **Congenital adrenal hyperplasia syndrome**: It is the result of an inherited enzyme defect in steroid biosynthesis and the condition might be fatal unless diagnosed early.
  - **Types** (21 α-Hydroxylase Deficiency **or** 11 β -Hydroxylase Deficiency).
  - **Biochemical characteristics**
  - **Clinical manifestations**
- **Disorders of Male Sexual Differentiation**: They are **rare** group of disorders
- **Testicular feminization syndrome (**Androgen Insensitivity Syndrome**)**:
  - 46,XY karyotype
  - X-linked recessive disorder