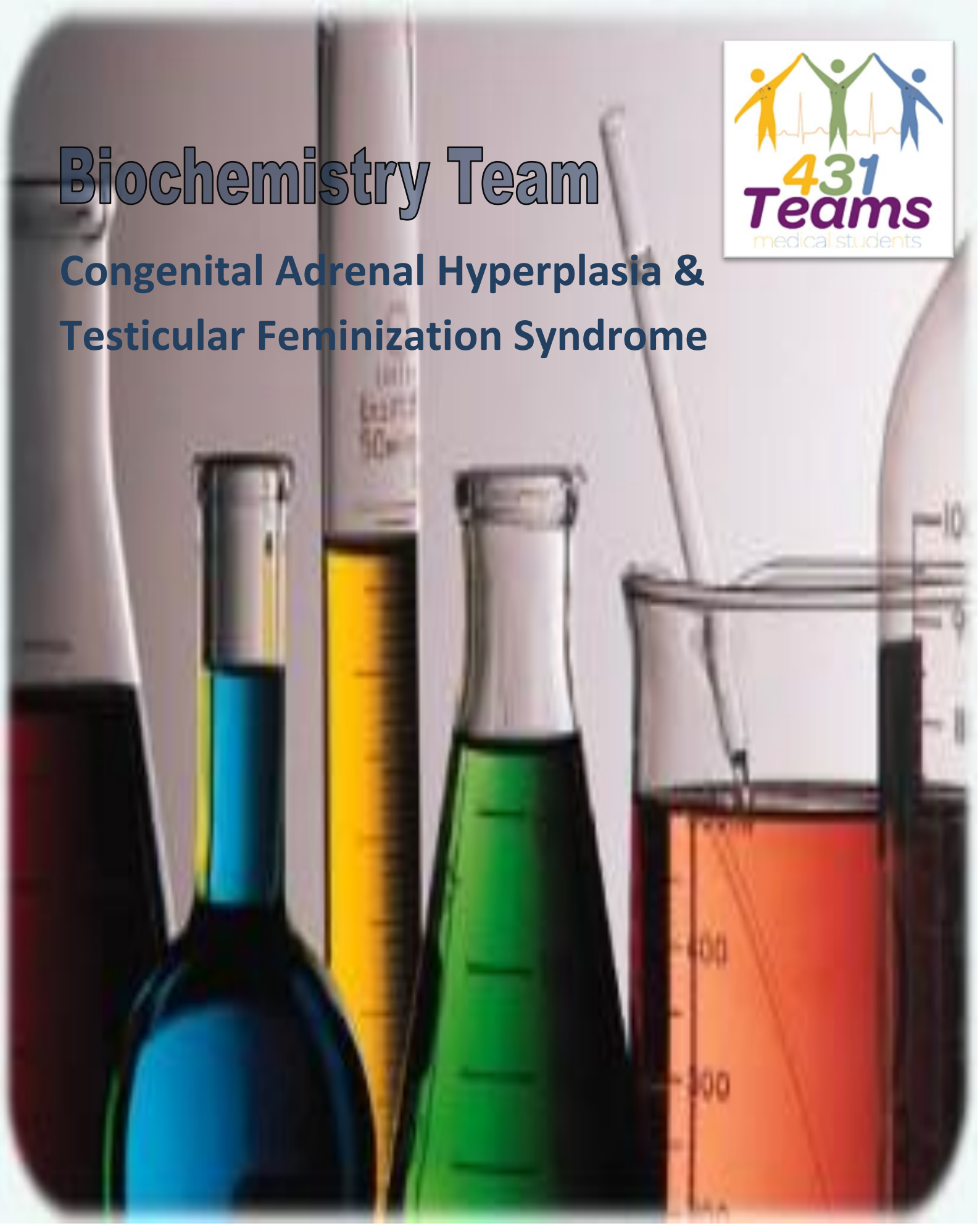
Biochemistry Team

Congenital Adrenal Hyperplasia & Testicular Feminization Syndrome



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❖ Team notes are in green and important notes are in red.

