[lecture 1]

Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

Biochemistry Team

Teams

The Objectives

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

Red = Import-ant

Blue = explain

Green = addition notes

Done By: Atheer alduaij & hessah aljadeed **Reviewed By:** Abdulaziz Alanazi

Biochemistry Team

Mind Map

I

Congenital adrenal hyperplasia syndrome

- Types
- Biochemical characteristics
- Clinical manifestations

II

Testicular feminization syndrome

- Clinical picture
- Diagnosis

Overview!

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 catecholamines (mainly epinephrine)

- **Glucocorticoids:** Steroids with cortisol-like activity"Potent metabolic regulators & immunosuppressants".
- **Mineralocorticoids:**Steroids with aldosterone-like activity

Promote renal sodium reabsorption

Hermaphroditism or Intersex

- **Intersex:** A person has neither standard male or standard female anatomy.
- Discrepancy between type of gonads and external genitalia
- True hermaphrodite (ovary plus testis)
- Female pseudohermaphrodite (FPH, only ovary)
- Male pseudohermaphrodite (MPH, only testis)

Congenital adrenal hyperplasia syndrome (CAH)

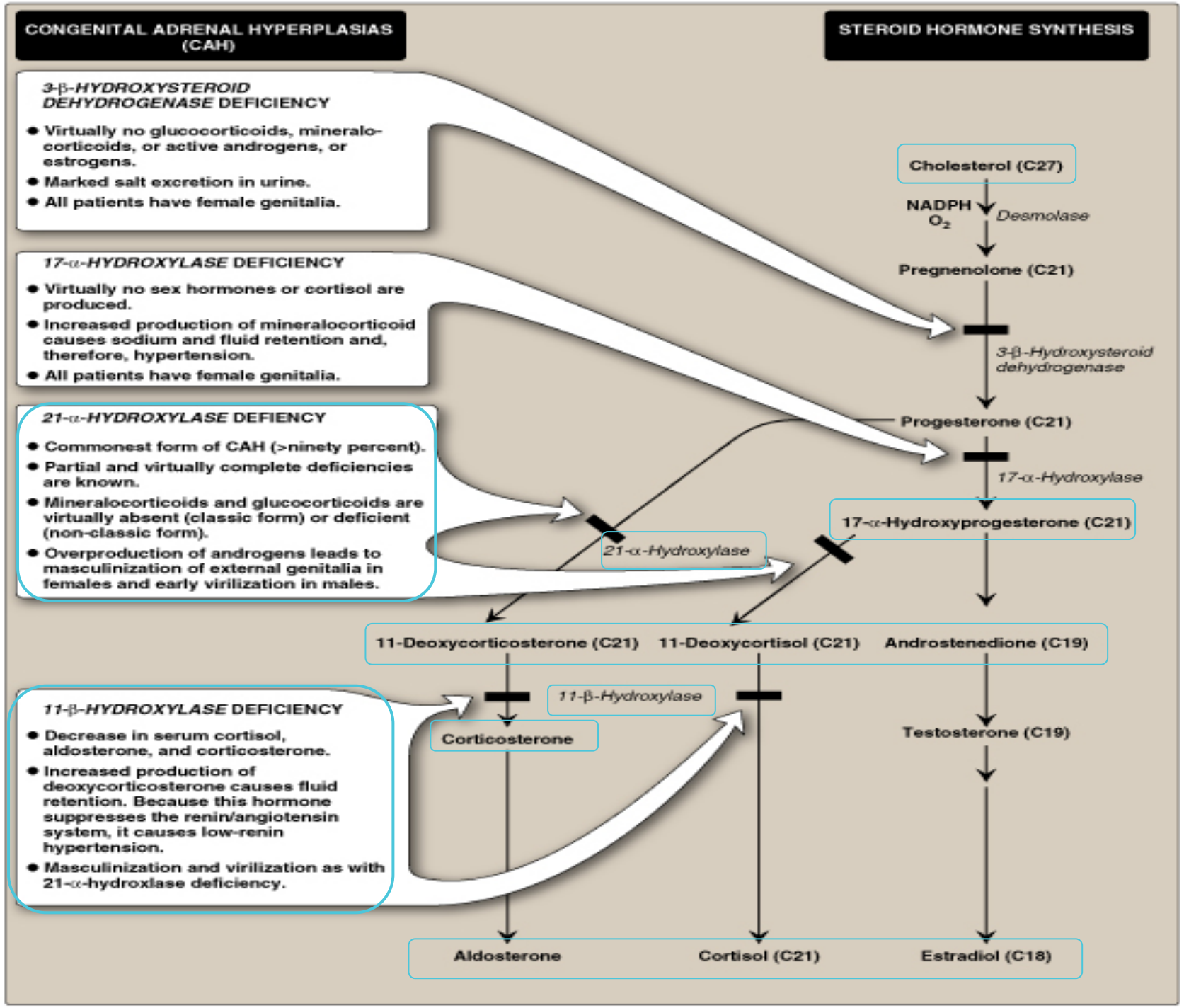
Congenital Adrenal Hyperplasia (CAH) Syndromes

