Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

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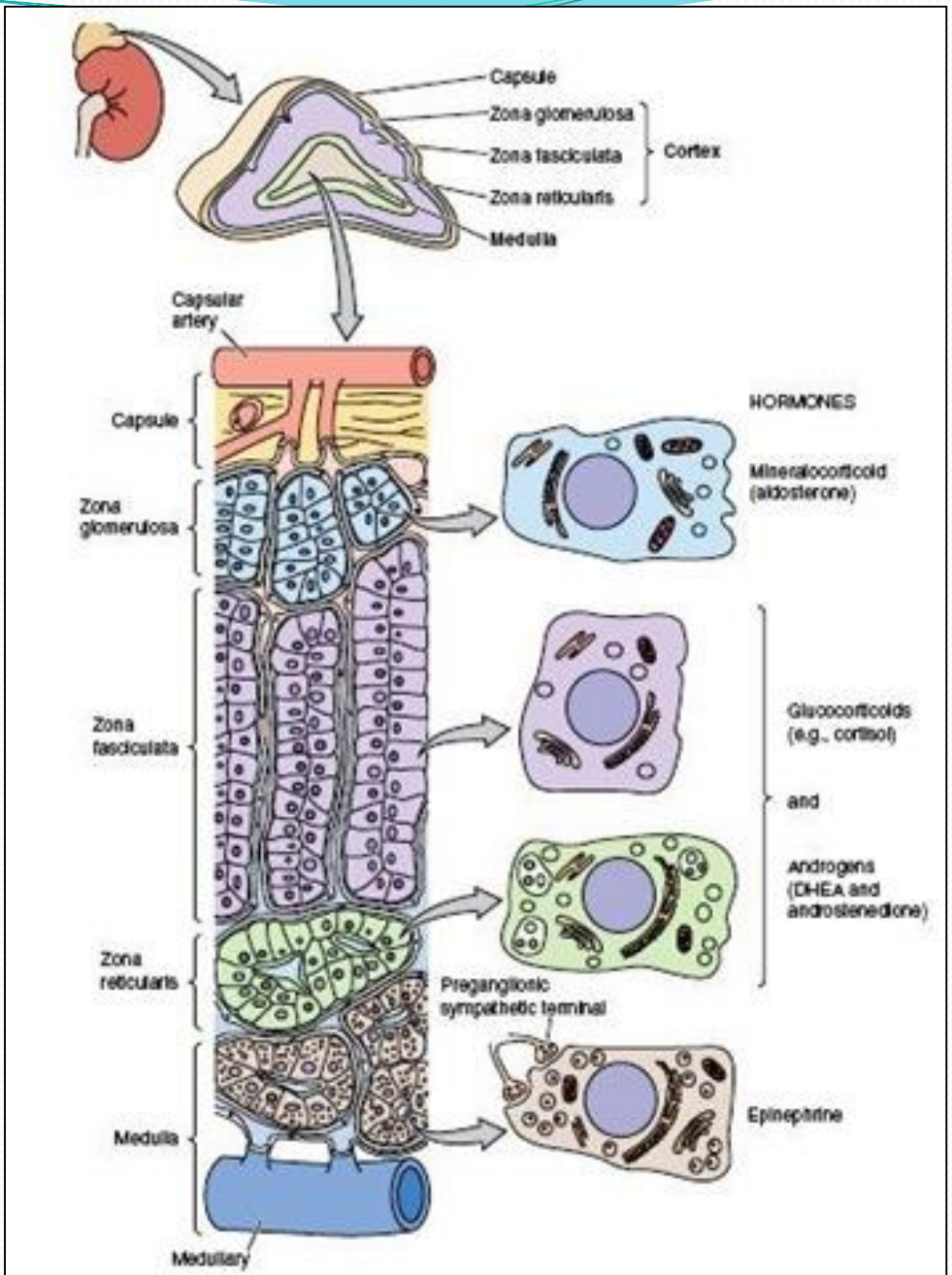
Objectives

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

Adrenal Glands

- 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)