The first two pages are introductory; the actual lecture starts at the 4th

Congenital Adrenal Hyperplasia Syndrome & Testicular Feminization Syndrome

The adrenal gland comprises 3 separate hormone systems:

1- **Zona Glomerulosa:** secretes aldosterone
2- **Zona Fasiculata and reticularis:** secretes cortisol and the adrenal androgens
3- **The adrenal medulla:** secretes catecholamines (mainly epinephrine)

Hermaphroditism or Intersex

- **Intersex:** A person has neither standard male or standard female anatomy.
- Discrepancy (difference) between type of gonads (internal genitalia) and external genitalia.
- **True hermaphrodite** (ovary + testis) Very Rare
- **Female pseudohermaphrodite** (FPH, only ovary) XX chromosome
- **Male pseudohermaphrodite** (MPH, only testis) XY Chromosome

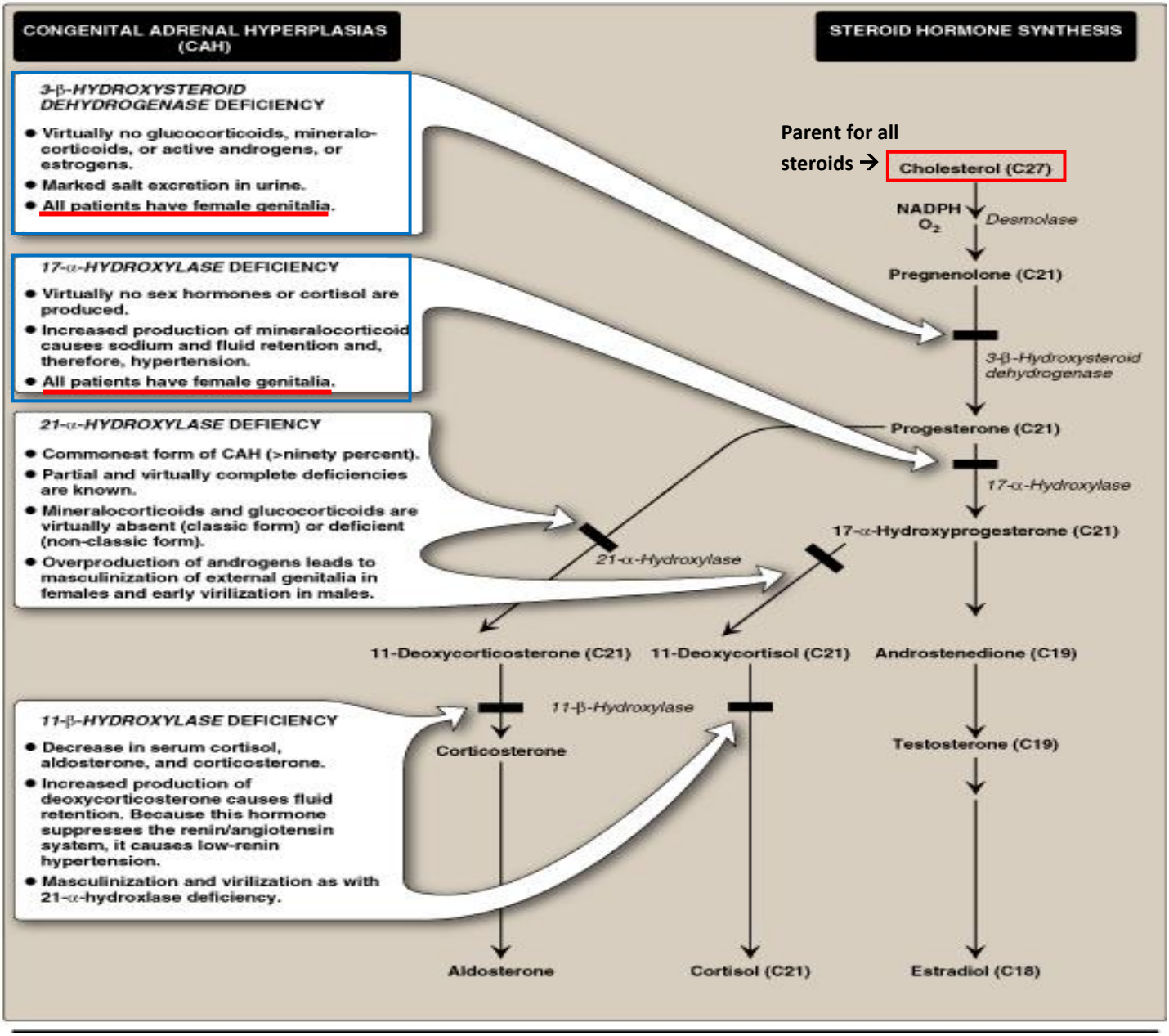
- Pseudo-hemaphroditism is a condition where the internal genitalia are normal but external genitalia resembles the opposite sex or it could be not clear
- Patients with FPH are genetically females, but they have more masculine characteristics

