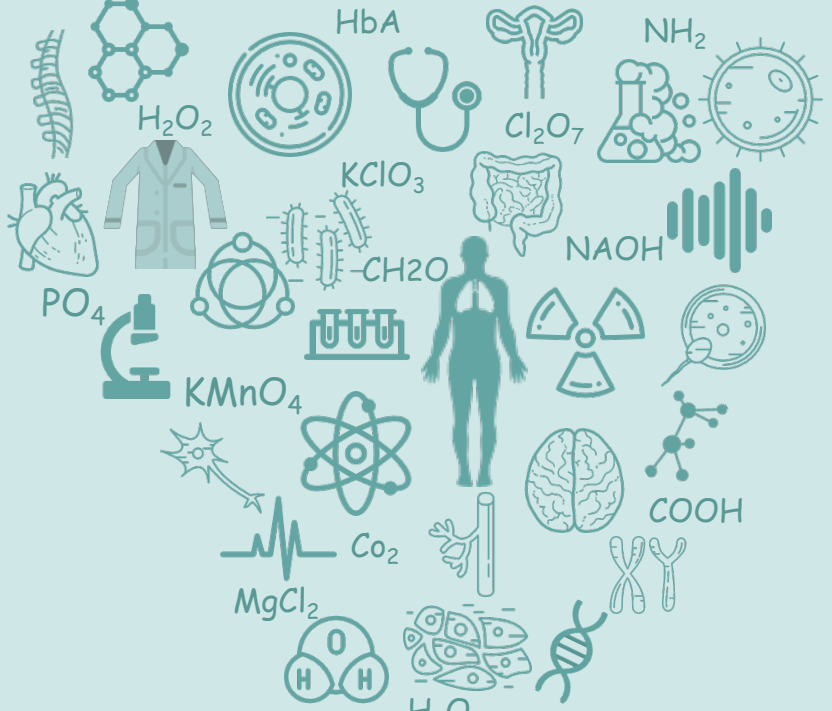


Important Doctors slides

Extra Information Doctors notes

Editing file

Biochemistry

CAH and testicular feminization syndromes

Say good bye to the basic sciences with doing your best in the last block ✌

OBJECTIVES

By the end of this lecture, the students should be able to know:

- Adrenal steroidogenesis

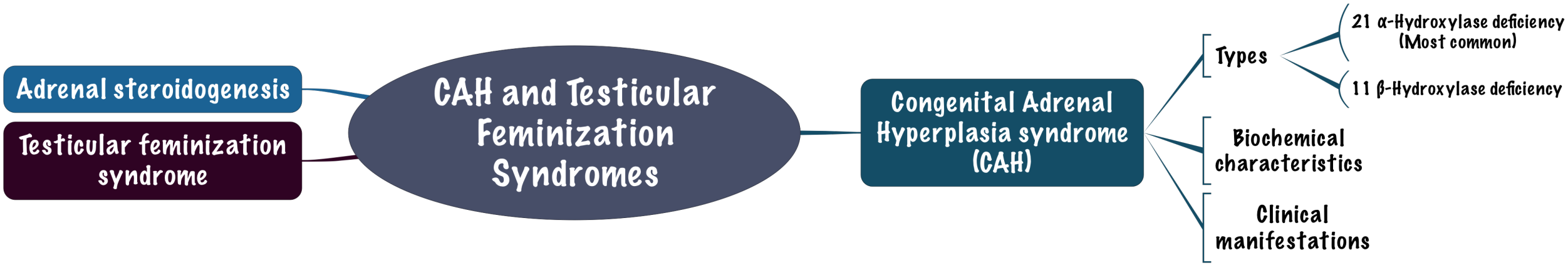
- Congenital adrenal hyperplasia syndrome

1. Types
2. Biochemical characteristics
3. Clinical manifestations

- Testicular feminization syndrome

CAH stands for Congenital adrenal hyperplasia

Overview


CAH and Testicular Feminization Syndromes
Adrenal steroidogenesis
Testicular feminization syndrome
Congenital Adrenal Hyperplasia syndrome (CAH)
Types
21 α-Hydroxylase deficiency (Most common)
11 β-Hydroxylase deficiency
Biochemical characteristics
Clinical manifestations

Adrenal Glands "to understand better"

