Biochemistry Bandits 434

Adrenal Congenital Hyperplasia & Testicular Feminization syndrome

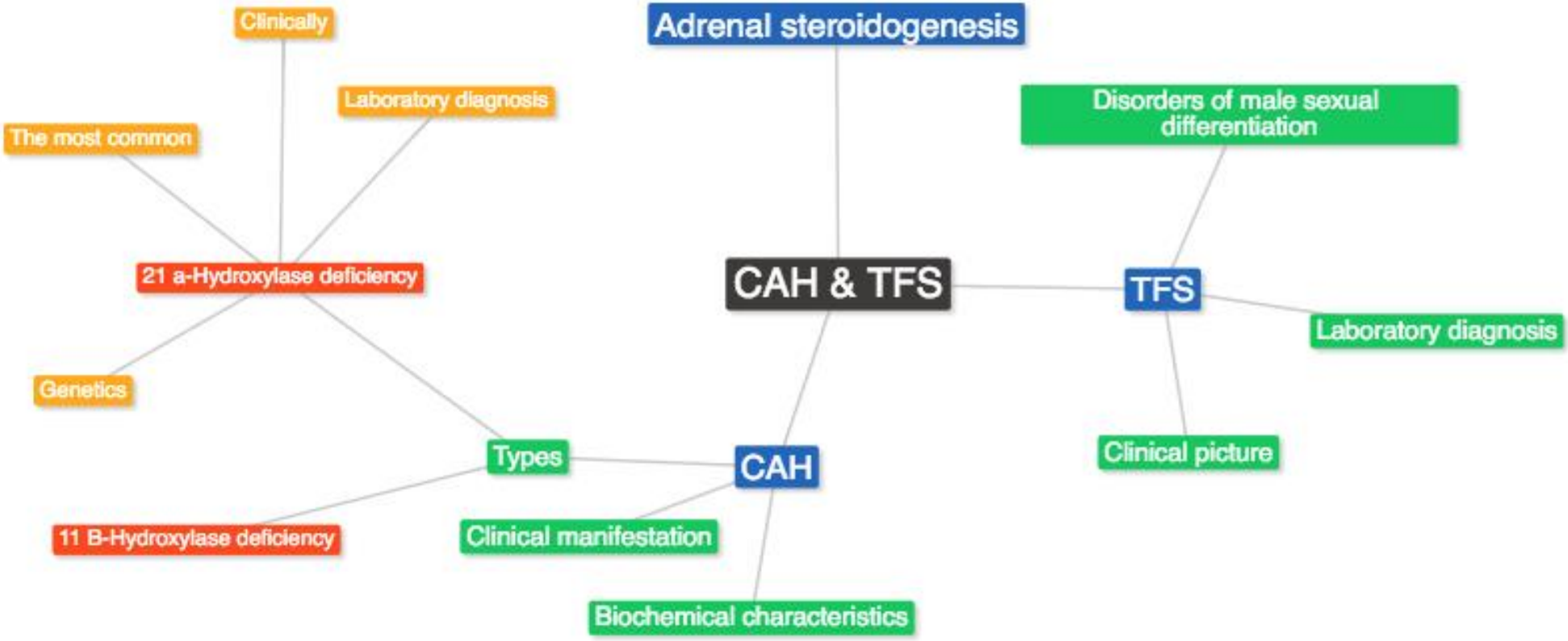
OBJECTIVES:

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

❖ Important ❖ Extra ❖ Biochemistry Edit

Reproductive Block

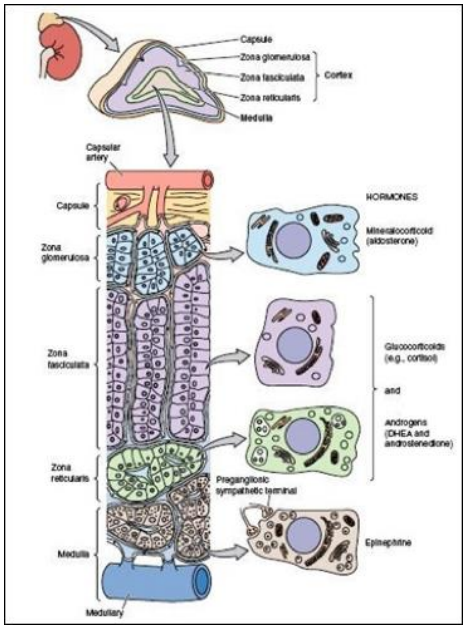
MIND MAP


Adrenal steroidogenesis
CAH & TFS
Clinically
Laboratory diagnosis
The most common
21 a-Hydroxylase deficiency
Genetics
Types
11 B-Hydroxylase deficiency
CAH
Clinical manifestation
Biochemical characteristics
Disorders of male sexual differentiation
TFS
Laboratory diagnosis
Clinical picture

Adrenal Gland : Quick recall !

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[1]

- ❖ Intersex: A person has neither standard male or standard female anatomy.
- ❖ Discrepancy between type of gonads and external genitalia
- ❖ True hermaphrodite[2] (ovary plus testis)
- ❖ Female pseudohermaphrodite (FPH[3], only ovary)
- ❖ Male pseudohermaphrodite (MPH[4], only testis)

1. intersex : خنثى

2. A diagnosis of True hermaphrodite is based solely on the presence of both ovarian and testicular tissue in the gonad and NOT on the characteristics of the internal and external genitalia.
3. FPH is a genetic female ”46,XX” with ovaries but virilized external genitalia. This arises from either endogenous androgens or exogenous androgen exposure e.g. maternal source.
4. MPH has a 46XY karyotype but deficient masculinization of the external genitalia.