Glucocorticoids & Mineralcorticoids:

- **Glucocorticoids:**
  - Steroids with cortisol-like activity
  - Potent metabolic regulators & immunosuppressants
- **Mineralocorticoids:**
  - Steroids with aldosterone-like activity
  - Promote renal sodium reabsorption and potassium excretion

Steroidogenesis and Congenital adrenal hyperplasia syndrome:

Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids.



- Steroid hormones are synthesized in adrenal and gonads from the initial substrate Cholesterol via a series of interconnected enzymatic steps.
- Any defect in one or more of these enzymes, will develop a condition called (Congenital Adrenal Hyperplasia syndromes). Almost all enzymes share the main clinical manifestation but with SOME DIFFERENCES

We need to know the substrate of each enzyme, because when there is deficiency of one of the enzymes → accumulation of its substrate

- 21 α-Hydroxylase deficiency (commonest one)
- 11 β-Hydroxylase deficiency (2nd most common, but still rare)
- 17 α-Hydroxylase deficiency (extremely rare <1% of the cases)
- 3 β-Hydroxysteroid dehydrogenase deficiency

Congenital Adrenal Hyperplasia (CAH) Syndromes:

- It is the result of an inherited enzyme defect in steroid biosynthesis , this condition is rare because it is autosomal recessive

> **Normal:** Hypothalamus secretes Corticotropin-releasing hormone (CRH), which acts on the anterior pituitary to give ACTH. ACTH acts on the adrenal cortex to secrete cortisol

- The adrenals :
  - 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)
  - Cannot secrete aldosterone → electrolyte disturbances (it could be life-threatening condition):
    - Hyponatremia and Hyperkalemia (Na^+ will not be reabsorbed from urine and K^+ will not be excreted in urine) → HYPOTENSION and acidosis
- The condition might be fatal unless diagnosed early.

21 α-Hydroxylase Deficiency:

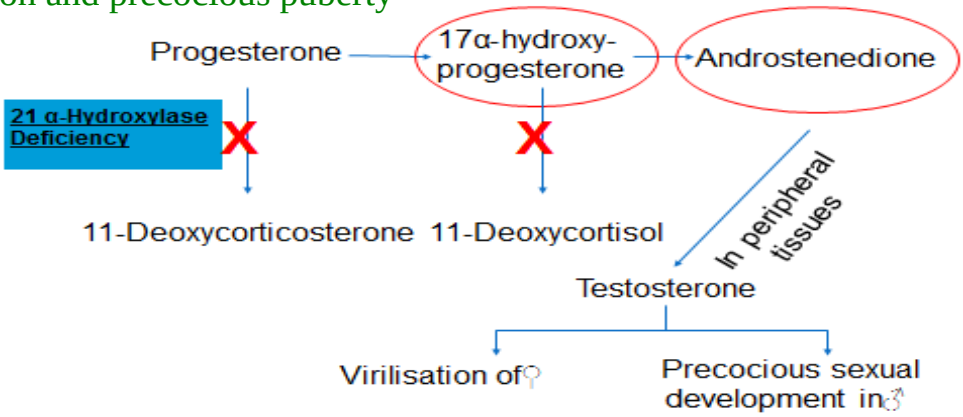
- **The most common type of CAH (90%)**
- **Clinically:**
  - Complete enzyme defect: (no aldosterone & cortisol)↑ stimulation of adrenal androgen production (too much testosterone)→ [1]virilization in baby girls & [2]precocious (v. early) puberty in boys.
  - Partial enzyme defect →late onset form→ [1] menstrual irregularity & [2] hirsutism in young females.
- **Laboratory diagnosis: ↑ plasma [17α-hydroxyprogesterone]** as early as 4 days after birth.