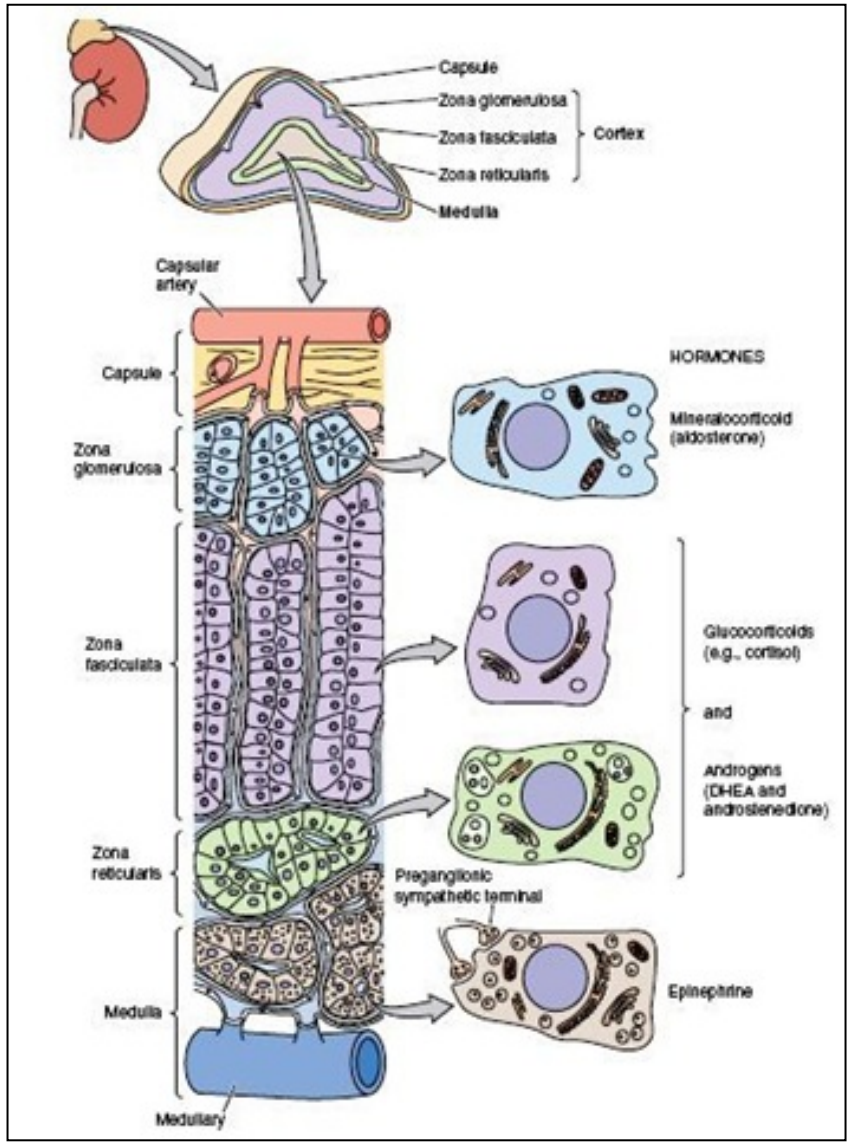
❖ The adrenal glands comprise 3 separate hormone systems

Zona Glomerulosa
- Secrete aldosterone

Fasciculata and Reticularis
- secrete cortisol & the adrenal androgens

Adrenal Medulla
- secretes catecholamines (mainly epinephrine)

Adrenal Cortex



Hermaphroditism or Intersex

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

Intersex (for example) : a male with normal testis but has female external genitalia (مخنث)
Female pseudo-hermaphrodite: a female with a male external genitalia

True hermaphrodite (rare)	(ovary plus testis)
Female pseudohermaphrodite	(FPH, only ovary)
Male pseudohermaphrodite	(MPH, only testis)