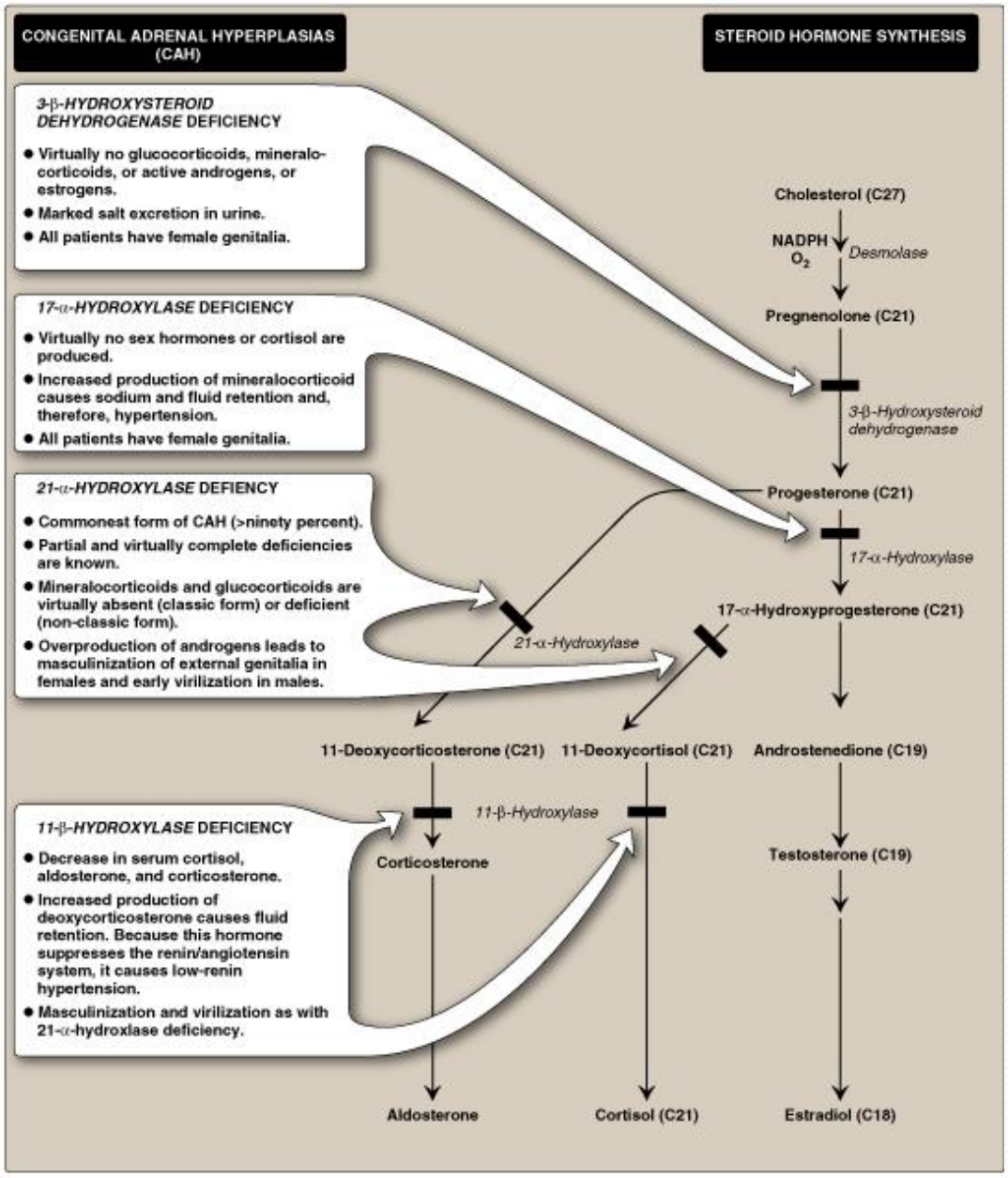
Hermaphroditism or Intersex

- **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)**

Glucocorticoids & Mineralocorticoids

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

Steroidogenesis and Congenital adrenal hyperplasia syndrome


CONGENITAL ADRENAL HYPERPLASIAS (CAH)
STEROID HORMONE SYNTHESIS
3-β-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY
Virtually no glucocorticoids, mineralocorticoids, or active androgens, or estrogens.
Marked salt excretion in urine.
All patients have female genitalia.
17-α-HYDROXYLASE DEFICIENCY
Virtually no sex hormones or cortisol are produced.
Increased production of mineralocorticoid causes sodium and fluid retention and, therefore, hypertension.
All patients have female genitalia.
21-α-HYDROXYLASE DEFIENCY
Commonest form of CAH (>ninety percent).
Partial and virtually complete deficiencies are known.
Mineralocorticoids and glucocorticoids are virtually absent (classic form) or deficient (non-classic form).
Overproduction of androgens leads to masculinization of external genitalia in females and early virilization in males.
11-β-HYDROXYLASE DEFICIENCY
Decrease in serum cortisol, aldosterone, and corticosterone.
Increased production of deoxycorticosterone causes fluid retention. Because this hormone suppresses the renin/angiotensin system, it causes low-renin hypertension.
Masculinization and virilization as with 21-α-hydroxlase deficiency.
Cholesterol (C27)
NADPH
O2
Desmolase
Pregnenolone (C21)
3-β-Hydroxysteroid dehydrogenase
Progesterone (C21)
17-α-Hydroxylase
17-α-Hydroxyprogesterone (C21)
21-α-Hydroxylase
11-Deoxycorticosterone (C21)
11-Deoxycortisol (C21)
Androstenedione (C19)
11-β-Hydroxylase
Corticosterone
Testosterone (C19)
Aldosterone
Cortisol (C21)
Estradiol (C18)

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

CAH Syndromes

- 21 α-Hydroxylase deficiency
- 11 β-Hydroxylase deficiency
- 17 α-Hydroxylase deficiency
- 3 β-Hydroxysteroid dehydrogenase deficiency

