Revised & Approved

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439

MED439
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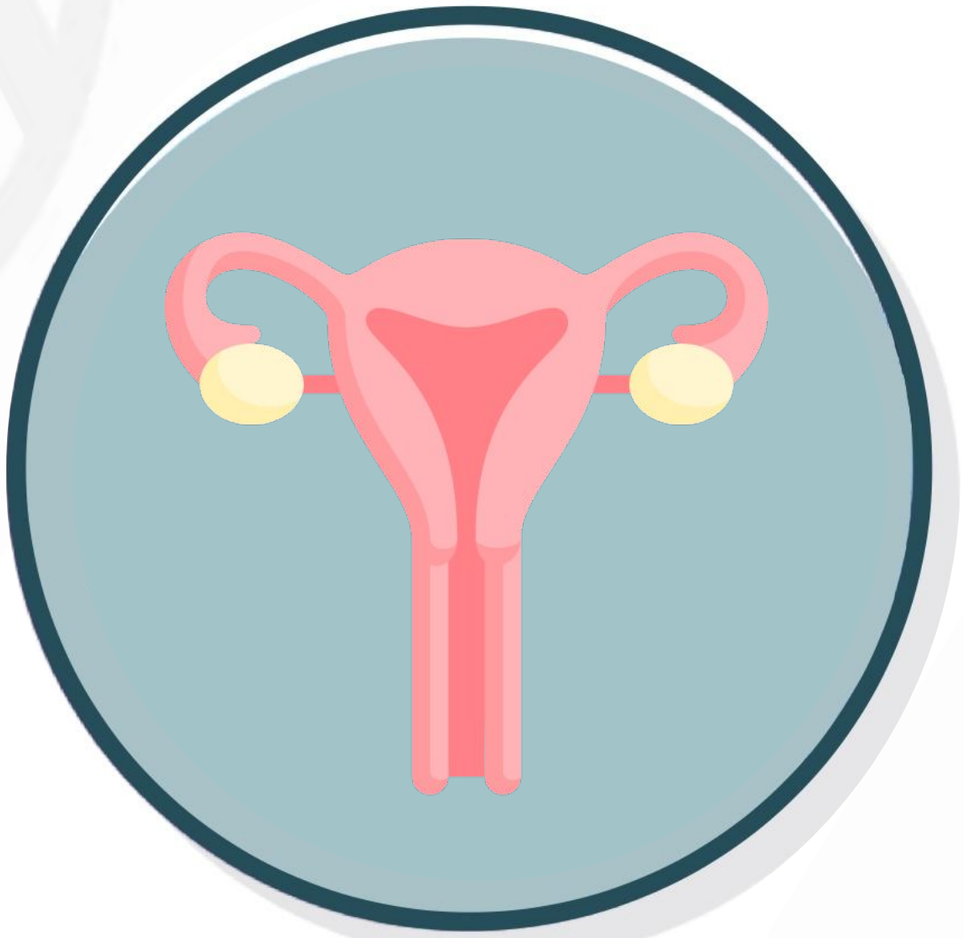


Congenital adrenal hyperplasia and testicular feminization syndrome

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

Objectives:

Adrenal steroidogenesis

Congenital adrenal hyperplasia syndrome

- Types
- Biochemical characteristics
- Clinical manifestations

Testicular feminization syndrome

Introduction

Glucocorticoids :