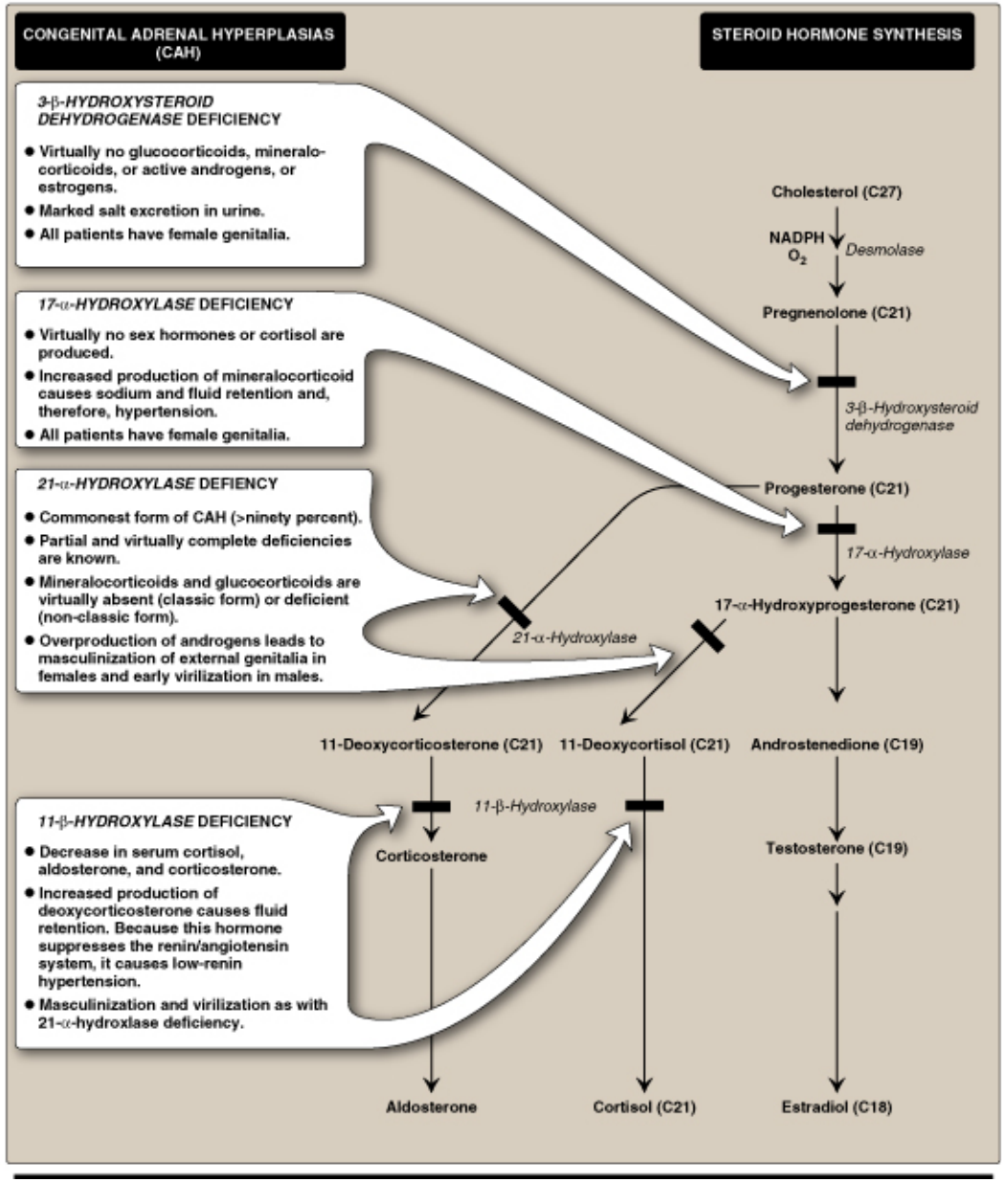
Recall what you studied before

Glucocorticoids	• Steroids with cortisol-like activity • Potent metabolic regulators & immunosuppressants
Mineralocorticoids	• Steroids with aldosterone-like activity • Promote renal sodium and water reabsorption, and excretion of potassium.

Steroidogenesis & CAH syndromes YOU NEED TO UNDERSTAN THESE TWO SLIDES ☺

In congenital adrenal hyperplasia we have enzymatic deficiency leading to appearance of signs and symptoms.
*Notice that any enzyme deficiency will lead to deficiency of cortisol.
*Remember the hypothalamic-pituitary-adrenal axis: Hypothalamus (CRH) > Pituitary (ACTH) > Adrenal (cortisol) and high levels of cortisol **will cause a negative feedback** and stop the production of CRH and ACTH. So if we don't have cortisol we don't have negative feedback and ACTH will be continually produced leading to adrenal hyperplasia.
*Aldosterone **does not cause negative feedback to CRH and ACTH,** it only causes negative feedback to renin-angiotensin system.
*لازم نعرف اذا فيه طريق مسدود الطريق الثاني بيكون زايد، ولاحظوا ان كل مانزل البلوكج بيصير النقص أقل.

Congenital Adrenal Hyperplasia
Congenital : Due to mutation of the gene responsible for synthesis of the required enzymes
Hyperplasia : Because we don't have cortisol



Steroidogenesis & CAH syndromes Cont.

