

29.1 Introduction

The biosynthesis of steroid hormones is a fascinating process in which the neutral lipid cholesterol, a normal constituent of lipid bilayers is transformed *via* a series of hydroxylation, oxidation and reduction steps into a vast array of biologically active compounds: mineralocorticoids, glucocorticoids and sex hormones. The majority of these transformations occur in the adrenal, testis and ovary although other tissues, such as liver, kidney, placenta, brain and skin are also quite active.

Steroid hormone action is a complex process that is only recently beginning to be understood. Steroid hormones bind to specific intracellular receptors which upon dimerization interact with the DNA in the nucleus. As a result, gene activity is modulated and a hormone-specific response occurs [1]. It is logical that abnormalities in any step of this cascade will interfere with the action of a particular hormone. Defects in the receptor or the post-receptor machinery will lead for the most part to abnormalities of action of one specific hormone. Abnormalities of steroid hormone production, however, can result in more profound and complex effects. A block in the pathway of steroid biosynthesis leads to the lack of hormones downstream and accumulation of the upstream compounds that can activate other members of the steroid receptor family. The consequences of such defects can be schematically categorised in three groups: 1) defects leading to abnormalities of sexual differentiation and salt-water balance, 2) defects leading to abnormalities of salt-water balance, 3) defects leading to abnormalities of sexual differentiation. Abnormalities of end-organ action of steroid hormones, exemplified by the hormone insensitivity syndromes can be grouped in a fourth category.

The first group of steroid biosynthesis defects include the so-called Congenital Adrenal Hyperplasia (CAH), a collective name given to a group of disorders characterised by inherited inability of the adrenals to secrete cortisol. The consequent compensatory rise of ACTH production causes hyperplastic growth of the adrenal glands. Blocks of the initial steps of the steroidogenic pathway impair the production of all the three types of steroids, causing abnormalities in the salt-water homeostasis and in sexual differentiation. That is the case in *lipoid adrenal hyperplasia*, where no conversion of cholesterol to

any steroid takes place. This rare cause of CAH is characterised by salt-loss and male pseudohermaphroditism in XY individuals. In XX subjects internal and external genitalia are female, and the syndrome cannot clinically be separated from congenital adrenal hypoplasia [2]. The molecular bases of such a defect have been recently clarified as mutations in the Steroidogenic Acute Response Protein (StAR) [3]. *17 α -Hydroxylase deficiency* leads to male pseudohermaphroditism, due to the lack of precursors for testosterone. In XX individuals, there is primary amenorrhea and absent development of estrogenic secondary sexual characteristics. Both sexes display hypertension and hypokaliemic alkalosis due to accumulation of mineralocorticoid precursors, which do not need 17 α -hydroxylation for their synthesis [4]. Adrenal hyperplasia and glucocorticoid deficiency are less marked than in the other types of CAH, because of the ability of corticosterone of suppressing ACTH. Male patients affected by CAH due to *3 β -hydroxysteroid dehydrogenase deficiency* display incomplete prenatal masculinization due to the impaired synthesis of bioactive androgens, and salt-loss due to lack of mineralocorticoid [5]. XX subjects have normal female external genitalia or mild virilization due to the action of the weak androgen DHEA. *21-Hydroxylase deficiency* accounts for most cases of CAH (80–90%, depending on the ethnic group). Clinical consequences of 21-hydroxylase deficiency arise from overproduction of androgens. Affected females with the *classical* 21-hydroxylase deficiency are born with ambiguous genitalia. Postnatally, untreated patients of both sexes manifest rapid somatic growth with accelerated skeletal maturation, early closure of the epiphyses, and short adult stature. Other symptoms include excessive pubic and body hair and decreased fertility. 75% of patients with classic 21-hydroxylase deficiency also have reduced synthesis of aldosterone with salt-loss. Patients with *nonclassical* disease are born without symptoms of prenatal androgen exposure. Subsequently they may remain asymptomatic or may develop signs of androgen excess. Deficiency of 21-hydroxylase is inherited as an autosomal recessive trait closely linked to the HLA major histocompatibility complex on the short arm of chromosome 6. While classic 21-hydroxylase deficiency is found in about 1 in 14,000 births, nonclassic deficiency is far more frequent, occurring in up to 3% of persons amongst certain ethnic groups [6]. Steroid *11 β -hydroxylase deficiency*, which is responsible for 10–20% of cases of CAH, produces symptoms of androgen excess similar to those in 21-hydroxylase deficiency. The blocked enzymatic step also results in accumulation of 11-deoxycorticosterone which has mineralocorticoid activity, leading in untreated patients to hypertension [6].

The second group of diseases includes rare defects in the final step in the biosynthesis of mineralocorticoid and glucocorticoid that lead to water-sodium disequilibrium. Adrenal *corticosterone methyl oxidase II deficiency* impairs the synthesis of aldosterone with consequent salt-loss in the neonatal period. Some patients, however, become completely asymptomatic later in life. *Glucocorticoid suppressible hyperaldosteronism* is an autosomal dominant

disease characterised by mineralocorticoid hypertension due to an abnormal stimulatory action of ACTH on aldosterone synthesis. This is due to unequal crossing over between the zona glomerulosa 11β -hydroxylase (angiotensin II regulated) and the zona fasciculata 11β -hydroxylase (ACTH regulated) genes [7]. Defects in the inactivation of cortisol, such as *11 β -hydroxysteroid dehydrogenase type II deficiency*, can lead to hypertension with hypokalemia in absence of elevated levels of mineralocorticoids. The mechanism underlying such phenomenon is the prolonged half-life of cortisol that binds to the relatively unselective mineralocorticoid receptor in the kidney and acts like a mineralocorticoid, causing the so-called apparent mineralocorticoid excess syndrome [8]. The disorder in which cortisone is overproduced was tentatively named "apparent cortisone reductase deficiency" (AERD). This seems to be a rare condition characterized by failure to convert cortisone to cortisol, a reaction catalyzed by 11β -hydroxysteroid dehydrogenase type I. This disease is caused by an increased metabolic rate for cortisol at the expense of ACTH-mediated androgen excess, without any clinical symptoms of hypercortisolism [9].