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

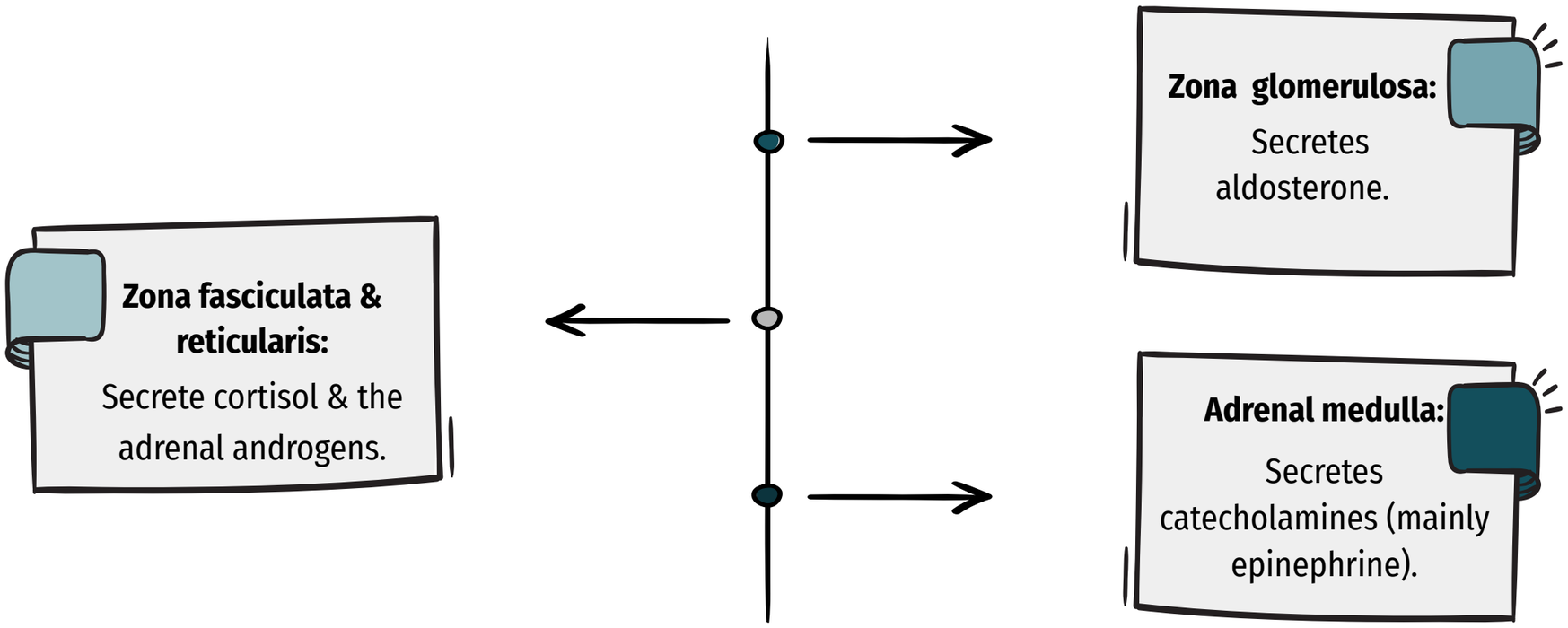
Mineralocorticoids :

- Steroids with aldosterone-like activity.
- Promote renal sodium reabsorption.