Steroidogenesis and Congenital adrenal hyperplasia syndrome

The pic is very IMPORTANTE

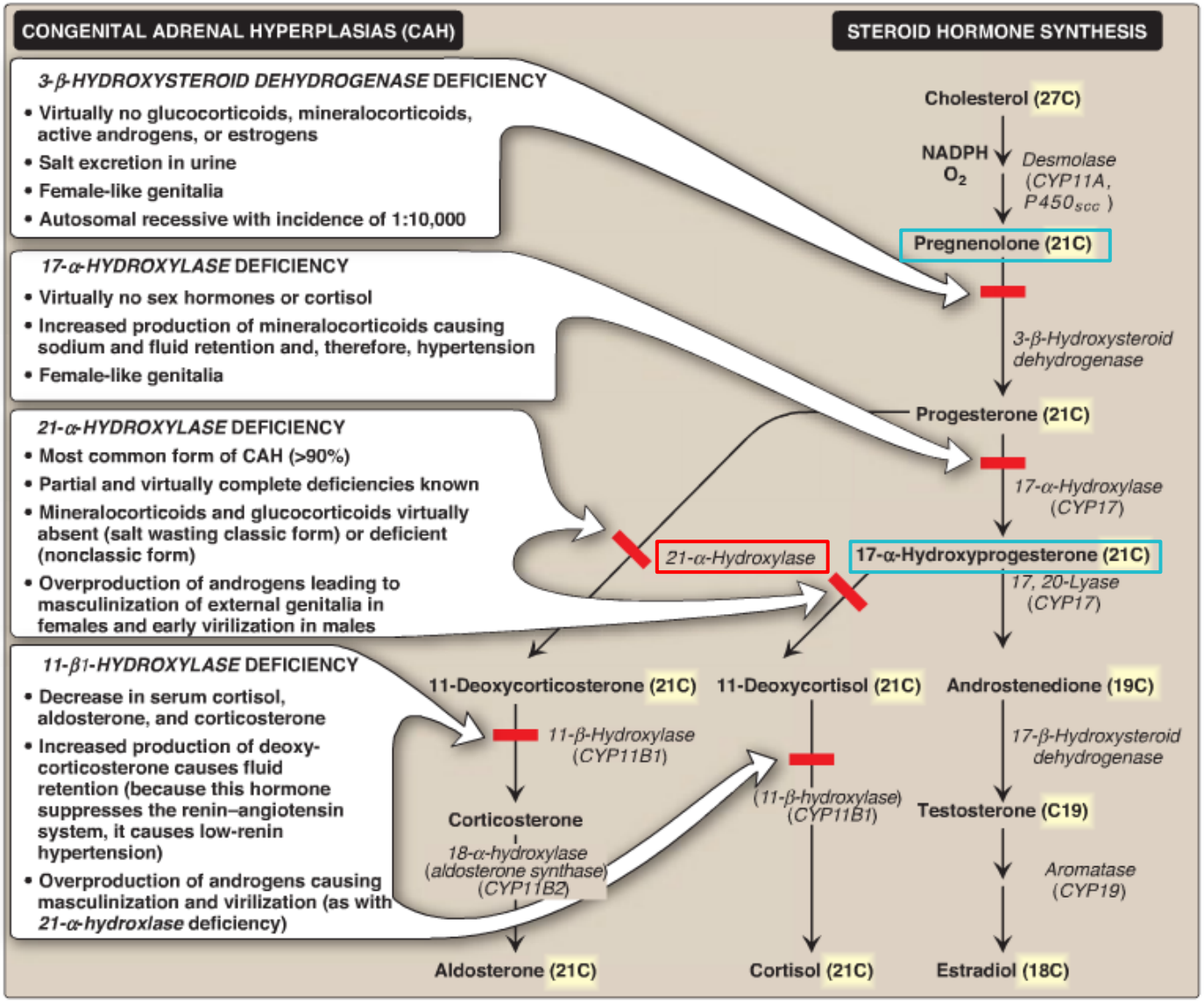


Figure 18.25
Steroid hormone synthesis and associated diseases. [Note: *3-β-Hydroxysteroid dehydrogenase*, *CYP17*, and *CYP11B2* are bifunctional enzymes. Synthesis of testosterone and the estrogens from cholesterol occurs primarily outside of the adrenal gland.] NADPH = nicotinamide adenine dinucleotide phosphate; CYP = cytochrome P450.

EXTRA:

Pregnenolone is the parent compound for all steroid hormones. It is oxidized and then isomerized to progesterone. which is further modified to the other steroid hormones by hydroxylation reaction that occur in the ER and mitochondria. like desmolase. a defect in the activity or amount of an enzyme in this pathway can lead to a deficiency in the synthesis of hormones beyond the affected step and to an excess in the hormones or metabolites before that step. because all members of the pathway have potent biologic activity, serious metabolic imbalance occur with enzyme deficiencies. collectively these disorders are known as the congenital adrenal hyperplasia

Congenital Adrenal Hyperplasia (CAH) Syndromes

❖ It is the result of an **inherited** enzyme defect in steroid biosynthesis

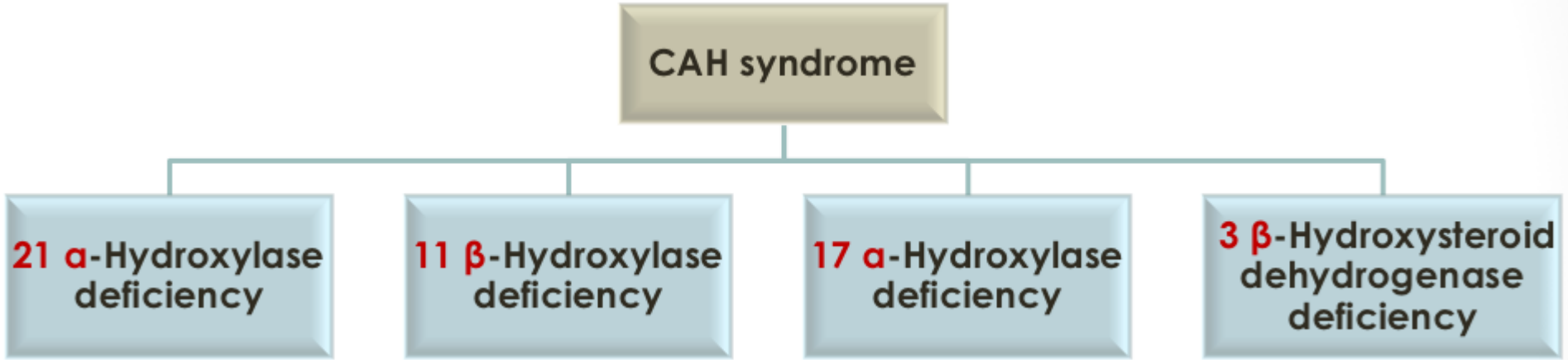
❖ The adrenals :