- **It is the result of an inherited enzyme defect in steroid biosynthesis**
- **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
    - Hyponatremia
    - Hyperkalemia
- The condition might be fatal unless diagnosed early

Causes :

- 21 α-Hydroxylase deficiency **(most common)**
- 11 β-Hydroxylase deficiency
- 17 α-Hydroxylase deficiency
- 3 β-Hydroxysteroid dehydrogenase deficiency

Steroidogenesis and Congenital adrenal hyperplasia syndrome



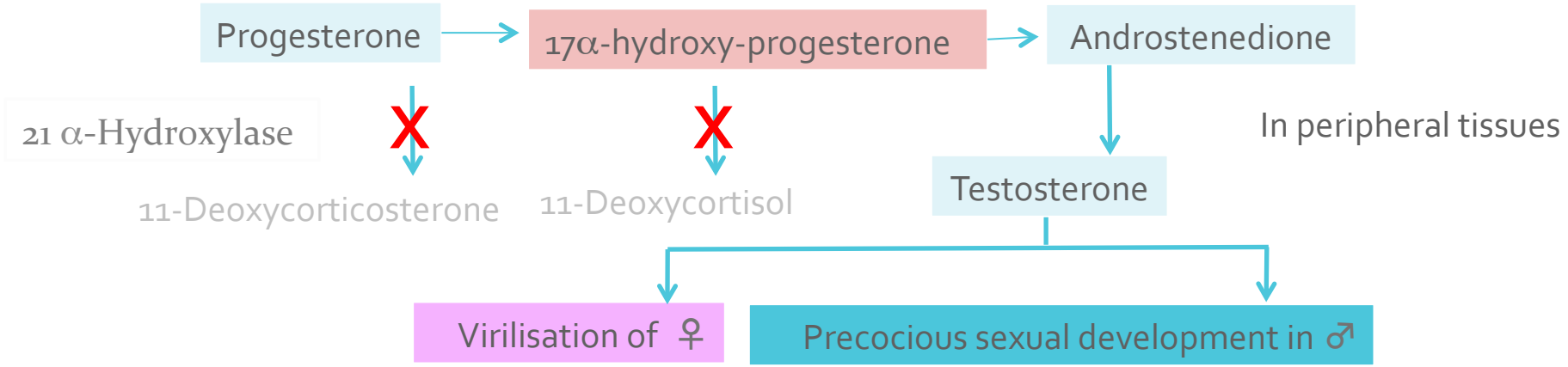
21 α-Hydroxylase Deficiency

The most common type of CAH (90%)

Clinically:	Laboratory diagnosis:	Diagnosis
✳ Complete enzyme defect: ✳ ↑ stimulation of adrenal androgen production → virilization in baby girls & precocious(Early) puberty in boys. ✳ **Partial** enzyme defect → late onset form → menstrual irregularity & hirsutism in young females (not severe)	✳ ↑ plasma [17-hydroxyprogesterone] as early as 4 days after birth ✳ 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 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	✳ 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