- H_2O/Na^+retention
- K^+ excretion

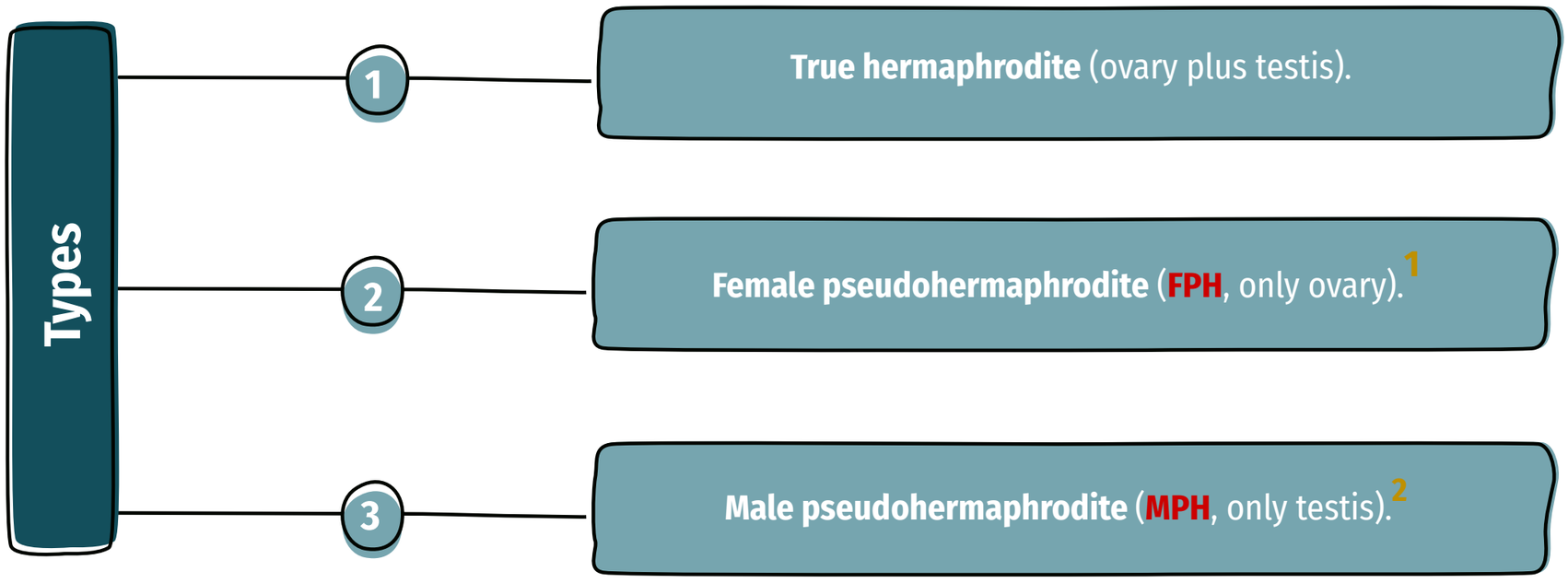
Adrenal gland

comprise 3 separate hormone systems:



★ Hermaphroditism or Intersex

Definition: A person who has neither standard male or standard female anatomy.
Discrepancy between the type of gonads and the external genitalia.



1- 46,XX: Ovaries are present. **Pseudo:** external genitalia are either virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

2- 46,XY: Testis present. **Pseudo:** external genitalia are either female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

Steroidogenesis and Congenital Adrenal Hyperplasia Syndrome

- The condition might be fatal unless diagnosed early.

- It is the result of an inherited enzyme defect in steroid biosynthesis.

3 1 4 2

Types of CAH syndromes:

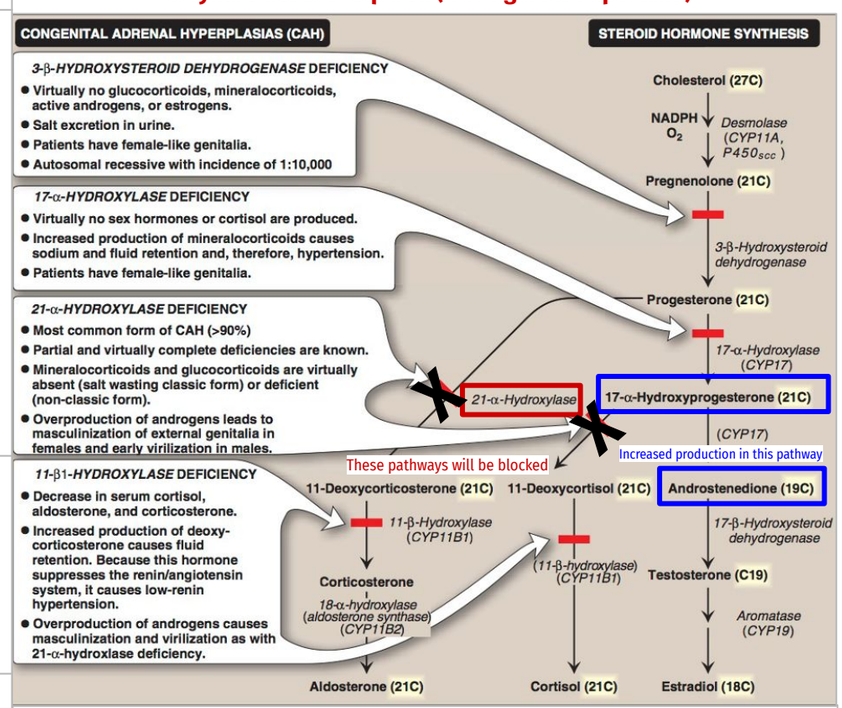
- **21 α-Hydroxylase deficiency.** Most common!
- **11 β-Hydroxylase deficiency.**
- **17 α-Hydroxylase deficiency.**
- **3 β-Hydroxysteroid dehydrogenase deficiency.**