- 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



21 α-Hydroxylase Deficiency

- The most common type of CAH **(90%)**
- Laboratory diagnosis: ↑ plasma [17-hydroxyprogesterone] as early as **4 days** after birth

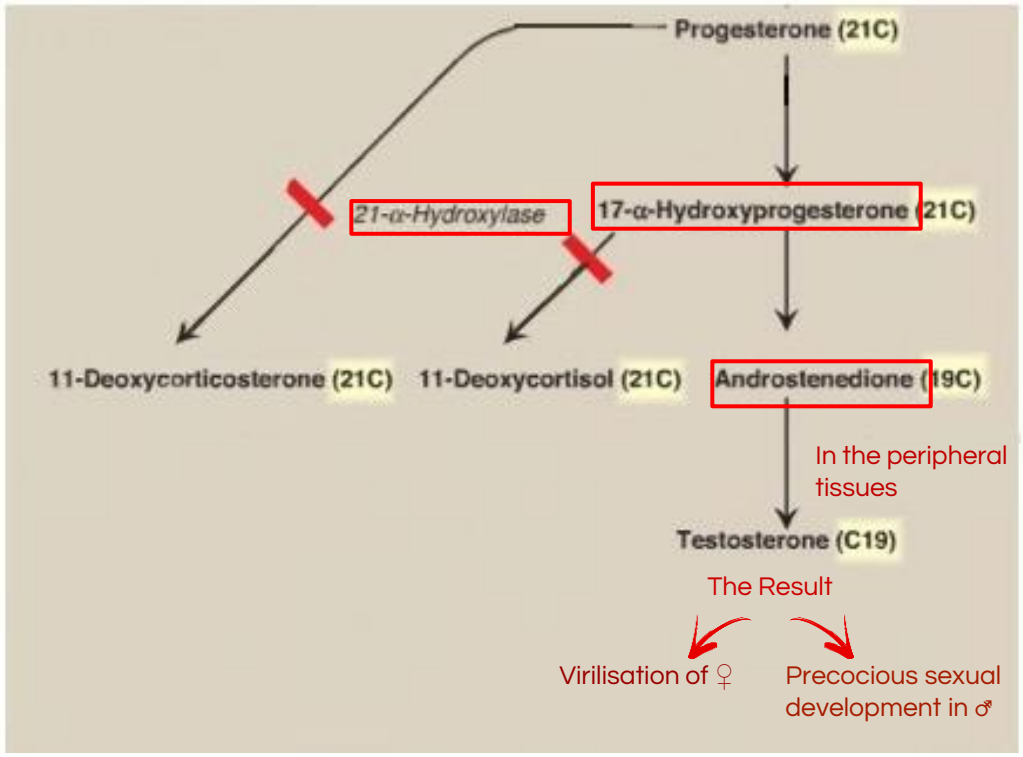
❖ **Clinically**	
Complete enzyme defect	**Partial** enzyme defect
↑ Stimulation of adrenal androgen production → virilization in baby girls & precocious (early) puberty in boys.	Late onset form → menstrual irregularity & hirsutism in young females.
❖ **Diagnosis**	
Serum sample taken at least **2 days** after birth (earlier samples may contain **maternally** derived **17-hydroxyprogesterone**)	
Characterized by markedly **elevated** serum levels of **17-hydroxyprogesterone**	May require **corticotrophin (ACTH) stimulation test**: • Measure base-line and stimulated levels of 17-hydroxyprogesterone. • High level of 17-hydroxyprogesterone after stimulation is diagnostic.