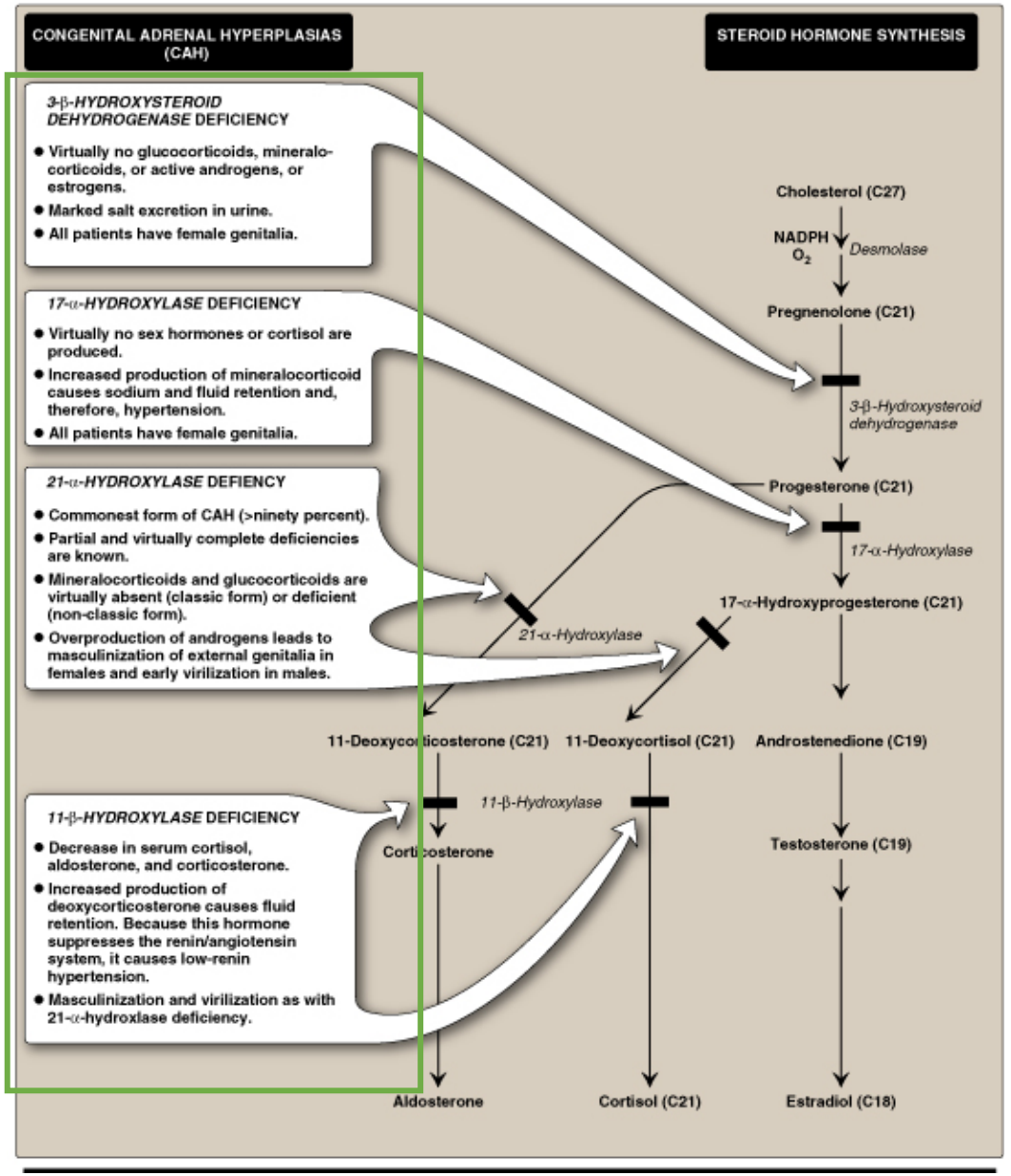
As you can see in the picture, we have 4 enzymes that could be deficient (21-alpha-hydroxylase being the most common)

1- 3-beta-hydrxysteroid dehydrogenase: a deficiency in this enzyme will lead to deficiency to all the end products and accumulation of pregnenolone.

2- 17-alpha-hydroxylase: a deficiency in this enzyme will lead to deficiency of cortisol, testosterone and estradiol and accumulation of progesterone and aldosterone "Aldosterone accumulate because its pathway is the only pathway that remains intact so the whole amount of progesterone get converted to it", leading to hypertension.

3- 21-alpha-hydroxylase: it catalyzes two reactions, so a deficiency in this enzyme will lead to deficiency of aldosterone and cortisol and accumulation of 17-alpha-hydroxyprogesterone leading to accumulation of testosterone and estradiol. ويصير شكل البنت زي الولد والولد شكله اكبر من عمره.

4- 11-beta-hydroxylase: a deficiency in this enzyme will lead to deficiency in cortisol and aldosterone and accumulation of 11-deoxycorticosterone (which has the same effect as aldosterone, but not stimulated by renin) and accumulation of 11-deoxycortisol and androstenedione leading to accumulation of testosterone and estradiol. The symptoms of this enzymatic deficiency are the same of that in 21-alpha-hydroxylase, the only difference is that 11-beta-hydroxylase deficiency patients have **hypertension.**



CAH syndromes

Congenital Adrenal Hyperplasia Syndromes	
❖ It is the result of an inherited enzyme defect in steroid biosynthesis ❖ The condition might be fatal unless diagnosed early due to water depletion and hypovolemia.	
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 1. Hyponatremia 2. Hyperkalemia
CAH Syndromes	1. 21 α-Hydroxylase deficiency 2. 11 β-Hydroxylase deficiency 3. 17 α-Hydroxylase deficiency 4. 3 β-Hydroxysteroid dehydrogenase deficiency

