Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

Introduction

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 & Mineralocorticoids	***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, as there is discrepancy[1] between type of gonads and external genitalia. **Types:** 1. **True hermaphrodite (ovary plus testis)** 2. **Pseudohermaphrodite:** • Female pseudohermaphrodite (FPH, only ovary, with male external genitalia) • Male pseudohermaphrodite (MPH, only testis, with female external genitalia)		

Steroidogenesis and Congenital adrenal hyperplasia syndrome

Steroidogenesis	• Cholesterol (C27) is converted into pregnenolone (C21) by Desmolase, NADPH & O2. Graph
Congenital adrenal hyperplasia (CAH) syndrome	• 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) ○ The adrenals Cannot secrete aldosterone → electrolyte disturbances (Hyponatremia & Hyperkalemia) • The condition might be fatal unless diagnosed early

Rare types	**3-β-Hydroxysteroid dehydrogenase deficiency**	**17-α-Hydroxylase deficiency**
Not imp.	3-β-Hydroxysteroid dehydrogenase converts pregnenolone into progesterone. If deficient: ○ Virtually no glucocorticoids, mineralocorticoids, active androgens or estrogens ○ Marked salt excretion in urine ○ All patients have female genitalia	17-α-Hydroxylase converts progesterone into 17-α-Hydroxyprogesterone, if deficient: ○ 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
Other types:	**21 α-Hydroxylase Deficiency** graph	**11 β -Hydroxylase Deficiency** graph
	○ The most common type of CAH **(90%)** ○ **Autosomal recessive** condition	

[1] **Discrepancy =** تعارض

Deficient steroids	• Mineralocorticoids (aldosterone) and glucocorticoids (cortisol) are virtually **absent (classic form)** or deficient (non-classic form) • ↓ [cortisol]→↑ ACTH secretion → Adrenal gland hyperplasia • Severe cases: mineralocorticoid deficiency → salt & H_2O loss → hypovolemia & shock → neonatal adrenal crisis • **Late presentation** (adult life) is possible in less severe cases	• Decrease in serum cortisol, aldosterone, and corticosterone.
Increased steroids	Accumulated **17-α-hydroxyprogesterone** are diverted to the biosynthesis of sex hormones → Androstenedione is converted into testosterone in peripheral tissues → signs of androgen excess: • Ambiguous genitalia in newborn girls (FPH) • **Rapid postnatal growth in both sexes**	• 11-deoxycortisol • 11-deoxy-corticosterone (mineralocorticoid effect) causes salt and water retention. 11-deoxy-corticosterone also suppresses renin/angiotensin system, leading to **low-renin hypertension**
Clinical picture	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.	• Masculinization in females (FPH) • **Early** virilization in males
Genetics	• Mutations in the CYP21 gene (Deletions, Nonsense, Missense) • DNA testing: For **prenatal** diagnosis and confirmation of diagnosis	
Laboratory diagnosis:	↑ plasma [17-hydroxyprogesterone] in serum sample taken as early as 4 days but not before **2 days after birth** (because 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: 1. Measure **base-line** levels of 17-hydroxyprogesterone	

	2. Measure **stimulated** levels of 17-hydroxyprogesterone. **High level** is diagnostic.	
	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 (graph)**	

	Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)	
Overview	• 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:	1. **Complete androgen insensitivity syndrome (CAIS):** female external genitalia with normal labia, clitoris, and vaginal introitus (MPH) 2. **Partial androgen insensitivity syndrome (PAIS):** mildly **virilized female** external genitalia (clitorimegaly without other external anomalies) - to mildly **undervirilized male** external genitalia (hypospadias[2] 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 • **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	

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[2] a congenital condition in males in which the opening of the urethra is on the underside of the penis.