The third group is characterised by deficiencies of enzymes responsible for the final steps of sex hormone synthesis, such as *17,20-lyase*, *17 β -hydroxysteroid dehydrogenase* (17β -HSD), *5 α -reductase and aromatase*. Deficient activity of 17,20-lyase, 17β -HSD and 5α -reductase enzymes leads to male pseudohermaphroditism with varying genital ambiguity in XY individuals. In XX individuals the genitalia are generally normal. In 17,20-lyase (or 17,20-desmolase) deficiency, there is no male or female pubertal development. Cortisol is normal, and there is no hypertension. The deficient enzyme is the same as in 17α -hydroxylase deficiency and it is unknown why the defect manifests itself as 17α -hydroxylase in some, and as 17,20-lyase deficiency in other families. Possibly, estrogen replacement induces a conversion to 17α -hydroxylase deficiency [10]. In 17β -HSD deficiency, there is some male pubertal development in XY individuals due to androstenedione, and often gynecomastia due to estrone. In XX individuals, there is mild virilization and insufficient development of estrogenic sexual characteristics. In 5α -reductase deficiency, male puberty is present in XY subjects because testosterone is sufficient, and dihydrotestosterone (DHT) is not necessary for expression of male sexual secondary characteristics. In XX individuals there are no symptoms. Interestingly, at the time of expected puberty the patients, affected by these deficiencies, display some degree of virilization. Particularly high is the incidence of 5α -reductase deficiency in the Dominican Republic [11]. Patients of both sexes affected by *aromatase deficiency* show a delayed somatic development and slower skeletal maturation, with consequent tall adult stature. Female patients affected by aromatase deficiency display various degrees of genital ambiguity, due to the lack of prenatal exposure to estrogens, and signs of hyperandrogenism, such as acne [12].

In the fourth class are grouped defects in the action of steroid hormones due to receptor defect. Androgens exert their effects in mediating the devel-

opment of normal male phenotype via a single receptor protein, the androgen receptor (AR), which is encoded on the X-chromosome. Abnormalities that alter the function of this receptor result in a range of abnormalities of male phenotypic development, called *complete and partial androgen insensitivity syndrome* (CAIS and PAIS respectively). These phenotypes range from normal female (female habitus, normal female breast development, absent pubic and axillary hair, female external genitalia, no internal genital organs and undescended testes) to those that are characterized by only minor degrees of undervirilization and/or infertility [13].

Estrogen resistance was described only in one case [14] a 28-year-old man with estrogen resistance. He was 204 cm tall and had incomplete epiphyseal closure, with a history of continued linear growth into adulthood despite otherwise normal pubertal development. He was normally masculinized and had bilateral axillary acanthosis nigricans. Serum estradiol and estrone concentrations were elevated, and serum testosterone concentrations were normal. Serum follicle-stimulating hormone and luteinizing hormone concentrations were increased. Glucose tolerance was impaired and hyperinsulinemia was present. Bone mineral density of the lumbar spine was 3.1 SD below the mean for age-matched normal women; there was no biochemical evidence of increased bone turnover. Administration of estrogen had no detectable effect. Although rare, the estrogen resistance was of crucial importance for the understanding of skeletal physiology, since it demonstrated that estrogen is important for bone maturation and mineralization in men as well as in women.

Progesterone prepares the endometrium for blastocyst implantation and allows maintenance of pregnancy. Complete end-organ resistance to progesterone would be incompatible with reproductive competence in females. Males would not be expected to be affected since progesterone has no known function in men. Failure of the uterus to respond to progesterone would lead to the development of a 'constantly proliferative' endometrium incompatible with blastocyst implantation. *Partial resistance to progesterone*, on the other hand, would be expected to be associated with various degrees of incomplete maturation of the endometrium, expressed clinically as infertility or early abortions. The syndrome presents with the clinical and histologic picture of a luteal phase defect in which the life span of the corpus luteum and the plasma progesterone concentrations are normal or slightly elevated [15].

Glucocorticoid resistance is characterized by high levels of cortisol (without stigmata of Cushing syndrome), resistance of the hypothalamic-pituitary-adrenal axis to dexamethasone, and an affinity defect of the glucocorticoid receptor. Some of the affected patients presented with hypertension and hypokalemia due to illegal activation of the mineralocorticoid receptor by cortisol [16].

Pseudohypoaldosteronism is characterised by salt wasting in infancy that is responsive to supplementary sodium but not to mineralocorticoids.

Marked aldosterone excess is present in all reported cases and the renin level is increased in most. Salt supplementation often can be discontinued after infancy without adverse effects, even though aldosterone excess is persistent. Sweat and salivary glands and colonic mucosa are unresponsive to mineralocorticoids as is the distal renal tubule. The basic defect in this disease resides in the mineralocorticoid receptor NR3C2 [17].