- **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**

21 α- Hydroxylase deficiency

General Info	● The **most common** type of CAH **(90%)**. ● **Autosomal recessive** condition.
Patho-genesis	● Impaired synthesis of both cortisol & aldosterone. ● ↓ [cortisol]→ ↑ACTH secretion → Adrenal gland hyperplasia. ● **Accumulated 17-α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones →signs of androgen excess:** ○ Ambiguous genitalia in newborn girls (**FPH**). Ovaries are present . ○ Rapid postnatal growth in both sexes. ● **Severe cases: mineralocorticoid deficiency** (complete) → salt & H2O loss → hypovolemia & **shock** → **neonatal adrenal crisis.** **Note:** Late presentation (adult life) is possible in less severe cases.
Clinical picture	1. **Complete enzyme defect** [1]→ ↑ stimulation of adrenal androgen production → **virilization** in baby girls & **precocious puberty** in boys. 2. **Partial enzyme defect** [2]→ late onset form → menstrual irregularity & hirsutism and late pregnancy in young females. Misdiagnosed with PCOS
Genetics	**Mutations in the CYP21 gene:** ● Deletions, Nonsense, Missense. **DNA testing of CYP21:** ● **For prenatal diagnosis** and confirmation of diagnosis.
Diagnosis	● Serum sample taken **at least 2 days after birth** (earlier samples may contain maternally derived 17-α-hydroxyprogesterone): ○ ↑ plasma [17-α-hydroxyprogesterone] as early as 4 days after birth. Measure the precursor not the enzyme itself 1. **Classic (complete) deficiency:** is characterized by **markedly elevated serum levels of 17-α-hydroxyprogesterone.** 2. **Late-onset (partial) deficiency**[3]**:** may **require corticotropin (ACTH) stimulation test:** ○ Measure baseline and stimulated levels of 17-α-hydroxyprogesterone. Because it's the most common ○ High level of 17-α-hydroxyprogesterone after stimulation is diagnostic.

All syndromes are required (The figure is important)



Dr's notes :

- it is the most common among other enzymes deficiencies
- Hyperplastic adrenal gland is a response of the continuous secretion of ACTH
- Hypotension is the result of the absent mineralocorticoids and glucocorticoids
- Overproduction of Androgens is an alternative pathway

1- Mutation of the active site of the enzyme .
2- Mutation of any part of the enzyme other than the active site.
3- When we give ACTH to :
Normal baby → high cortisol level
Baby with deficient enzyme → high 17-α-hydroxyprogesterone