21 α-Hydroxylase Deficiency

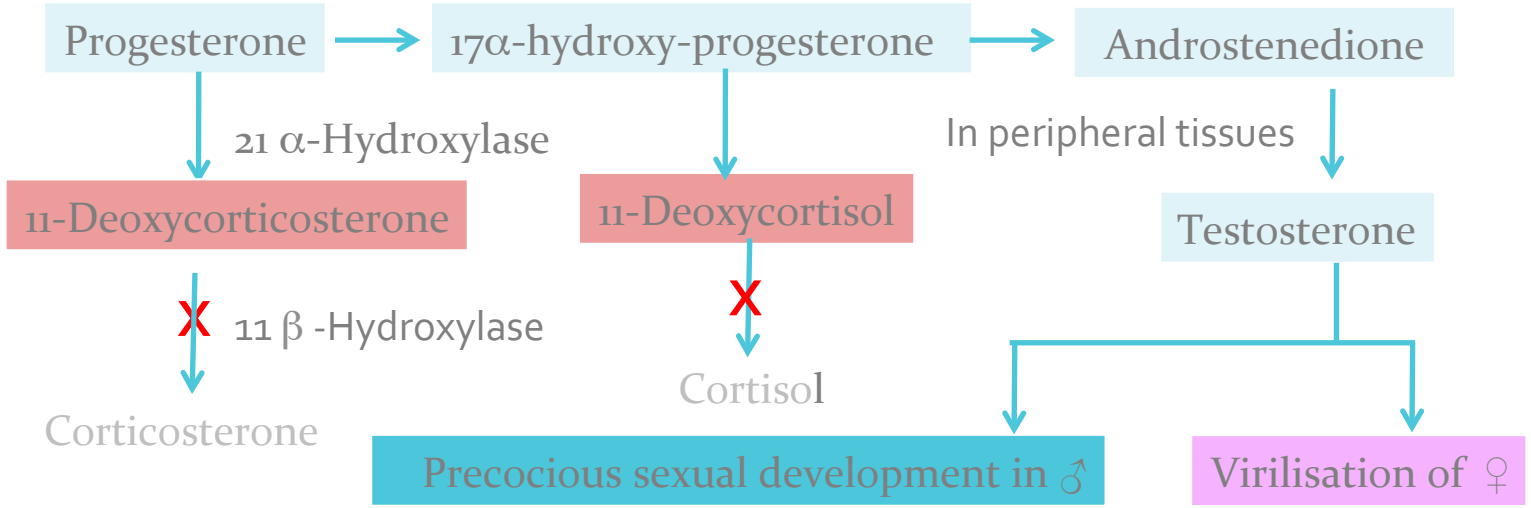
What happens (at the molecular levevl)??



Genetics :

- ♣ Mutations in the CYP21 gene
  - Deletions
  - Nonsense
  - Missense
- ♣ DNA testing:
  For prenatal diagnosis and confirmation of diagnosis