29.2 Nomenclature

No.	Disorder-affected component	Tissue distribution	Chromosomal localisation	McKusick
29.1	Lipoid adrenal hyperplasia (StAR deficiency)	Adrenals-gonads	8p11.2	201710
29.2	Congenital adrenal hyperplasia (17 α -hydroxylase deficiency)	Adrenals-gonads	10q24–25	202110
29.3	Congenital adrenal hyperplasia (3 β -hydroxysteroid dehydrogenase type II deficiency)	Adrenals-gonads	1p11–q13	201810
29.4	Congenital adrenal hyperplasia (21-hydroxylase deficiency)	Adrenals-gonads	6p21.3	201910
29.5	Congenital adrenal hyperplasia (11 β -hydroxylase type I deficiency)	Adrenals	8q21–22	202010
29.6	Corticosterone methyl oxidase II deficiency	Adrenals	8q21–22	124080
29.7	Glucocorticoid suppressible hyperaldosteronism (11 β -hydroxylase I/II)	Adrenals	8q21–22	103900
29.8	Apparent mineralocorticoid excess (HSD11B2 deficiency))	Kidneys, adrenals, placenta	16q22	218030
29.9	Apparent cortisone reductase deficiency (HSD11B1 defect)	Liver	1	600713
29.10	17,20-lyase deficiency	Adrenals-gonads	10q24–25	202110
29.11	17 β -hydroxysteroid dehydrogenase type III deficiency	Gonads	9	264300
29.12	Pseudovaginal perineoscrotal hypospadias (5 α -reductase type II deficiency)	Gonads, prostate, genital skin fibroblasts	2p23	264600
29.13	Aromatase deficiency	Gonads, adipose, placenta	15q21.1	107910
29.14	Androgen insensitivity syndrome (AIS)	Testes and accessory organs of male reproduction (e.g. prostate), skeletal muscles, heart, placenta	Xq11–q12	300068
29.15	Estrogen resistance (ESR1 defect)	Ovaries and accessory organs of female reproduction (e.g. uterus and mammary gland)	6q25.1	133430
29.16	Progesterone resistance (PGR defect, pseudocorpus luteum deficiency)	Ovaries and accessory organs of female reproduction.	11q22	264080
29.17	Glucocorticoid resistance (NR3C1 defect)	Liver, muscle, lymphoid, adipose	5q31	138040
29.18	Pseudohypoaldosteronism (NR3C2 defect)	Kidney, colon, salivary gland	4q31.1	264350

29.3 Metabolic Pathway

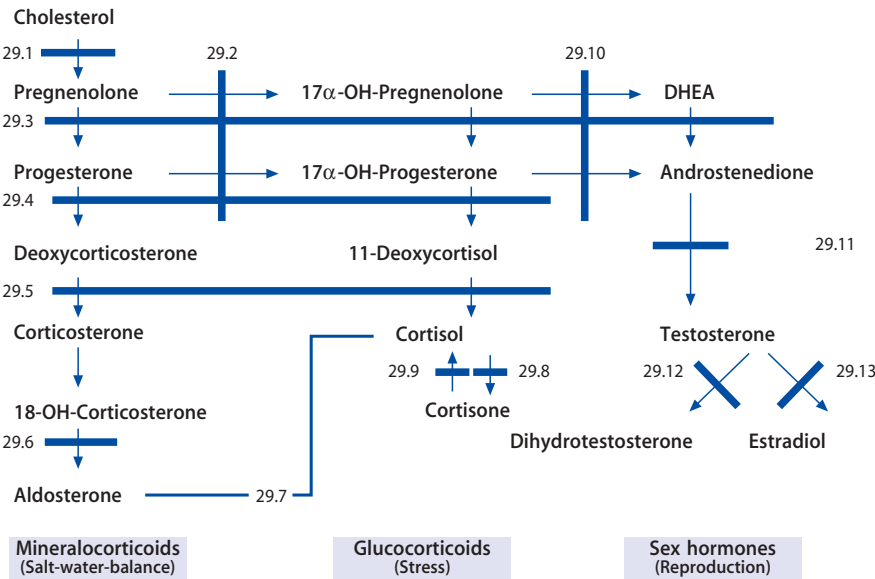


Fig. 29.1. Steroid synthetic pathway: █ block; — unequal crossing-over between CYP11B1 and CYP11B2 (see text for details)

29.4 Signs and Symptoms

Table 29.1. Lipoid adrenal hyperplasia

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Dehydration	\pm	\pm	\pm	\pm
	Female external genitalia regardless genetic sex	+	+	+	+
Routine laboratory	Alkalosis (B)	+	+	\pm	\pm
	Potassium (P)	\uparrow	\uparrow	N- \uparrow	N- \uparrow
	Sodium (P)		\downarrow	\downarrow -N	\downarrow -N
Special laboratory	Steroids (U, P)	\downarrow	\downarrow	\downarrow -N	\downarrow -N
	ACTH (P)	\uparrow	\uparrow	\uparrow	\uparrow
External genitalia Gonads	Infantile female	+	+	+	+
	Undescended testes (XY)	+	+	+	+

Table 29.2. 17 α -Hydroxylase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Episodic vomiting	+	+	+	+
	Headache	N/A	N/A	N/A	N/A
	Hypertension	\pm	+	+	+
	Female external genitalia	+	+	+	+
	Lack of sexual development	N/A	N/A	+	+
Routine laboratory	Alkalosis (B)	+	+	+	+
	Potassium (P)	\downarrow	\downarrow	\downarrow	\downarrow
	Sodium (P)	\uparrow	\uparrow	\uparrow	\uparrow
Special laboratory	Deoxycorticosterone, corticosterone (P)	\uparrow	\uparrow	\uparrow	\uparrow
	cortisol, sex hormones, aldosterone (P)	\downarrow	\downarrow	\downarrow	\downarrow
External genitalia	Infantile female	+	+	+	+
Gonads	Undescended testes (XY)	+	+	+	+