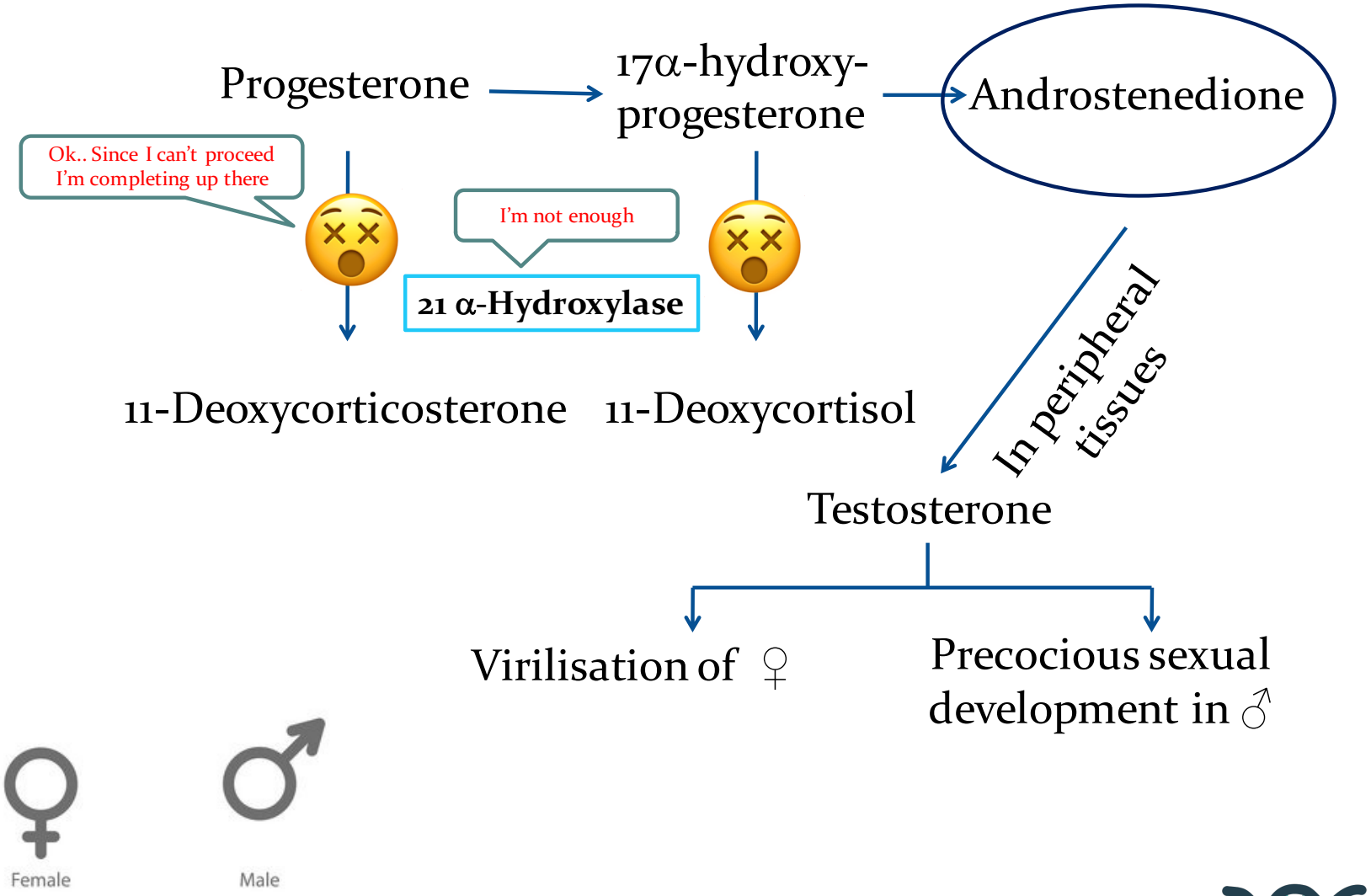
21 α-Hydroxylase deficiency

- The most common type of CAH (90%)

- Clinically:
  - ✓ **Complete** enzyme defect: ↑ 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.

- Laboratory diagnosis: ↑ plasma [17-hydroxyprogesterone] as early as 4 days after birth عادةً بعد يومين

In laboratory diagnosis, we measure the molecules not the enzymes.
The most important molecule to be measure is 17-hydroxyprogesterone.



21 α-Hydroxylase deficiency

- Autosomal recessive condition
- 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** (we don't know if it's a female or a male) genitalia in newborn girls (**FPH**)
  - Rapid postnatal growth in both sexes
- Severe cases: **mineralocorticoid** deficiency → salt & H_2O loss → **hypovolemia & shock** → **neonatal adrenal crisis**
- **Late** presentation (adult life) is possible in less severe cases

Genetics

- Mutations in the **CYP21** gene
  - **Deletions**
  - **Nonsense**
  - **Missense**
- DNA testing:

  For **pre**natal diagnosis and **confirmation** of diagnosis

21 α-Hydroxylase Deficiency: Diagnosis

- Serum sample taken at **least 2 days after birth** (earlier samples may contain maternally derived 17-hydroxyprogesterone)