11 β- Hydroxylase deficiency

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

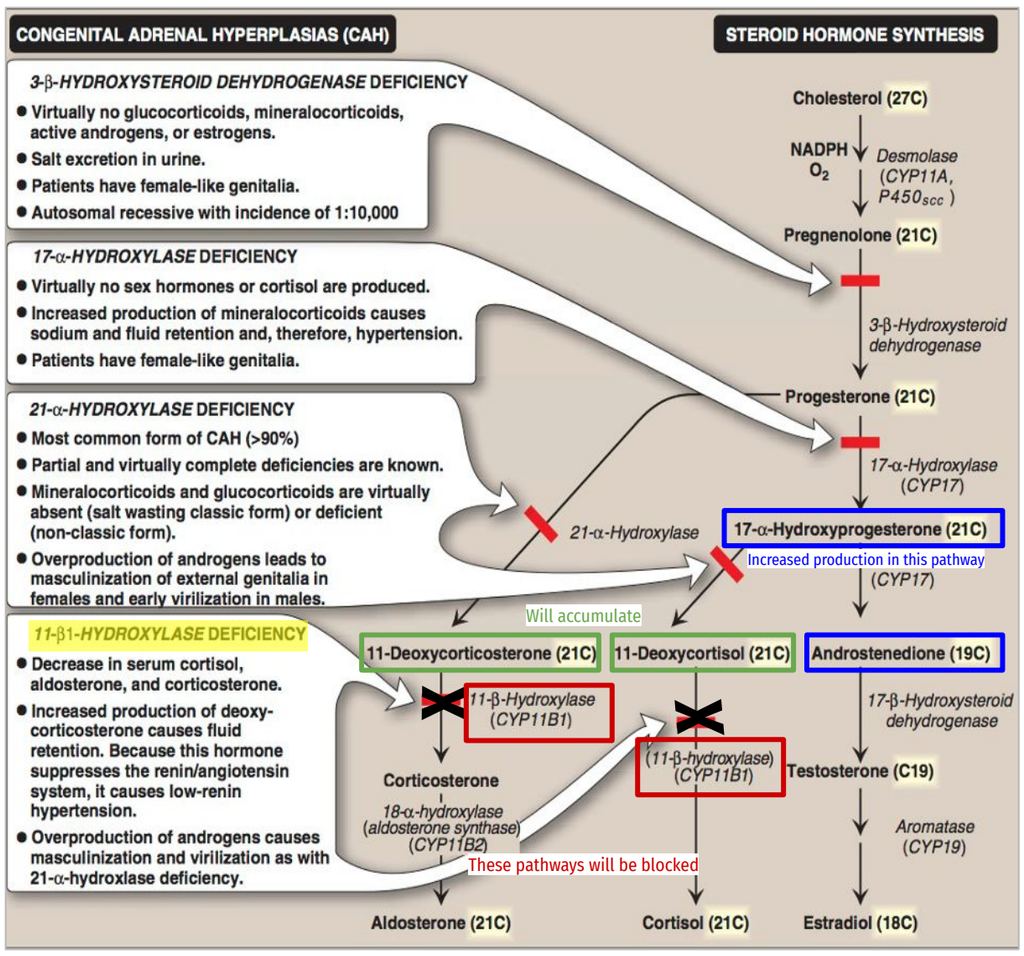
Leads to high concentrations of 11-deoxycortisol.

Leads to high levels of 11-deoxycorticosterone with mineralocorticoid effect (**salt and water retention**).

Suppresses renin/angiotensin system → low-renin hypertension.

Masculinization and Precocious sexual development in females (**FPH** : female pseudohermaphrodite) and early virilization in males.

All syndromes are required (The figure is important)