Table 29.3. 3 β -Hydroxysteroid dehydrogenase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Dehydration	\pm	\pm	\pm	\pm
	Ambiguous genitalia (XY and XX)	+	+	+	+
	Post-natal virilization (XX)	N/A	N/A	+	+
Routine laboratory	Potassium (P)	\uparrow	\uparrow	\uparrow	\uparrow
	Sodium (P)	\downarrow	\downarrow	\downarrow	\downarrow
Special laboratory	Δ_5 Steroids (17OH-pregnenolone, DHEA) (P)	\uparrow	\uparrow	\uparrow	\uparrow
	Ratio Δ_5/Δ_4 steroids (U,P)	\uparrow	\uparrow	\uparrow	\uparrow
	Aldosterone, cortisol, sex hormones (P)	\downarrow	\downarrow	\downarrow	\downarrow
	ACTH (P)	\uparrow	\uparrow	\uparrow	\uparrow
External genitalia	Various degree of genital ambiguity:				
	XY: hypospadias	+	+	+	+
	XX: cliteromegaly	\pm	\pm	\pm	\pm
Gonads	XY: undescended tests	+	+	+	+

Table 29.4. 21-Hydroxylase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Dehydration	±	±	±	±
	Various degrees of genital ambiguity (XX)	+	+	+	+
	Advanced somatic development (both sexes)	N/A	-	-	+
	Short stature	N/A			
Routine laboratory	Potassium (P)	↑	↑	N-↑	N-↑
	Sodium (P)	↓	↓	↓-N	↓-N
	Inappropriate natriuresis	+	+	±	±
	17OH-progesterone (P)	↑↑	↑↑	↑↑	↑↑
Special laboratory	DHEA, androstenedione and testosterone (P)	N-↑	↑	↑	↑
	Pregnantriol and androgen metabolites (17 keto-steroids) (U)	N-↑	↑	↑	↑
	Aldosterone and cortisol	↓	↓	↓	↓
	Plasma renin activity (PRA) (P)	↑	↑	↑	↑
External genitalia	ACTH (P)	↑	↑	↑	↑
	XX: various degree of genital ambiguity (from clitoral enlargement to penile urethra)	+	+	+	+
Bone age	Advanced	±	+	+	+
Fertility	XY: decreased (low sperm count)	N/A	N/A	N/A	+

The described clinical picture is referred to the most common classical type of the disease, i.e. the salt losing form. The simple virilizing is identical to the salt losing form except for the absence of salt loss. The nonclassical (late-onset; attenuated) form displays only signs of postnatal androgen excess.

Table 29.5. 11 β -Hydroxylase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	XX: genital ambiguity	+	+	+	+
	Episodic vomiting	±	+	+	+
	Headache	±	+	+	+
	Hypertension	±	+	+	+
	Advanced somatic development (both sexes)	N/A	+	+	+
	Short stature	N/A	-	-	+
Routine laboratory	Potassium (P)	↓	↓	↓	↓
	Sodium (P)	↑	↑	↑	↑
Special laboratory	Deoxycorticosterone, 11-deoxycortisol, androgens (P)	↓	↓	↓	↓
	Cortisol and aldosterone (P)	↓	↓	↓	↓
	Plasma renin activity (PRA) (P)	↓	↓	↓	↓
	ACTH (P)	↓	↓	↓	↓
External genitalia	XX: various degree of genital ambiguity (see 29.4)	+	+	+	+
Bone age	Advanced	±	+	+	+

Table 29.6. Corticosterone methyl oxidase II deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Dehydration	+	±		
	Failure to thrive	+	+		
Routine laboratory	Potassium (P)	↑	N-↑	N	N
	Sodium (P)	↓	↓-N	N	N
Special laboratory	Aldosterone (P)	↓	↓	↓-N	↓-N
	18-OH-corticosterone (P)	↑	↑	N-↑	N-↑

Table 29.7. Glucocorticoid-suppressible hyperaldosteronism

System	Symptom/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Headache	-	+	+	+
	Hypertension	+	+	+	+
Routine laboratory	Potassium (P)	↓	↓	↓	↓
Special laboratory	Aldosterone (P)	↑	↑	↑	↑
	Aldosterone after dexamethasone (P)	↓	↓	↓	↓
	18-Oxocortisol (U)	↑	↑	↑	↑

Table 29.8. 11 β -Hydroxysteroid dehydrogenase type II deficiency (apparent mineralocorticoid excess)

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Headache	-	+	+	+
	Hypertension responsive to low sodium diet ^a	+	+	+	+
Routine laboratory	Potassium (P)	↓	↓	↓	↓
Special laboratory	Tetrahydrocortisol/tetrahydrocortisone ratio (U)	↓	↓	↓	↓

^a See Special tests section.

Table 29.9. 11 β -Hydroxysteroid dehydrogenase type I deficiency (apparent cortisone reductase deficiency)

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Hirsutism and other signs of androgen excess in women only	–	–	+	+
Routine laboratory	All parameters	N/A	N/A	N	N
Special laboratory	Cortisol (P)			N	N
	ACTH (P)			N	N
	Adrenal androgens (DHEA, androstendione) (P)			↑↑	↑↑
	All 17-ketosteroids (androsterone, etiocholanolone, DHEA) (U)			↑↑	↑↑
	Cortisol and cortisone metabolites (THF, THE) (U)			↑↑	↑↑

Table 29.10. 17,20-Lyase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Male: various degrees of genital ambiguity	+	+	+	+
Special laboratory	17-OH-progesterone (P)	↑	↑	N–↑	N–↑
	Cortisol aldosterone (P)	N	N	1–N ^a	1–N ^a
	DHEA, androstenedione testosterone (P)	↓	↓	↓	↓
External genitalia	XY: ambiguous	+	+	+	+
Gonads	XY: undescended testes	+	+	+	+