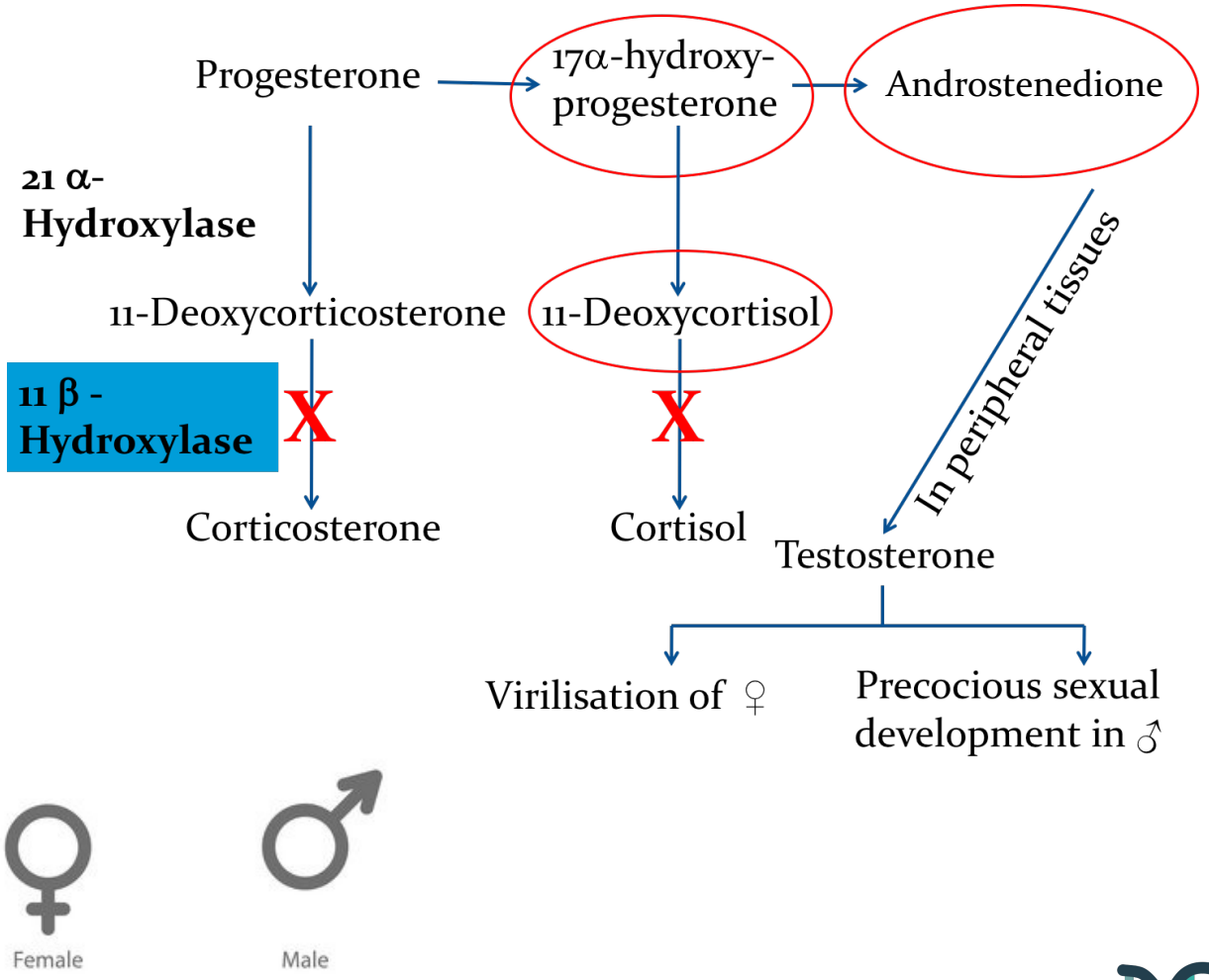
Classic (complete) deficiency is characterized by markedly **elevated** serum levels of **17-hydroxyprogesterone**

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

أحياناً لما يسوون الفحص يطلع عندنا borderline results
فما نقدر نحدد هو مرتفع ولا نازل
وش نسوي طيب؟
ACTH is given to the patient and if the levels of 17-alpha-hydroxyprogesterone increase > the diagnosis is confirmed

