Done By :

Ismael Raslan

Arwa Al-Madani

Sarah Bin-Hussain

Bedoor Al-Qadrah

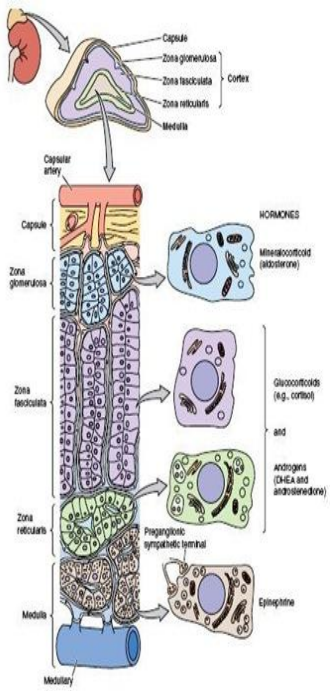
Reham Al-Henaki

Congenital adrenal hyperplasia and testicular feminization syndromes

Adrenal Glands:

The adrenal glands comprise 3 separate hormone systems:

The zona glomerulosa:	The zona fasciculata & reticularis:	The adrenal medulla:
secretes aldosterone "mineralocorticoids"	secrete cortisol "glucocorticoids"& the adrenal androgens	secretes adrenaline "chatecholamines"



Hermaphroditism or Intersex:

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

1. **Female pseudohermaphrodite is**
   a. **A person with XX chromosomes (female)**
   b. **MALE external genitals**
   c. **Person has ovaries**
2. **Male pseudohermaphrodite is**
   a. **A person with XY chromosome (male)**
   b. **FEMALE external genitals**
   c. **Person has testis**

Definitions:

Glucocorticoids:

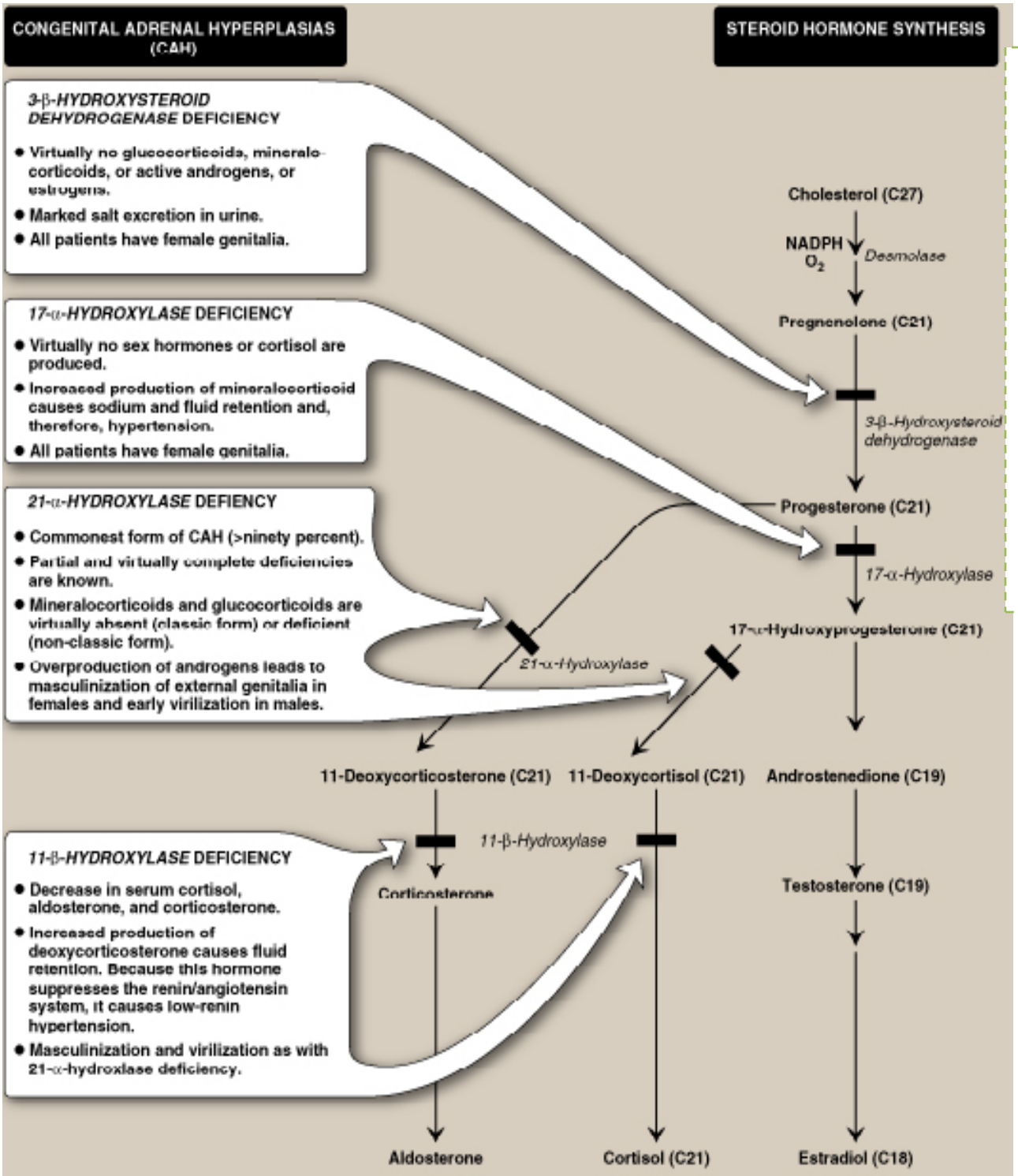
- **Steroids with cortisol-like activity**
- **Potent metabolic regulators & immunosuppressants**