^a Under estrogen replacement.**Table 29.11.** 17 β -Hydroxysteroid dehydrogenase type III deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Unique clinic findings	XY: external genitalia from female to ambiguous	+	+	+	+
	Undescended testes	+	+	+	+
	Gynecomastia	N/A	N/A	+	+
Special laboratory	Androstenedione and estrone (P)	N–↑	N–↑	N–↑	↑
	Testosterone and estradiol (P)	↓	↓	↓	↓
	Follicle stimulating hormone and luteinizing hormone (P)	N/A	N	↑	↑
External genitalia	Various degree of ambiguity	+	+	+	+
Gonads	Undescended testes	+	+	+	+

Table 29.12. 5 α Reductase type II deficiency (pseudovaginal perineoscrotal hypospadia)

System	Symptom/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	XY: various degree of genital ambiguity: blind pouch vagina with micropenis resembling a clitoris	+	+		
	Undescended testes	+	+		
Special laboratory	Virilization			+	+
	Testosterone/dihydrotestosterone ratio (P)	N/A	N/A	↑	↑
	T/DHT ratio after human chorionic gonadotropin (P)	↑	↑	↑	↑
	5 α /5 β reduced C19 steroids ratio (U)	↓	↓	↓	↓
	5 α -reductase activity in genital skin fibroblasts	↓-N	↓-N	↓	↓
External genitalia	Ambiguity	+	+	+	+
Gonads	Undescended testes	+	+	-	-

Table 29.13. Aromatase deficiency

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	XX: ambiguous genitalia	+	+	+	+
	Delayed somatic development			+	+
	Tall stature	N/A	N/A	+	+
	Obesity	N/A	N/A	+	+
Special laboratory	Androgens (U, P)	N	N	N-↑	N-↑
	Estrogens (P)	↓	↓	↓	↓
	Luteinizing hormone and follicle stimulating hormone (P)	N/A	N-↑	↑	↑
External genitalia	XX: ambiguous	+	+	+	+
	XY: normal				
Bone age	Delayed	+	+	+	+
Skin	Acne	+	+	+	+
	Hirsutism				

Table 29.14. Androgen insensitivity syndrome

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Genetic male with female-ambiguous external genitalia	+	+	+	+
	Absent uterus	+	+	+	+
	Abdominal or inguinal testes	+	+	+	+
	Female breast development	N/A	N/A	+	+
	Absent pubic and axillary hair	N/A	N/A	+	+
Special laboratory	Androgens (U, P)	N	N	↑	↑
	LH (FSH) (P)	↑	↑	↑	↑
	Karyotype: normal male (46 XY)	+	+	+	+
External genitalia	From female (complete androgen insensitivity syndrome) to hypospadias (incomplete androgen insensitivity)	+	+	+	+
Bone age	Normal	+	+	+	+

Table 29.15. Estrogen resistance

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Tall stature	N/A	N/A	+	+
	Incomplete epiphyseal closure				
	Normal pubertal development	N/A	N/A	+	N/A
Special laboratory	Glucose tolerance	N	N	↓	↓
	Androgens (U, P)	N	N	N	N
	Estrogens (P)	↑	↑	↑	↑
	LH (FSH) (P)	↑	↑	↑	↑
	Karyotype: normal male (46 XY)	+	+	+	+
External genitalia	Normal male	+	+	+	+
Bone age	Delayed	+	+	+	+

Table 29.16. Progesterone resistance (pseudocorpus luteum deficiency)

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Female infertility	N/A	N/A	+	+
	Menstrual cycle	N/A	N/A	N	N
	Luteal phase duration	N/A	N/A	N	N
Special laboratory	Progesterone (P)	N/A	N/A	N	N
	Androgens (U, P)	N	N	N	N
	Estrogens (P)	N	N	N	N
	LH (FSH) (P)	N	N	N	N
External genitalia	Normal female	+	+	+	+
Endometrium	Immature	N/A	N/A	+	+

Table 29.17. Glucocorticoid resistance

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Hypertension	N/A	N/A	+	+
	Hypokaliemic alkalosis	N/A	N/A	N	N
	Cushing stigmata	None	None	None	None
Special laboratory	Cortisol (P)	N	N	↑	↑
	Free cortisol (U)	N	N	↑↑	↑↑
	Dexamethasone suppression test	N/A	N/A	Unresponsive	Unresponsive
	ACTH	N/A	N/A	N-↑	N-↑

Table 29.18. Pseudohypoaldosteronism

System	Symptoms/marker	Neonatal	Infancy/ childhood	Puberty	Adulthood
Characteristic clinical findings	Renal salt loss	N/A	N/A	+	+
Special laboratory	Aldosterone (P, U)	N/A	N/A	↑	↑
	Sodium	N/A	N/A	↓	↓
	Potassium	N/A	N/A	↑	↑
	PRA	N/A	N/A	↑	↑
	THE/THF	N/A	N/A	N	N