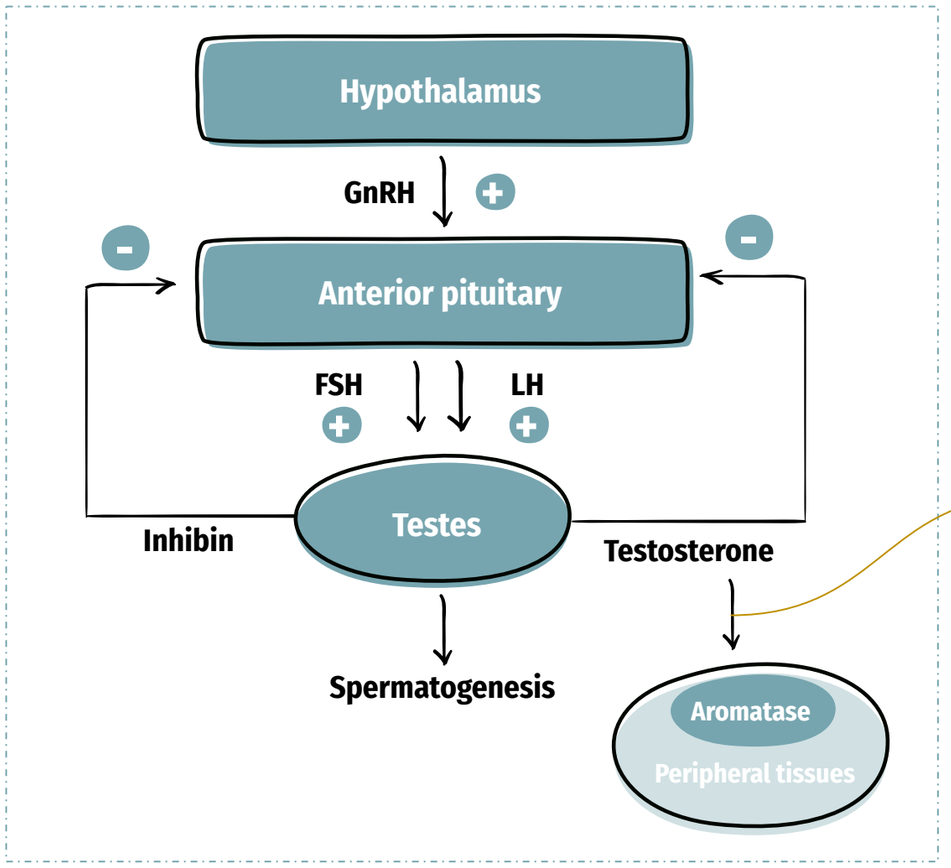


Disorders of Male Sexual Differentiation

- They are rare group of disorders
  - The pathway is normal
  - The receptors are mutated

- The **defect** may be in: **Androgen receptors** (inactive by a mutation androgen receptors in target tissues cannot respond to stimulation by circulating Anterior pituitary testosterone ; e.g., **Testicular feminization syndrome**)

Control of testicular function by the gonadotropins



Large amounts of unutilized Testosterone are converted to Estradiol in the peripheral tissues

Testicular Feminization Syndrome
(Androgen Insensitivity Syndrome)

- 46, XY karyotype (Normal Male).

- **X-linked recessive disorder.**

Androgen receptor resistance. (can't bind to receptor) → 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 tissue factor (MIF)1**, therefore, affected individuals **do not have** fallopian tubes, a uterus, or a proximal (upper) vagina .

- **Med438 :** Sertoli cells secrete Müllerian inhibitory factor (MIF also known as, antimullerian hormone) that suppresses Estradiol development of paramesonephric ducts.

Clinical picture

Clinical picture

Complete androgen insensitivity syndrome (CAIS)

- Female external genitalia with normal labia.
- Clitoris.
- Vaginal introitus (**MPH**: male pseudohermaphrodite).

Partial androgen insensitivity syndrome (PAIS)

- **Mildly virilized female external genitalia** female external genitalia (clitorimegaly without other external anomalies) to **mildly undervirilized male external genitalia** (hypospadias and/or diminished penile size).

Laboratory diagnosis

All of these results indicate that the patient is a male with TFS

Karyotype
differentiate an under-masculinized male from a masculinized female.
Result : 46, XY

Fluorescent in situ hybridization (FISH):
Presence 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.

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

Increased (or normal) testosterone and dihydrotestosterone blood levels.

Imaging Studies "Pelvic ultrasound"
Absence of fallopian tubes and uterus.