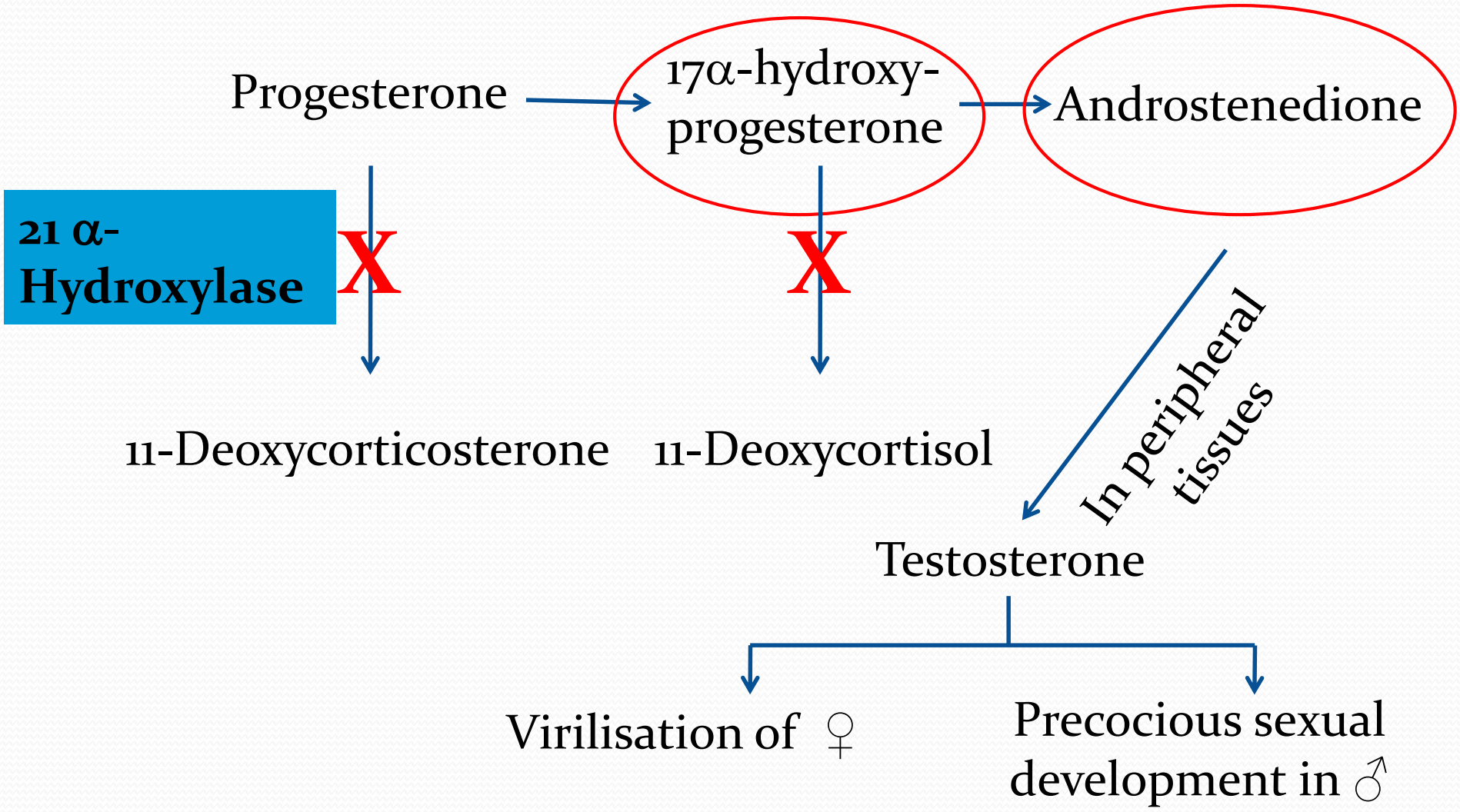
21 α-Hydroxylase Deficiency

- 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

21 α-Hydroxylase Deficiency



21 α-Hydroxylase Deficiency CONT'D

- 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

21 α-Hydroxylase Deficiency: Genetics