29.5 Reference Values

■ Plasma

Age	ACTH pmol/l	FSH/LH mIU/ml	17OHP nmol/l	DHEA nmol/l	Δ_4 A nmol/l	T nmol/l	DHT nmol/l	E2 pmol/l	Aldo pmol/l	DOC pmol/l	B pmol/l	F μ mol/l
<6 yr	4.4–22–2	N/A	0.3–9.5	Male: 0.9–2.5 Female: 0.7–1.5	N/A	Male: 0.28–0.49 Female: 0.17–0.45	Male: <0.1–0.4 Female: <0.1–0.3	Male: <37 Female: <26	N/A	1.5–7.5	0.6–2.16	AM 0. 14–0.55 PM 0.07–0.28
8–10 yr	4.4–22–2	N/A	0.3–9.5	Male: 1.8–4.7 Female: 2.6–6.2	N/A	Male: 0.28–0.49 Female: 0.17–0.45	Male: <0.1–0.4 Female: <0.1–0.3	Male: <37 m: 83–250 j: 11–832 ^a Female: 30–65		1.5–7.5	0.6–2.16	AM 0.14–0.55 PM 0.07–0.28
10–12 yr	4.4–22–2	N/A	0.3–9.5	Male: 6.3–12.3 Female: 8.1–18.3	N/A	Male: 0.28–0.49 Female: 0.17–0.45	Male: <0.1–0.4 Female: <0.1–0.3	Male: <37 m: 83–250 j: 11–832 Female: 30–65		1.5–7.5	0.6–2.16	AM 0.14–0.55 PM 0.07–0.28
14–16 yr	4.4–22–2	FSH: male: 2–17 Female: 4–20 LH: male: 4–18 Female: 5–25	0.3–9.5	Male: 8.3–18 Female: 7.8–21.2	1.4–7.9	Male: 2.91–6.24 Female: 0.31–0.83	Male: 1–10.4 Female: 0.2–1.1	Male: 62–85 Female: 73–250	m: 83–250 j: 11–832	1.5–7.5	0.6–2.16	AM 0.14–0.55 PM 0.07–0.28
Adult	"	"	0.3–9.5	Male: 10.6–29 Female: 9.8–27.7	1.4–7.9	Male: 10.4–34.7 Female: 1.04–2.43	Male: 1–10.4 Female: 0.2–1.1	Male: 62–184 Female: follicular 73–367 luteal 367–1836	m: 83–250 j: 11–832	1.5–7.5	0.6–2.16	AM 0.14–0.55 PM 0.07–0.28

ACTH, adrenocorticotropin hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; 17OHP, 17-hydroxyprogesterone; DHEA, dehydroepiandrosterone, Δ_4 A, androstenedione; T, testosterone; DHT, dihydrotestosterone; E2, estradiol; Aldo, aldosterone; DOC, deoxycorticosterone; B, corticosterone; F, cortisol.

^a Sodium intake 100–200 meq/d recumbent (m) upright: (j); sodium intake 10 meq/d recumbent: 333–999 upright: 472–3800.

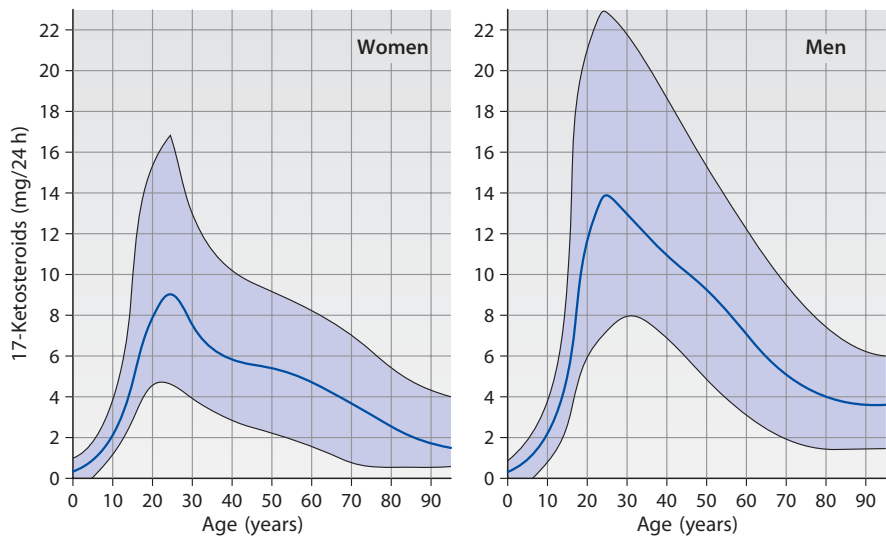


Fig. 29.2. Total 17-ketosteroids: normal values

29.6 Pathological Values/Differential Diagnosis

■ Plasma

Variant	ACTH	FSH/H	17OHP	DHEA	Δ_4 A	T	DHT	E2	Aldo*	DOC	B	F
29.1	↑↑		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
29.2	↑	↑	↓	↓	↓	↓	↓	↓	↓	↑↑	↑↑	↓
29.3	↑	↑	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
29.4	↑	↑	↑↑	↑	↑	↑	↑		↓	↓	↓	↓
29.5	↑	↑		↑	↑	↑	↑		↓	↑	↓ ^a	↓
29.6									↓ ^b	↑		
29.7									↑ ^b			
29.8 ^c												
29.9									N-↑			↑
29.10		↑	↑	↓	↓	↓	↓	↓				
29.11		↑			↑	↓		↓				
29.12		↑				N-↑						
29.13		↑				N-↑		↓				
29.14		↑			↑	↑↑	↑	N-↑				
29.15		↑				↑		↑				
29.16		N	N			N		N				
29.17	↑											↑↑
29.18									↑↑	N	N	

Footnotes see p. 566.

ACTH, adrenocorticotropin hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; 17OHP, 17-hydroxy progesterone; DHEA, dehydroepiandrosterone; Δ_4 A, androstenedione; T, testosterone; DHT, dihydrotestosterone; E2, estradiol; Aldo, aldosterone; DOC, deoxycorticosterone; B, corticosterone; F, cortisol.

^a Low 18-oxocortisol (aldosterone urinary metabolite, not detectable *via* gas chromatographic urine profile).

^b Elevated 18-oxocortisol (aldosterone urinary metabolite not detectable *via* gas chromatographic urine profile).

^c No direct metabolite of testosterone measurable, not detectable *via* gas chromatographic urine profile. *Sodium intake 100–200 meq/d recumbent (m) upright: (j); sodium intake 10 meq/d recumbent: 333–999 upright: 472–3800.