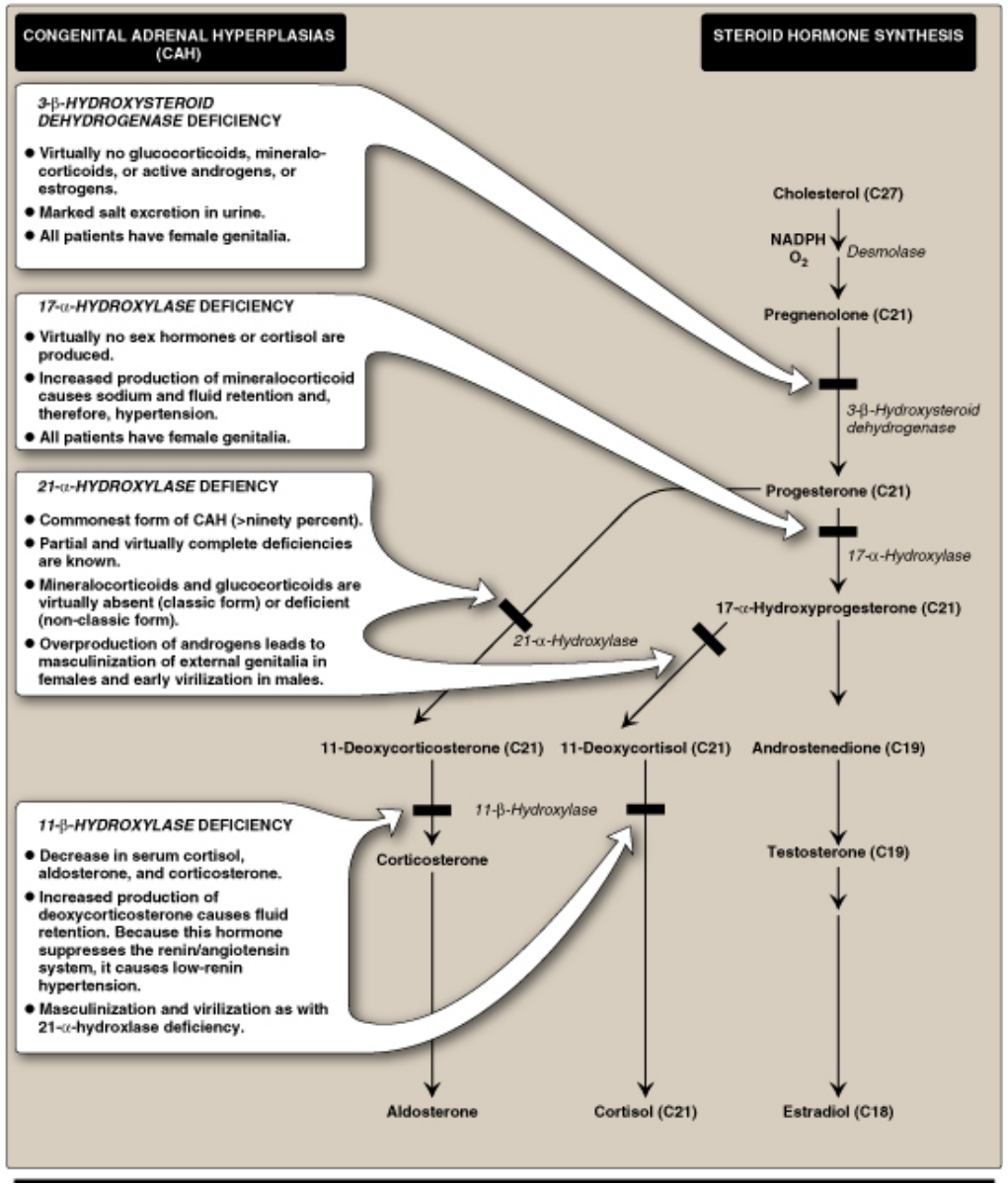
11 β -Hydroxylase Deficiency

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



To summarize

Questions from this picture:
*Which enzymatic deficiency would cause virilization?
*Which enzymatic deficiency would cause deficiency of estradiol?

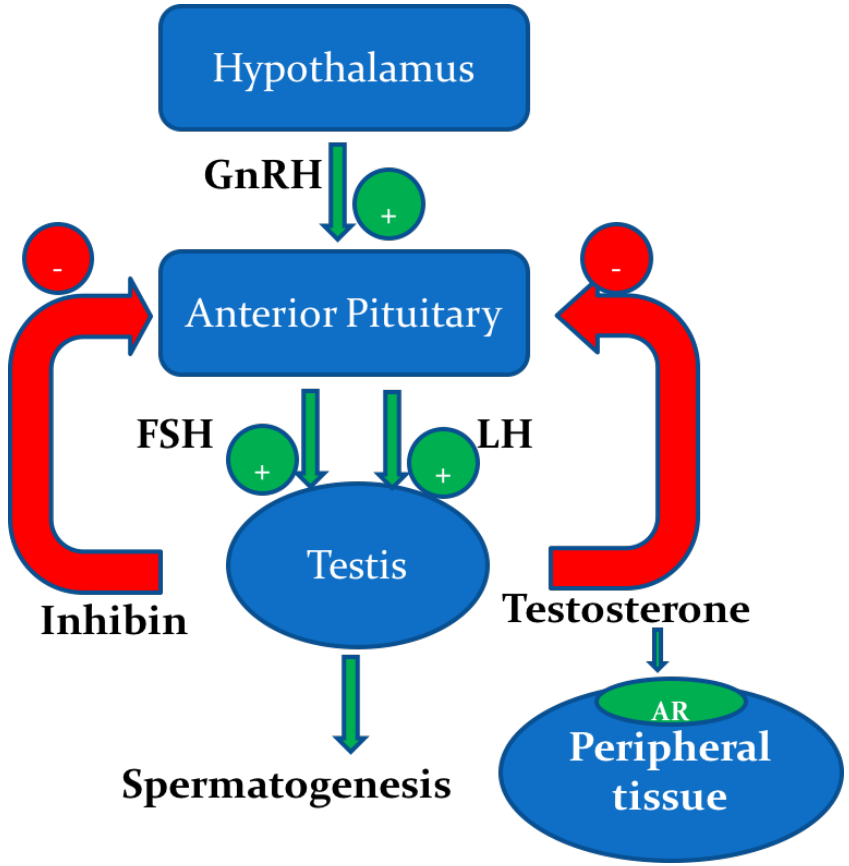


Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

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
X-linked **recessive** disorder

Androgen receptor resistance leading to 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)** (the function of this factor is inhibition of the production of uterus and fallopian tubes), therefore, affected individuals **Do Not have** fallopian tubes, a uterus, or a proximal (upper) vagina.