- Mutations in the CYP21 gene
  - Deletions
  - Nonsense
  - Missense

- DNA testing:

  For prenatal 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

11 β -Hydroxylase Deficiency

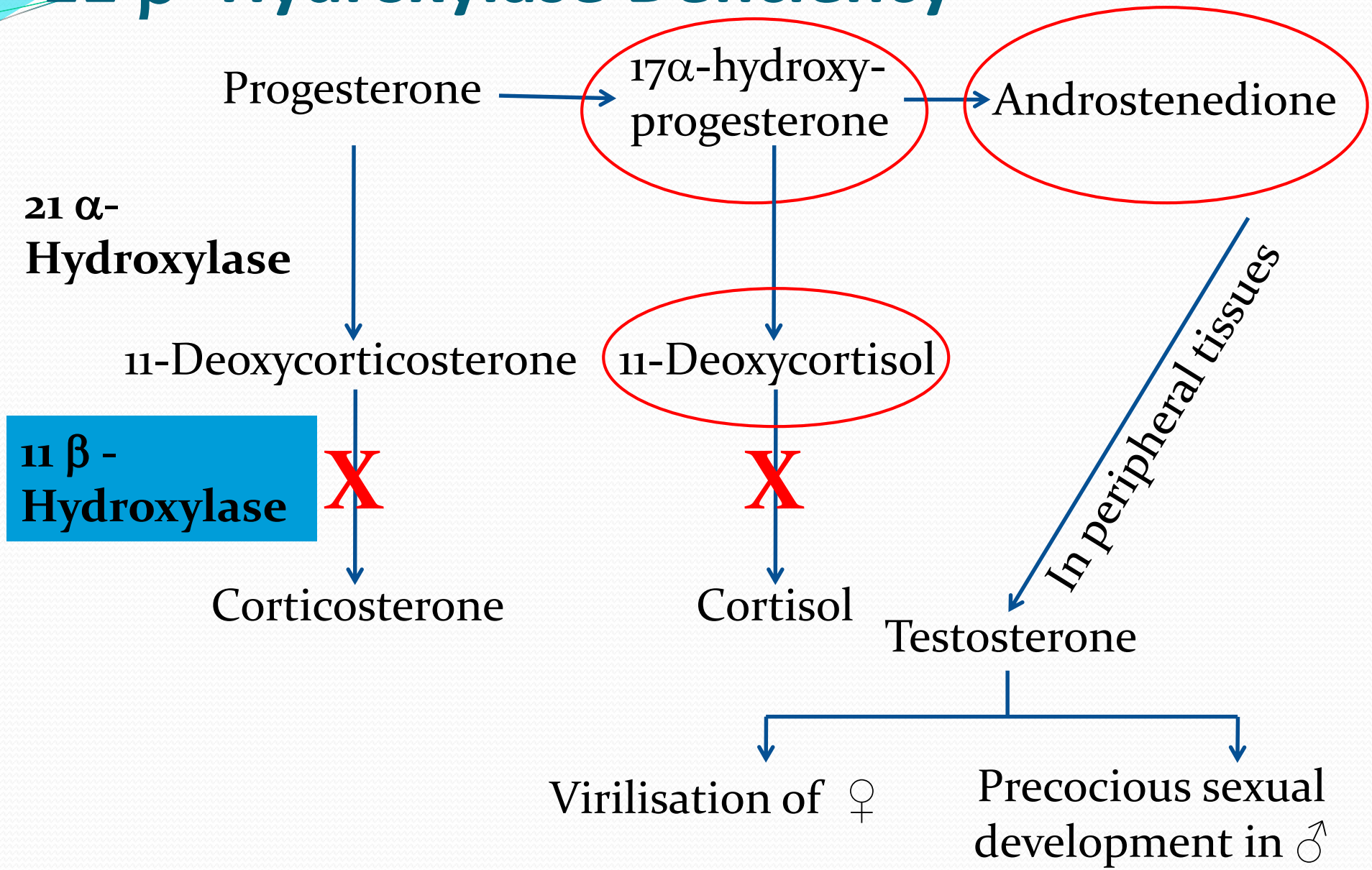
leads to high concentrations of 11-deoxycortisol