■ Urine

Vari- ant	PD	PT	PTL	PT'	THB	16- OH- PN'L*	AN	ET	DHA	11- Keto AN	16- OH- DHA*	11- OH AN	THS	THA	THE	THF	allo THF	α - corto- lone	β - corto- lone
29.1	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
29.2	↑	↓	↓	↓	↑	↑	↓	↓	↓	↓	↓	↓	↓	↑	↓	↓	↓	↓	↓
29.3	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
29.4	↑	↑↑	↑	↓	↓	↓	↑	↑	↑	↑	↓	↓	↓	↓	↓	↓	↓	↓	↓
29.5			↓		↑		↑	↑	↑	↑		↓	↑	↑	↓	↓	↓	↓	↓
29.6 ^a																			
29.7 ^b																			
29.8															↓	↑	↑	↓	↓
29.9							↑	↑					↑		↑↑↑	↑↑	↑↑	↑	↑
29.10	↑	↑	↑				↓	↓	↓	↓		↓							
29.11 ^c							↑	↑								N	↓		
29.12							↓	↑											
29.13							↑	↑											
29.14							↑	↑											
29.15							↑	↑											
29.16																			
29.17							↑	↑							↑	↑	↑	↑	↑
29.18					↑									↑					

PD, pregnandiol; PT, pregnantriol; PTL, pregnantriolone; PT', pregnentriol; THB, tetrahydrocorticosterone; PN'L, 16-hydroxy pregnenolone; AN, androsterone; ET, etiocholanolone; DHA, dehydroepiandrosterone; 11-keto AN, 11-hydroxyandrosterone; THS, tetrahydrodeoxycortisol; THA, tetrahydro compound A; THE, tetrahydrocortisone; THF, tetrahydrocortisol; * normally present only in newborn.

^a Low 18-oxocortisol (aldosterone urinary metabolite, not detectable *via* gas chromatographic urine profile).

^b Elevated 18-oxocortisol (aldosterone urinary metabolite not detectable *via* gas chromatographic urine profile).

^c No direct metabolite of testosterone measurable, not detectable *via* gas chromatographic urine profile.

The interpretation of the numerical values of urinary metabolites obtained via gas chromatographic urinary steroid profiles is extremely complex since several parameters, e.g. bone age, pubertal stadium etc., must be taken into consideration