Notes:

- Aldosterone will be low ➔ hyponatremia, hypercalemia, hypotension & electrolytes disturbance
- Cotrisol will be low ➔ hypoglycemia

} **adrenal crisis**

- High level of 17 α-hydroxyprogesterone , Androstenedione and Testosterone
- In female : Clitoral hypertrophy, urogenital abnormalities and labioscrotal fusion (it will be like testis)
- Virilization and precocious puberty



- Autosomal recessive condition (both of the parents are carriers)
- Impaired synthesis of both cortisol & aldosterone
- ↓ Cortisol → ↑ ACTH secretion → Adrenal gland hyperplasia
- Accumulated 17α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones → signs of androgen excess:
  - Ambiguous genitalia in newborn girls (FPH): enlarged clitoris "similar to penis"
  - Rapid postnatal growth in both sexes
- **Severe cases:** mineralocorticoid deficiency → salt & H_2O loss→ hypovolemia & shock → **neonatal adrenal crisis** (unless the treatment is started v. early)
- **Late** presentation (adult life) is possible in **less severe cases**

Scenario: female with no menstruation, excess of pubic hair, hirsutism and other male characteristics → 21 α-Hydroxylase Deficiency (late presentation)

Genetics of 21 α-Hydroxylase Deficiency :

- Mutations in the CYP 21 gene:

- Deletions: is a mutation (a genetic aberration) in which a part of a chromosome or a sequence of DNA is missing.
- Nonsense: is a point mutation in a sequence of DNA that results in a premature stop codon
- Missense: is a point mutation where a single nucleotide is changed to cause substitution of a different amino acid.
  - DNA testing: For prenatal diagnosis and confirmation of diagnosis

Diagnosis of 21 α-Hydroxylase Deficiency:

- Serum sample **taken at least 2 days after birth** (because earlier samples may contain maternally derived 17-hydroxyprogesterone)
- **Classic (complete) deficiency** is characterized by **markedly elevated serum levels of 17-hydroxyprogesterone**
  (because it is the compound that the 21α-hydroxylase will act on >>> and that enzyme is deficient , so accumulation of 17α-hydroxyprogesterone will occur)

- **Late-onset (partial) deficiency** (usually seen with late presentation) may require corticotropin (ACTH) stimulation test:
  - Measure base-line and stimulated levels of 17-hydroxyprogesterone .
  - **High** level of 17-hydroxyprogesterone **after stimulation** is **DIAGNOSTIC**

We need to do ACTH stimulation test, because there is an elevation in 17-hydroxyprogesterone but it is not marked. So we can't be sure without doing the test.

11β -Hydroxylase Deficiency:

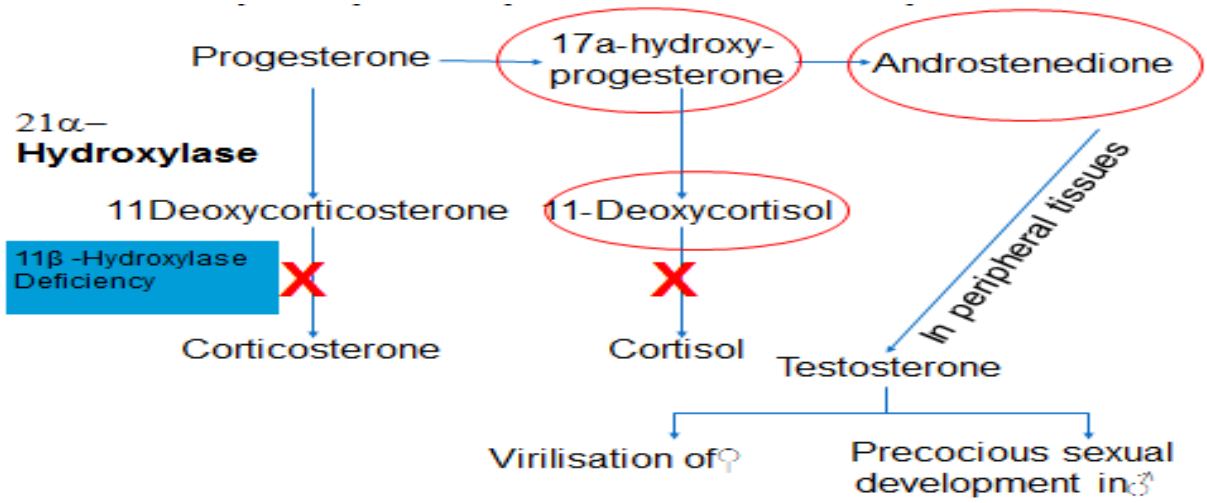
- Leads to **high concentrations of 11-deoxycortisol**
- Leads to **high levels of 11-deoxy-corticosterone** with mineralocorticoid effect **(salt and water retention)**

> ✓ 11-deoxycorticosterone is a less potent mineralocorticoid, but in this condition the overproduction of in-vivo 11-deoxycorticosterone will be high, causing salt retention, despite the failure of aldosterone production.

- **There is no adrenal crisis**
- High levels of 11-deoxy-corticosterone → Suppresses renin/angiotensin system → **low renin HYPERtension (IMP!!)**

> Normally, when a normal subject has low rennin >> that will lead to hypotension, but in this case the rennin is low because of the effect of mineralocorticoid which will lead to hypervolemia and hypernatremia >> Hypertension and that will suppress the RAAS system .

- Musculanization in females (FPH) and early virilization in males

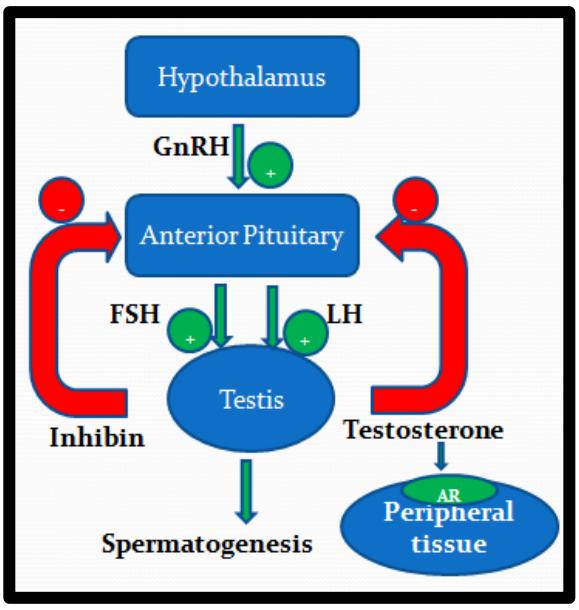


Testicular Feminization Syndrome

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



Control of testicular function by the gonadotrophins:

Testicular Feminization Syndrome:

- ✓ 46,XY karyotype (MALE)
- ✓ 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 (**female internal genitalia**)

When androgen receptors in the peripheral tissue are insensitive to testosterone → body interprets it as less testosterone → it will keep producing more and more testosterone → will affect the testis to produce more inhibin → less synthesis of FSH → inhibition of the spermatogenesis → infertility

MIF: inhibits the development of the Müllerian ducts (develop to form the Fallopian tubes, uterus, cervix, and the proximal vagina) in the male embryo.

Clinical picture :

The clinical presentation is primary amenorrhea (as long as HE is male)

- **Complete androgen insensitivity syndrome (CAIS):** 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)

Hypospadias: is a birth defect of the urethra in the male that involves an abnormally placed urinary meatus.