Mineralocorticoids:

- **Steroids with aldosterone-like activity**
- **Promote renal sodium retention**

3. **MCQ** : all of the following are correct except regarding MPH ?
   a. Has female external genitals
   b. XY chromosome
   c. <u>Has ovaries</u>
   d. None

Steroidogenesis and Congenital adrenal hyperplasia syndrome



The first 2 boxes we do not have to study it !

*there are 4 enzymes in

This map

1-dehydrogenase

Other 3

Hydroxylase

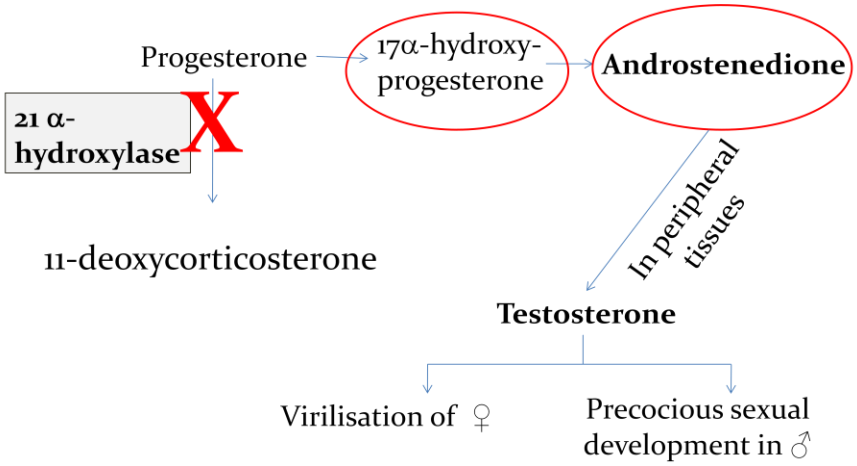
ACTH The hormone stimulator for the production and release of corticosteroids

Congenital Adrenal Hyperplasia (CAH):

- **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**
  a. **Hyponatraemia** (because aldesterone causes sodium water retention)
  b. **Hyperkalaemia** (because aldersterone causes K+ secretion out side the body)
- **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 3-4 days after birth.-" diagnoses "**
- **↑ stimulation of adrenal androgen production → virilization in baby girls (FPH), & precocious puberty in boys.**
- **Partial enzyme defect → late onset form → menstrual irregularity & hirsutism in young females.**

Congenital adrenal hyperplasia syndrome:

❖ 21 α-Hydroxylase Deficiency



- **Autosomal recessive condition**
- **May impair synthesis of cortisol & aldosterone**
- **Accounts for ~ 95% of all cases of CAH**
- **↓ [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**

1. What is **dexamethasone** ? (treatment 4 adrenal insufficiency – male's dr. mention it)
   - Synthetic glucocorticoid that has all the actions of cortisol including negative feedback on ACTH secretion
   - Summary : inhibits release of ACTH
   - Decreased ACTH levels causes

❖ 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 .**

1. because 21 α-Hydroxylase enzyme is deficient it will cause progesterone to take another pathway causing increased levels of androgens
2. May impair synthesis of cortisol & aldosterone
3. There will be no or few mineralocorticoid synthesis depending on the severity
4. In severe mutations it will cause mineralocorticoid deficiency > leads to hypovolumia and shock >> medical ER

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**

❖ 11 β -Hydroxylase Deficiency:

- **leads to high levels of:**
  - ✓ **11-deoxycortisol**
  - ✓ **11-deoxy-corticosterone: (with mineralocorticoid effect→salt and H2O retention)**
- **Suppresses renin/angiotensin system → low-renin hypertension**
- **Musculanization in females (FPH) and early virilization in males**

1. 11 β -Hydroxylase Deficiency leads to >>> high levels of 11-deoxy-corticosterone
2. 11-deoxy-corticosterone has a mineralocorticoid action so it will cause menralocorticoid effect
3. What is the meniralocorticoid effect ? sodium and water retention
4. That leads to suppression of renin/angiotensin >>>>> LOW RENIN HYPERTENSION
5. If in the question he presents with hypertension then think of 11 β -Hydroxylase Deficiency

Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

❖ **Disorders of Male Sexual Differentiation:**

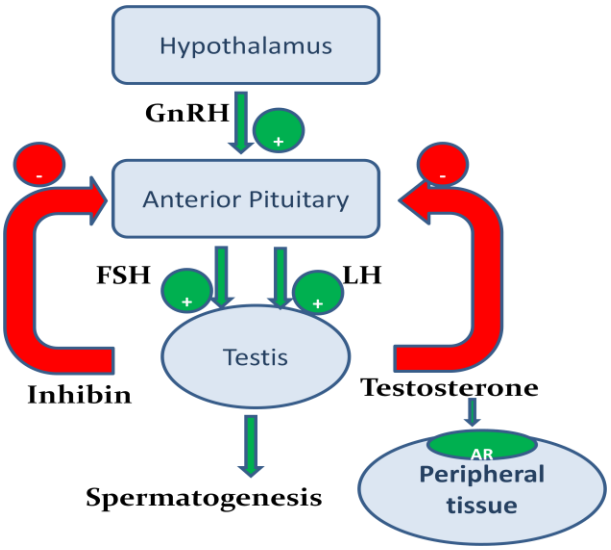
- **They are rare group of disorders**
- **The defect may be in:**
  - ✓ **Testosterone production (impaired testosterone production)**
  - ✓ **Androgen receptors sensitivity (inactive androgen receptors → target tissues cannot respond to stimulation by circulating testosterone; e.g., Testicular feminization syndrome)**

❖ **Control of testicular function by the gonadotrophins:**

Androgen Insensitivity Syndrome is a disease of receptor resistance

Same in

diabetes mellitus when insulin cannot bind to the receptors



➢ Clinical Diagnosis:

❖ **Three phenotypes:**

Most sever

- **Complete androgen insensitivity syndrome (CAIS) Female ("testicular feminization", MPH)**
- **Partial androgen insensitivity syndrome (PAIS)**
- **Mild androgen insensitivity syndrome (MAIS) Male ("undervirilized male syndrome")**

❖ 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**

➢ Diagnosis of Testicular Feminization Syndrome:

1. **Clinical picture** " the most imp "
2. **Laboratory Diagnosis:**
   - ✓ **Increased (or normal) testosterone blood level**
   - ✓ **Increased luteinizing hormone (LH) production by the pituitary gland**