❖ Genetics

- ❖ Mutations in the CYP21 gene: ❧ Deletions ❧ Nonsense[1] ❧ Missense[2]
- ❖ DNA testing: For prenatal diagnosis and confirmation of diagnosis

1. A nonsense mutation is the substitution of a single base pair that leads to the appearance of a stop codon where previously there was a codon specifying an amino acid.
2. A missense mutation is when the change of a single base pair causes the substitution of a different amino acid in the resulting protein.

21 α-Hydroxylase Deficiency



Note that when there is a deficient in **21 α-hydroxylase** enzyme. The **11-Deoxycorticosterone** & **11-deoxycortisol** will not synthesized from **progestearone** & **17 α-hydroxyprogesterone** respectively → This will lead to lack of both aldosterone & cortisol.

On the other hand, there is excess of **Androstenedione** that will convert to **testosterone** in the peripheral tissue finally the result will be Virilisation of females and precocious sexual development in males.

Remember : **21 α-hydroxylase** acts on both **progesterone & 17 α-hydroxyprogesterone**

- Autosomal **recessive** condition
- Impaired synthesis of both **cortisol** & **aldosterone**
- ↓ [cortisol] → ↑ACTH secretion → Adrenal gland hyperplasia
- Accumulated 17a-hydroxyprogesterone are diverted to the biosynthesis of sex hormones → signs of androgen excess:
  - Ambiguous genitalia[1] 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

1. Ambiguous genitalia is a condition in which an infant's external genitals don't appear to be clearly either male or female.

11 b -Hydroxylase Deficiency

leads to high concentrations of 11-deoxycortisol

↓

The high levels of 11-deoxy-corticosterone has mineralocorticoid effect (salt and water retention)