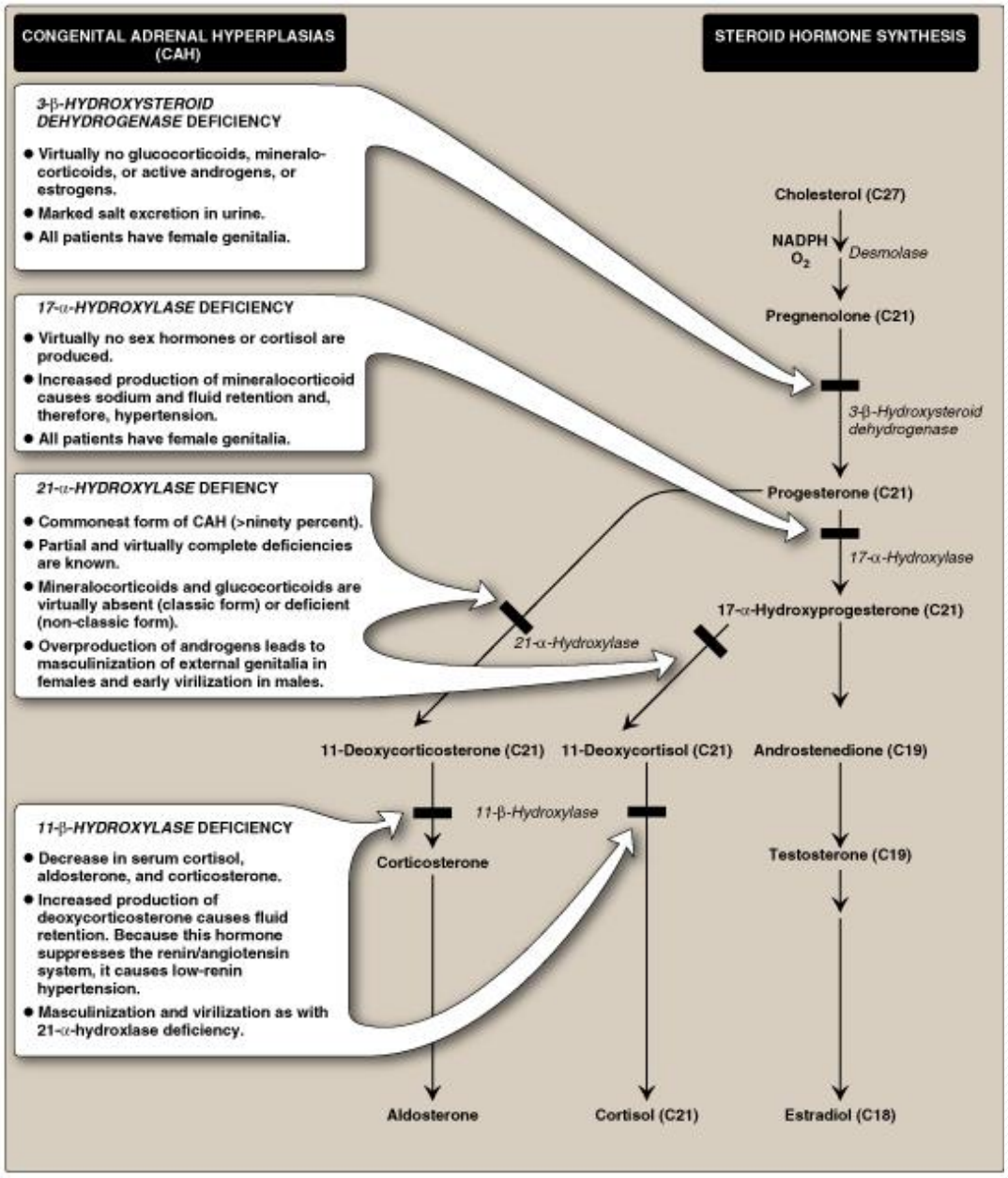
Leads to high levels of 11-deoxy-corticosterone with mineralocorticoid effect (salt and water retention)