Laboratory Diagnosis :

- Karyotype: differentiate an **undermasculinized male** from a **masculinized female** . (sex chromosomes)
- **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
- DNA tests and mutation analysis for **androgen receptor gene**:
- Complete or partial gene deletions, point mutations, or small insertions/deletions
- **Imaging Studies "Pelvic ultrasound :"**
  - Absence of fallopian tubes and uterus

SRY gene is responsible for production of TDF (Testes Determining Factor)

Questions

1- The most common enzyme deficiency in CAH (Congenital Adrenal Hyperplasia) is:

A- 11β- Hydroxylase
B- 21α-hydroxylase
C- 3β-hydroxylase
D- 17α-hydroxylase

2- Which one of the following will be accumulated in case of 21a-hydroxylase ?

A- 11Deoxycortisone
B- 11Deoxycorticosterone
C- 17α-hydroxyprogesterone
D- Aldosterone

3- A baby is born, without complications, to a healthy mother . physical examination reveals a dangerously hypotensive neonate with ambiguous genitalia, fused labia, and an enlarged clitoris. Intravenous fluids are started … what is the most likely diagnosis?

A- 21α-hydroxylase Deficiency
B- 3β-hydroxylase Deficiency
C- 11β-hydroxylase Deficiency
D- All are wrong

4- A 17 year-old girl presents to the clinic for primary amenorrhea. She reports that she has never had a period. Physical examination reveals normally developed breast, the lack of axillary and pubic hair and a small right inguinal mass. What is the most likely diagnosis?

A- Congenital Adrenal Hyperplasia (CAH)
B- Testicular Feminization syndrome
C- Ovarian carcinoma
D- Constitutional Delay of Growth and Puberty .

Answers : B,C,A,B

Further information for the 4th Q :

Q:What is the most likely diagnosis ?

A: Androgen insensitivity syndrome (also known as testicular feminization syndrome) should be suspected in a woman with primary amenorrhea, little or no axillary/pubic hair, and an inguinal mass. The disease affects approximately 1:100,000 chromosomal males.

Q: What is the clinical presentation of this condition ?

A: There are two main presentations of this disorder :

•In newborns it presents as an inguinal mass.

•In adolescents it presents as primary amenorrhea.

The inguinal mass seen in newborns is caused by aberrant descent of the testes, which usually remain in the abdomen.

Q: What is the pathophysiology of this condition?

A: This disorder results from dysfunction of the androgen receptors in a genetically male patient. The testes are present and secrete testosterone and müllerian inhibiting factor (MIF). However, the person cannot respond to this testosterone because the peripheral receptors are nonfunctional. Instead, the testosterone is converted into estradiol in peripheral tissues (especially adipose tissue), which initiates breast development. The vagina is often present but may be short and blind-ending. The MIF secretion inhibits normal development of the ovaries and uterus.

Q:What would confirmatory testing show in this condition?

•On karyotype, these patients are 46,XY.

•Pelvic ultrasound can show testes and the absence of a uterus and ovaries.

•Polymerase chain reaction assay can show mutations of the androgen receptor.

•Testosterone and dihydrotestosterone (DHT) levels should also be measured. Both should be normal or high. Low testosterone may indicate testicular dysgenesis or Leydig cell aplasia/hypoplasia. If testosterone levels are normal but DHT levels are low, 5α-reductase deficiency is suspected because testosterone is converted to DHT by 5α-reductase.

Q: What is the appropriate treatment for this condition?

A: Initially, removal of the testes is performed because of the high risk of cancer development without such a procedure. Thereafter, treatments are mainly hormone replacement therapy and psychological support. Estrogen, but not progesterone, is given because no uterus is present. Estrogen is given to replace the loss of sex hormone production with the removal of the testes. Psychological therapy is given because of the potential for gender confusion. Surgical reconstruction may be needed to create a "functional" vagina, although if found earlier the use of dilators may obviate surgical intervention