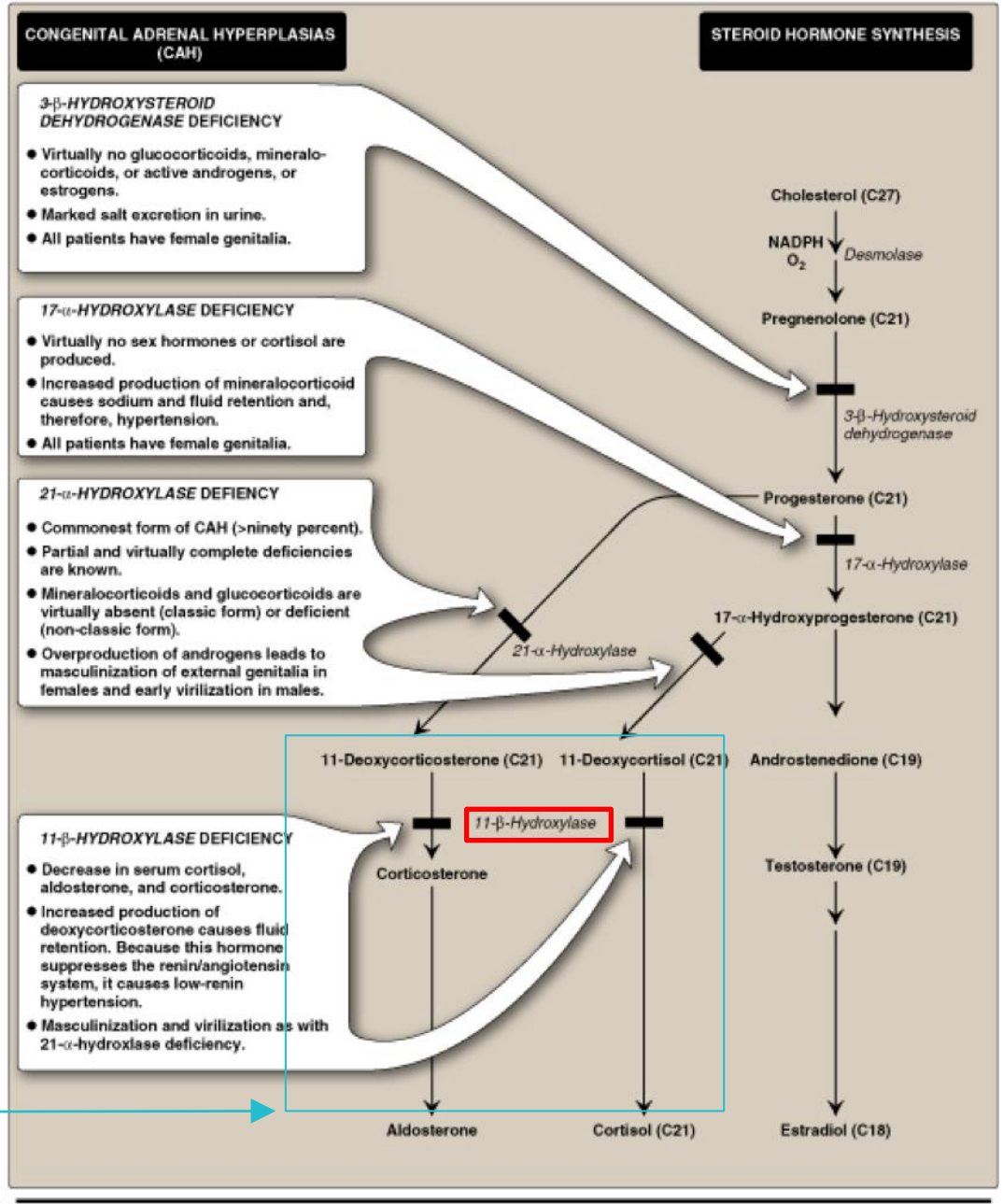
↓

Suppresses renin/angiotensin system low renin hypertension *this point is very important feature of the disease*

↓

Masculinization in females (FPH) and early virilization in males due to androgens

Androstendion will be high & converted in peripheral tissue to testosteron causing :
1- Virilisation of ♀
2-Precocious sexual development in ♂



Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

They are **rare** group of disorders.

The defect may be in:

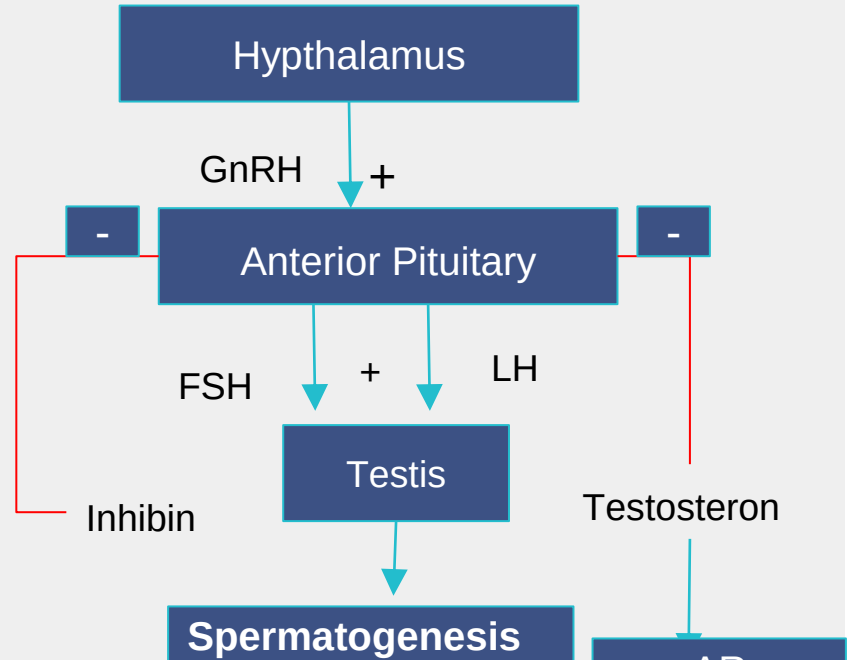
Testosterone production (impaired testosterone production)

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

- **46,XY karyotype**** "Normal so he is boy"
- 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.