Suppresses renin/angiotensin system ⟶ low renin hypertension

Musculanization in females (FPH) and early virilization in males

11 β -Hydroxylase Deficiency

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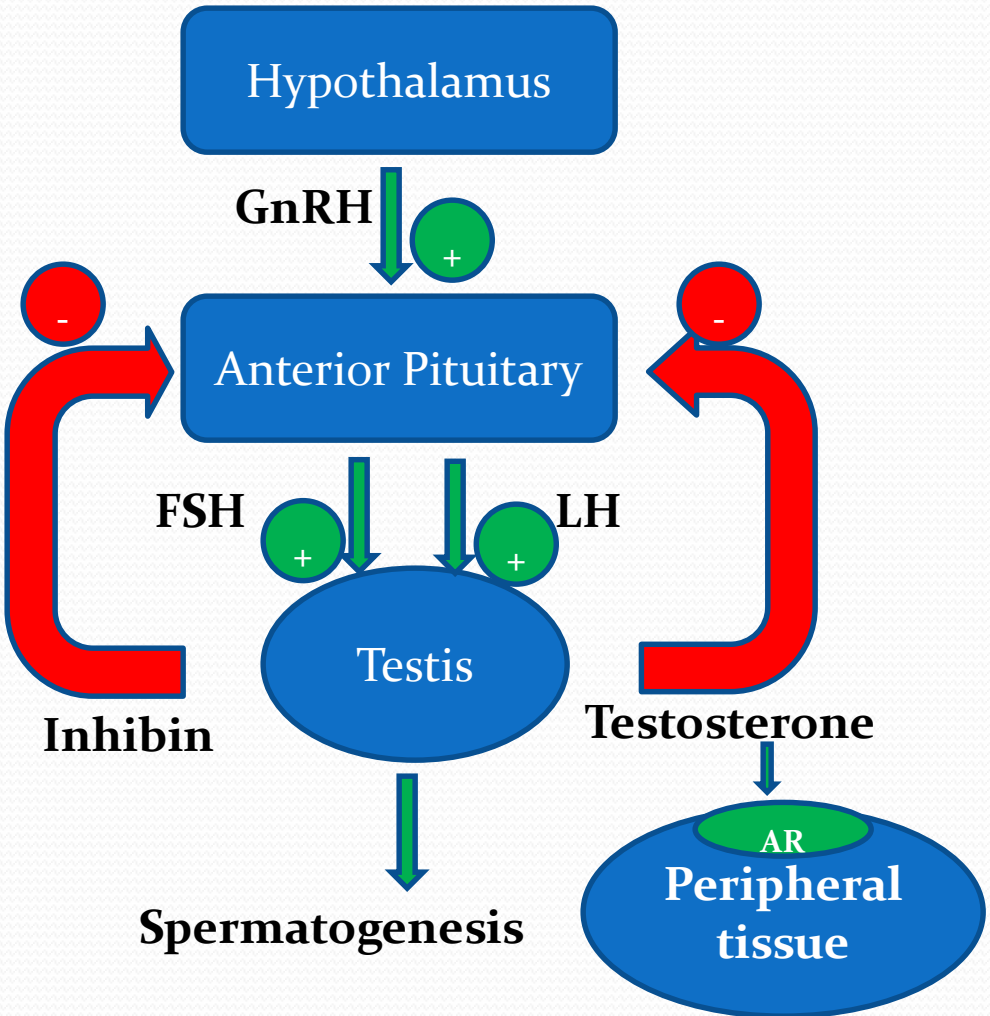
Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

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)

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

Laboratory Diagnosis CONT'D

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