Clinical Picture

- **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)

Laboratory Diagnosis

1. **Karyotype:** differentiate an **under**masculinized male from a masculinized female.

2. **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.

3. **Increased (or normal) testosterone and dihydrotestosterone blood levels**

4. **DNA tests and mutation analysis for androgen receptor gene:**
   - Complete or partial gene deletions, point mutations, or small insertions/deletions

5. **Imaging Studies "Pelvic ultrasound":**
   - **Absence** of fallopian tubes and uterus

Summary

21-a-hydroxylase

- Autosomal recessive
- based on severity of enzyme defect:
  - complete enzyme defect
    - increase adrenal androgen production
  - partial defect
    - late onset (menstrual irregularity)
- severe cases: mineralcorticoid defeciency leads to hypovolemia and shock (neonatal adrenal crisis)
- Accumulated 17-a-hydroxyprogesterone > sex hormones
- Signs: ambiguous genitalia and rapid postnatal growth
- Lab:
  - high plasma 17 hydroxyprogesterone (4 days after birth)
  - classic: elevated serum levels of 17 hydroxyprogesterone
  - late onset: ACTH stimulation test shows high 17 hydroxyprogesterone
- genetics: mutation in CYP21
- prenatal testing to confirm and diagnose

11-B-hydroxylase

- high levels of 11 deoxycortisol and 11 deoxy-corticosterone
- salt and water retention
- suppress renin/Ag system> low renin hypertension
- Decrease in cortisol, aldosterone, and corticosterone
- clinical picture: masculinization in females and early virilization in females

QUIZ

Q1 : Which of the following is the most common cause of congenital adrenal hyperplasia?

A. 21 alpha hydroxylase deficiency
B. 11 beta hydroxylase deficiency
C. 17 alpha hydroxylase deficiency
D. 23 beta hydroxylase deficiency

Q2 : Which of the following is a late complication of partial 21 alpha hydroxylase deficiency ?

A. Virillization in baby girls
B. Precocious puberty in boys
C. Gigantism
D. Hirsutism

Q3 : Which one of the following leads to high concentration of 11-deoxycortisol?

A. 21 alpha hydroxylase deficiency
B. 11 beta hydroxylase deficiency
C. 17 alpha hydroxylase deficiency
D. 23 beta hydroxylase deficiency

Q4 : Active estrogens absent glucocorticoids and absent mineral corticoids is related to which one of the following?

A. 17-alpha hydroxylase deficiency
B. 21-alpha hydroxylase deficiency
C. 11-Beta hydroxylase deficiency
D. 3 Beta hyroxysteroid dehydrogenase deficiency

Q5 : Which of the following explains testicular feminization syndrome ?

A. Androgen receptors resistance
B. Deficiency of hormones
C. Hypothalamus pituitary axis defect
D. X-linked dominant disorder

Q6 : Which of the following is correct about complete androgen insensitivity ?

A. XY karyotype with external female genitalia
B. Mildly virilized female external genitalia
C. Undervirilized male external genitalia
D. Hypospadias

QUIZ

Q7 : 8 month old infant was brought to your clinic with his mother.
She says that her son has weird looking genitalia for his gender, her husband told her that she is imagining things but she insisted on visiting a physician.
Upon clinical inspection and examination you found that her son has female genitalia.
Upon karyotyping, XY karyotype was found.

A) Mention the name of this condition.
- Complete androgen insensitivity syndrome.

B) Explain the clinical presentation of this condition.
- Male infant but with **external** female genitalia and female exterior caused by androgen receptor insensitivity.

C) Name 3 tests used to diagnose this condition.
1. Karyotype
2. FISH
3. DNA tests and maturation analysis for androgen receptor gene

D) How can we make sure of absence of uterus and Fallopian tubes in this condition?
- Through imaging studies, specifically the pelvic ultrasound.

Suggestions and recommendations

1) A 2) D 3) B 4) D 5) A 6) A

Biochemistry Team 436

THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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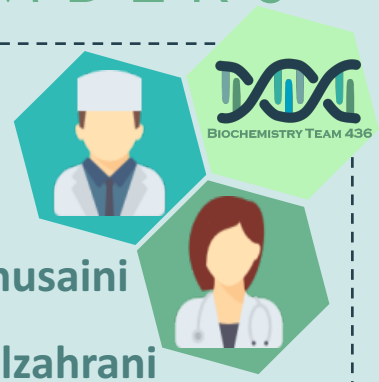

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