Extra Summary

Hermaphroditism or intersex	**Definition**	A person who has neither standard male or standard female anatomy. Discrepancy between the type of gonads and the external genitalia.
	Types	1. True hermaphrodite (ovary plus testis) 2. Female psuedohermaphrodite (FPH, only ovary) 3. Male psuedohermaphrodite (MPH, only testis)
CAH	**Overview**	• 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**
	Types	• **21 α-Hydroxylase deficiency.** • **11 β-Hydroxylase deficiency.** • **17 α-Hydroxylase deficiency.** • **3 β-Hydroxysteroid dehydrogenase deficiency.**
21 α- Hydroxylase deficiency	**Pathogenesis**	• Impaired synthesis of both cortisol & aldosterone. • ↓ [cortisol]→ ↑ACTH secretion → Adrenal gland hyperplasia. • **Accumulated 17-α-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 & H2O loss → hypovolemia & **shock** → **neonatal adrenal crisis**
	Clinical picture	1. **Complete enzyme defect** → ↑ stimulation of adrenal androgen production → **virilization** in baby girls & **precocious puberty** in boys. 2. **Partial enzyme defect** → late onset form → menstrual irregularity & hirsutism in young females.
	Diagnosis	1. **Classic (complete) deficiency:** is characterized by **markedly elevated serum levels of 17-α-hydroxyprogesterone.** 2. **Late-onset (partial) deficiency:** may **require corticotropin (ACTH) stimulation test**
11 β- Hydroxylase deficiency	**Overview**	• It is the result of an inherited enzyme defect in steroid biosynthesis. • **Leads to high concentrations of 11-deoxycortisol.** • Leads to high levels of 11-deoxycorticosterone with mineralocorticoid effect (salt and water retention). • **Suppresses renin/angiotensin system → low-renin hypertension.** • Masculinization and Precocious sexual development in females (FPH) and early virilization in males.
Testicular feminization syndrome	**Overview**	• X-linked recessive disorder. • High resistance of androgen receptor → high testosterone blood levels → in peripheral tissues testosterone will be converted by aromatase into estradiol → feminization • Patients have normal testes & produce normal amounts of müllerian-inhibiting tissue factor (MIF)1, therefore, affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina.
	Clinical picture	• **Complete androgen insensitivity syndrome :** Female external genitalia, Clitoris, Vaginal introitus (MPH). • **Topic partial androgen insensitivity syndrome :** Mildly virilized female external genitalia female external genitalia to mildly undervirilized male external genitalia
	Diagnosis	Karyotype, FISH, ↑or normal testosterone and DHEA blood levels, imaging studies (pelvic ultrasound)

MCQs

1- Which of the following enzyme deficiency is most common in CAH?			
A- 11 β-Hydroxylase	B- 21 β-Hydroxylase	C- 17 α-Hydroxylase	D- 21 α-Hydroxylase
2- Which of the following is a late complication of partial 21 α hydroxylase deficiency?			
A- Virilization in baby girls	B- Precocious puberty in boys	C- Hirsutism	D- Gigantism
3- Which of the following will be low in case of 21 α hydroxylase?			
A- Aldosterone	B- Androstenedione	C- Cortisol	D- A&C
4-11 β- Hydroxylase deficiency leads to?			
A-low-renin hypertension & low concentrations of 11-deoxycortisol.	B- High-renin hypertension	C-low-renin hypertension & high concentrations of 11-deoxycortisol.	D-low concentrations of 11-deoxycortisol.
5- In Testicular Feminization Syndrome the defect is in?			
A- GnRH	B-ACTH	C-Testosterone	D-Androgen receptors
6-In peripheral tissue, testosterone will be converted by .....into estradiol.			
A-21 α-Hydroxylase deficiency.	B- aromatase	C-11 β-Hydroxylase deficiency.	D-Hydroxylase

Answers key

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

SAQs

1- What are the types of Hermaphroditism?

1. True hermaphrodite (individual is born with both ovary and testicles)
2. Female pseudohermaphrodite (Only ovary)
3. Male pseudohermaphrodite (Only testis)

2- What are the 2 clinical pictures in 21 α-Hydroxylase deficiency?

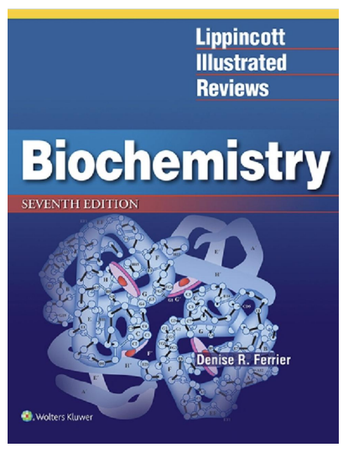
1. **Complete enzyme defect** → ↑ stimulation of adrenal androgen production → virilization in baby girls & precocious puberty in boys.
2. **Partial enzyme defect** → late onset form → menstrual irregularity & hirsutism in young females.

3- What is the mechanism in 11 β- Hydroxylase deficiency ?

-inherited enzyme defect in steroid biosynthesis.
-high concentrations of **11-deoxycortisol.**
-high levels of **11-deoxycorticosterone** with mineralocorticoid effect (**salt and water retention**).
-**Suppresses renin**/angiotensin system → **low-renin hypertension.**
-**Masculinization** and Precocious sexual development in **females** (FPH) and early virilization in males.

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.