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

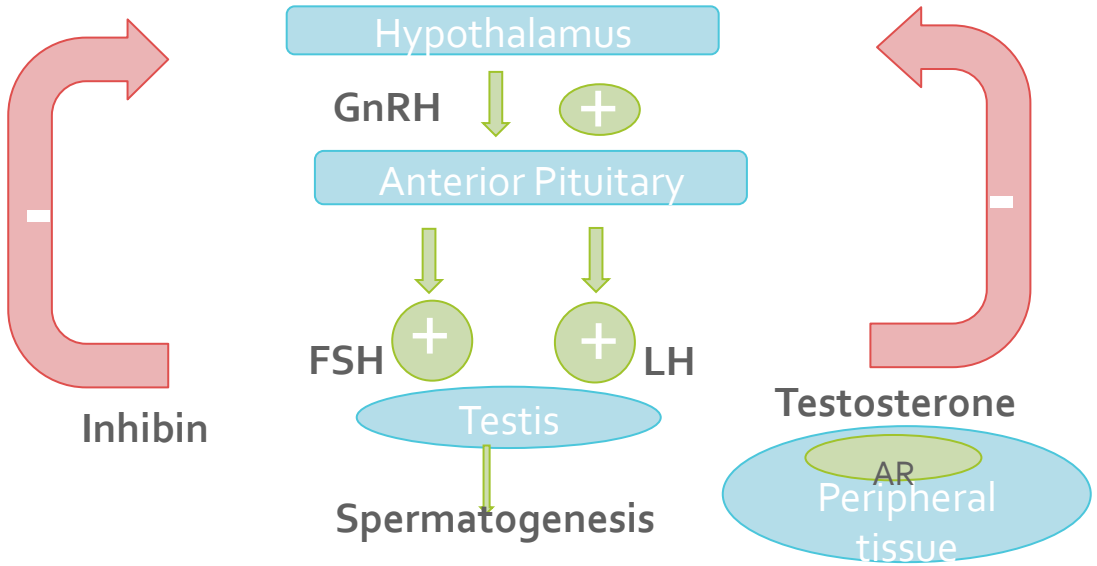
Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

Disorders of Male Sexual Differentiation

- ☆ They are rare group of disorders

- ☆ The defect may be in:
  - ✪ Testosterone production (impaired testosterone production)
  - ✪ Androgen receptors (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 → 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.

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)

*Hypospadias: when the opening of the urethra Doesn't reach the end of the penis.

Laboratory Diagnosis

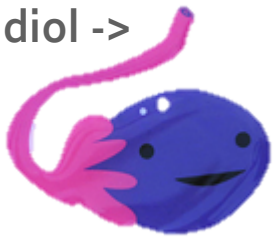
- **Karyotype:** differentiate an undermasculinized male from a masculinized female.
- **Fluorescent in situ hybridization (FISH):** Presence of a Y chromosome can be confirmed by probes for the SRY region of the Y chromosome. These offer a much quicker turnaround time than conventional karyotypes.
- **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.

Summary

- 21 α-Hydroxylase Deficiency The most common type of CAH (90%) Impaired synthesis of both cortisol & aldosterone (Dx : ↑ plasma **17-hydroxyprogesterone**).
- [cortisol]→↑ ACTH secretion → Adrenal gland hyperplasia , Accumulated 17α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones.
- 11 β -Hydroxylase Deficiency 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 (leads to high concentrations of **11-deoxycortisol**).
- Testicular Feminization Syndrome karyotype: 46,XY (X-linked recessive disorder).
- Testicular Feminization Syndrome (Androgen Insensitivity Syndrome) Androgen receptor resistance -> high testosterone blood level In peripheral tissue, testosterone will be converted by **aromatase** into estradiol -> feminization.



Test your knowledge ..!

Q1: The most common cause of Congenital Adrenal Hyperplasia (CAH) Syndrome ?

A) 11 β-Hydroxylase deficiency
B) 21 α-Hydroxylase deficiency
C) 17 α-Hydroxylase deficiency

Q2: To diagnose 21 α-Hydroxylase Deficiency we have to take ..... sample at least ..... After birth.

A) urine - 2 Days
B) serum - 3 Days
C) serum - 2 Days

Q3: 11 β -Hydroxylase Deficiency will cause high concentration of ?

A) Cortisol
B) 11-deoxycortisol
C) Corticosterone

Q4: Patient with Testicular Feminization Syndrome will have a normal level of ?

A) müllerian-inhibiting factor (MIF).
B) estrogen
C) progesterone

Q4: A
Q3: B
Q2: C
Q1: B

Biochemistry
Team

If you find any mistake, please contact us:)
Biochemistryteam@gmail.com

Biochemistry team leaders:
Basil AlSuwaine And Manar AlEid

Thank you