29.7 Diagnostic Flow Charts

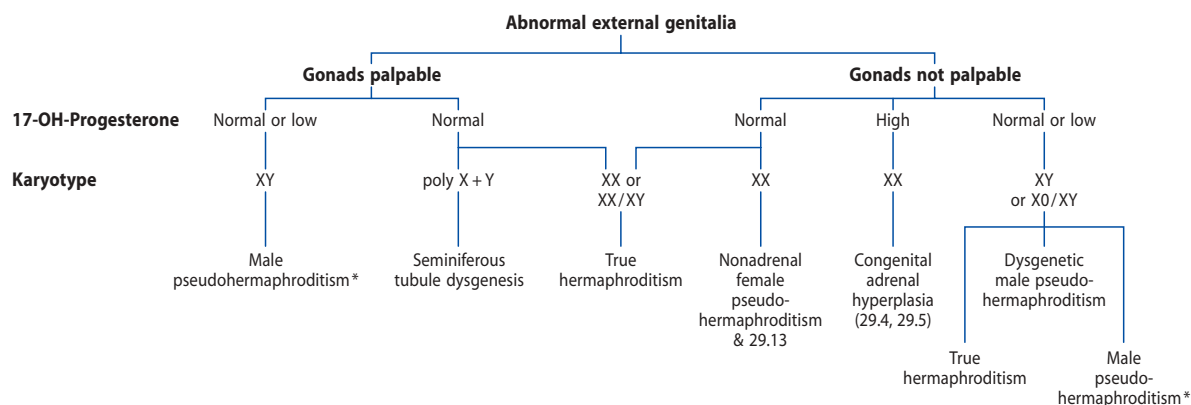


Fig. 29.3. Diagnosis of intersexuality* 29.1, 29.2, 29.3, 29.10, 29.11, 29.14

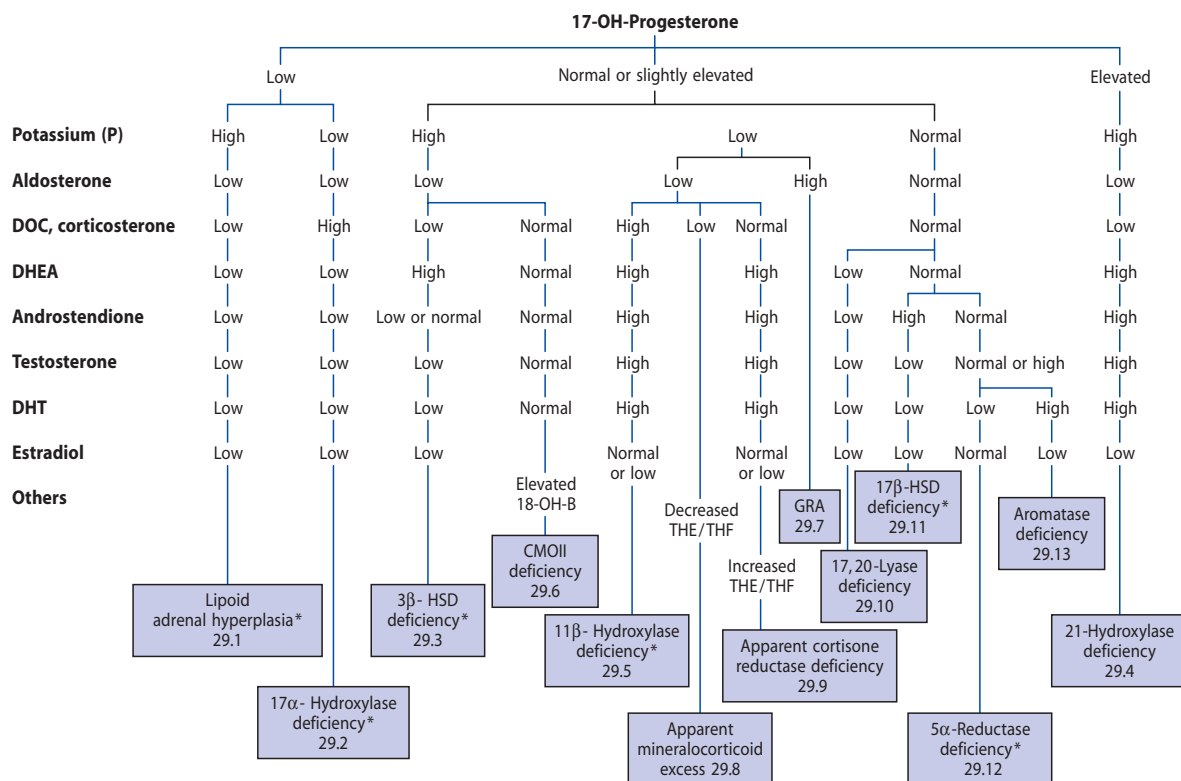


Fig. 29.4. Diagnosis of steroidogenic defects. For initial screening of intersexuality see Fig. 26.3. Other: female pseudohermaphroditism. 18OH-B: 18-hydroxycorticosterone. * Male pseudohermaphroditism.

29.8 Special Tests

Disorder	Test	Procedure	Results
29.8	Sodium (P) restriction	3–5 days of 10 mmol sodium intake. Aldosterone morning plasma levels	Increase 2–3fold over basal levels
29.7	Dexamethasone suppression test	1 mg dexametasone for 2 days p.o. Cortisol morning plasma levels	Decrease of aldosterone
29.17			Decrease of cortisol

29.9 Specimen Collection

Test	Pre-conditions	Material	Handling	Pitfalls
Plasma or serum quantitative steroids, ACTH and gonadotropins	None	Frozen plasma or serum	Keep frozen (–20 °C) until analyzed	None, except laboratory error
Urine for gas-chromatographic analysis of urinary metabolites	None	Fresh or frozen 24 h urine (discard the morning urine of the first day but collect the morning urine of the second and final day)	Keep frozen (–20 °C) until analyzed	None, except laboratory error

29.10 Prenatal Diagnosis

Disorder	Material	Timing, trimester
All disorders (except 29.9 & 29.15–18 that are adult onset diseases)	CV, AF	I, II

29.11 Initial Treatment

■ Disorders 29.1, 29.3 29.6 (Salt-Losing Forms)

1. Parenteral isotonic saline
2. Deoxycortisone acetate (DOCA) 2–5 mg i.m.
Note: salt-loss symptoms do not appear before 7–10 days after birth.

■ Disorders 29.2, 29.5, 29.7, 29.8, 29.17
(Hypertensive, Hypokaliemic Forms)

1. Restoration of potassium concentrations
2. Diuretic therapy to reduce blood pressure.

■ Disorders 29.1, 29.2, 29.3, 29.4, 29.5, 29.10, 29.11, 29.12, 29.14
(Intersex)

1. Sex assignment (sex reassignment may be necessary after the laboratory results have been obtained)
2. Reconstructive genital surgery around 6–12 months of life.

29.12 Summary/Comments

Defects in steroid biosynthesis and action lead to complex and profound clinical consequences that can be grouped in four categories: 1) defects of salt-water homeostasis and sexual differentiation; 2) defects of salt-water homeostasis; 3) defects of sexual differentiation; 4) end-organ steroid hormone resistance. Among the members of the first group, lipid adrenal hyperplasia is characterized by lack of all steroid hormones, with consequent male pseudohermaphroditism and salt-loss in the first weeks of life. 17α -Hydroxylase deficiency leads also to male pseudohermaphroditism associated with hypertension and hypokalemia. 3β -Hydroxysteroid dehydrogenase deficiency causes incomplete virilization in male fetuses, together with salt-loss. 21 -Hydroxylase deficiency, whose nonclassic form is one of the most common autosomal recessive diseases in humans, is responsible for female ambiguous genitalia at birth and salt-loss. 11β -Hydroxylase deficiency differs from 21 -hydroxylase deficiency for the absence of salt-wasting and later presence of hypertension and hypokalemia.

Enzymatic defects of the second group cause either salt-wasting symptoms in the neonatal period, spontaneously resolving in adulthood, as in the case of corticosterone methyl oxidase II deficiency, or hypertension and hypokalemia as in the cases of glucocorticoid-suppressible hyperaldosteronism and apparent mineralocorticoid excess. The third group of defects includes enzymatic blocks of the last steps of sex hormones biosynthesis. $17,20$ -Lyase, 17β -hydroxysteroid dehydrogenase and 5α -reductase deficiencies determine incomplete virilization of the male fetus. In $17,20$ -lyase deficiency, there is no spontaneous puberty in males and females, in the latter two male puberty occurs. Aromatase deficiency is a cause of nonadrenal female pseudohermaphroditism. The end-organ resistance syndromes, which are still an exclusion diagnosis, represent a further challenge for future diagnostic and therapeutic applications. The treatment of these defects is

based on exogenous administration of the deficient hormones and corrective surgery in intersexuality. Given the rarity of most of these diseases prenatal diagnosis is possible only in a family at risk. In the case of 21-hydroxylase deficiency, however, advances in prenatal diagnosis allowed *in utero* treatment. Progress in molecular analysis of steroid biosynthesis and action defects will allow a better prenatal diagnosis and treatment of such diseases.

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