** important :)

Control of testicular function by the gonadotrophins



*Increase level of testosterone will cause – feed back → inhibit LH secretion
*The presence of inhibin will inhibit FSH secretion

❖ Clinical Picture:

Complete androgen insensitivity syndrome (CAIS):	Partial androgen insensitivity syndrome (PAIS):
female external genitalia with normal labia, clitoris, and vaginal introitus[1]) مولجMPH)	mildly virilized female external genitalia (clitorimegaly without other external anomalies) to mildly undervirilized male external genitalia (hypospadias[2] and/or diminished penile size)

1.The vaginal introitus is the opening that leads to the vaginal canal.
2.Congenital condition in males in which the opening of the urethra is on the underside 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

21α-Hydroxylase Deficiency (The most common type of CAH) (90%)

- Impaired synthesis of both cortisol & aldosterone => (↑ plasma 17-hydroxyprogesterone).
- Cortisol lead to ↑ ACTH secretion lead to Adrenal gland hyperplasia
- Accumulated 17α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones

11β-Hydroxylase Deficiency:

Leads to high levels of 11-deoxy-corticosterone which has a mineralocorticoid effect (salt and water retention) Suppresses renin/angiotensin system => low renin hypertension Masculinization in females (FPH) and early virilization in males (leads to high concentrations of 11-deoxycortisol).

Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

- karyotype: 46,XY (X-linked recessive disorder)
- Androgen receptor resistance
- High testosterone blood level In peripheral tissue, testosterone will be converted by aromatase into estradiolà feminization.

MCQs & SAQs

1- To diagnose Late-onset (partial) 21a-Hydroxylase deficiency we should do:
A. CRH stimulation test.
B. TSH stimulation test.
C. ACTH stimulation test.
D. GnRH stimulation test.

2- A patient with 21 a-Hydroxylase deficiency will have :
A. Hypertension.
B. Excess androgens.
C. Na retention.
D. Excess cortisol.

3- A patient with 17 a-Hydroxylase deficiency will have :
A. Less mineralocorticoids.
B. More cortisol.
C. More sex hormones .
D. Less sex hormones .

4- 21 a-Hydroxylase deficiency disease is :
A. Autosomal recessive.
B. X-linked recessive.
C. X-linked dominant.
D. Autosomal dominant.

5- In case of Testicular Feminization Syndrome there is no fallopian tubes nor uterus because of:
A. Testosterone.
B. Dihydrotestosterone.
C. Müllerian-inhibiting factor.
D. None of the above.

6- A patient with 11- beta-Hydroxylase deficiency will have hypertension due to increase levels of :
A. Corticosterone.
B. Aldosterone.
C. Cortisol.
D. Deoxycorticosterone.

Q1-List Different Enzymes that may be Deficient in CAH:

21 a-Hydroxylase deficiency
11 b-Hydroxylase deficiency
17 a-Hydroxylase deficiency
3 b-Hydroxysteroid dehydrogenase deficiency

Q2- Where are the defect in Testicular Feminization Syndrome?

1/Testosterone production (impaired testosterone production)
2/Androgen receptors (inactive androgen receptors)

Q3-What is the result in laboratory diagnosis using Imaging Studies "Pelvic ultrasound" in Testicular Feminization Syndrome ?

Absence of fallopian tubes and uterus

1-C
2-B
3-D
4-A
5-C
6-D

Biochemistry Bandits 434

Thank you

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